STATISTICAL ANALYSIS PLAN

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
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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

List of Abbreviations

5-ASA	5-Aminosalicylate
6-MP	6-Mercaptopurine
ANCOVA	Analysis of Covariance
AZA	Azathioprine
BLQ	Below the Limit of Quantitation
CMV	Cytomegalovirus
CRP	C-Reactive Protein
EBV	Epstein-Barr virus
ECG	Electrocardiogram
e-CRF	Electronic Case Record Form
ESR	Erythrocyte Sedimentation Rate
FAS	Full Analysis Set
GEE	Generalized Estimating Equations
HBcAb	Hepatitis B Core Antibody
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HEENT	Head, Eyes, Ears, Nose, and Throat
HIV	Human Immunodeficiency virus
ICH	International Conference on Harmonisation
IL-6	Interleukin 6
IL-6R	IL-6 Receptors
IMP	Investigational Medicinal Product
ITT	Intention-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities

MMRM	Mixed Model Repeated Measures model
MTX	Methotrexate
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PT	Preferred Term
Q2W	Biweekly
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
sIL-6R	Soluble IL-6 Receptor
SOC	System Organ Class
TB	Tuberculosis
UC	Ulcerative Colitis
WHO DD	World Health Organization Drug Dictionary

Definition of Pharmacokinetic Terms

$AUC_{0\text{-}inf}$	Area under the concentration-time curve from time zero (pre-dose) extrapolation to infinite time
$AUC_{0\text{-}t}$	Area under the concentration-time curve from time zero (pre-dose) to time of last quantifiable concentration
AUC_{τ}	Area under the concentration-time curve over the dosing interval
C_{max}	Maximum concentration observed
C_{trough}	Pre-dose (trough) concentration at the end of the dosing interval, immediately before next administration
T_{max}	Time of maximum observed concentration (C_{max})
CL	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

1 Introduction

Clinical trial with Protocol No. CTJ301UC201, is a multicenter, randomized, double-blind, placebo-controlled phase II study, which is aim to evaluate the safety and efficacy of TJ301 in patients with active ulcerative colitis.

This statistical analysis plan (SAP) for Clinical Trial CTJ301UC201, describes the statistical analysis methods, and provides the Shells to display data to clinical study report (CSR).

The English version of SAP is a translation of SAP CN V1.0 dated 22 Dec 2020, which was developed based on the protocol CN V4.0 dated 15 Jan 2020 and e-CRF V4.0 dated in 27 Mar 2020 and finalized before the database locked date.

Some of the analyses detailed here are more explicit or in some aspects slightly different than those stated in the protocol. In case of differences, this SAP supersedes the statistical sections in the protocol.

When developing this SAP, Guidance of Data Management and Statistical Analysis Plan and Report for Clinical Trials (released by NMPA), Guidance of Biostatistics for Clinical Trials (released by NMPA), ICH E3 (Structure and Content of Clinical Study Reports), ICH E9 (Statistical Principles for Clinical Trials)[1-4] were referred.

2 Objectives

2.1 Primary Objective

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

2.2 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.

2.3 Exploratory Objectives

- To explore the relationship between PK and PD of TJ301 in patients with active ulcerative colitis.

3 Endpoints

3.1 Primary Endpoints

- The percentage of subject achieving clinical response per Full Mayo score (defined as 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
- Frequency and Severity of Adverse events, vital signs, 12-lead Electrocardiography (ECG), and clinical safety laboratory abnormalities.

3.2 Secondary Endpoints

- The percentage of subject achieving clinical remission per Full Mayo score (defined as a full Mayo score ≤2, no individual subscore >1, rectal bleeding subscore = 0) at week 12.
- The percentage of subject achieving clinical remission per Partial Mayo score(defined as a stool frequency subscore=0, rectal bleeding subscore = 0, and 9-point partial Mayo score ≤1) at Weeks 4, 6, 8, 10, and 12.
- The percentage of subject achieve clinical response per Partial Mayo score (defined as 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.
- The percentage of subject achieve 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.
- The percentage of subject achieve FDA-defined remission(defined as per modified Mayo score, Stool frequency subscore≤1, Rectal bleeding subscore=0, and Endoscopy subscore =0 or 1) at Week 12.
- Immunogenicity: Anti-TJ301 antibodies.
- PK subgroup: $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, C_{max}, T_{max}, CL, V_z, $t_{½}$, and MRT_{inf} (if applicable); trough (pre-infusion) TJ301 serum concentration in all subjects.
- Change from Baseline to Weeks 4, 8, and 12 in exploratory biomarkers (erythrocyte sedimentation rate [ESR], C-reactive protein (CRP), IL-6, s-IL6R, IL-6/sIL-6R complex, neutrophil and platelet count, faecal calprotectin).

3.3 Exploratory Endpoints

- The relationship between exposure of TJ301 and biomarkers.

4 Study Procedure

4.1 Study Design

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

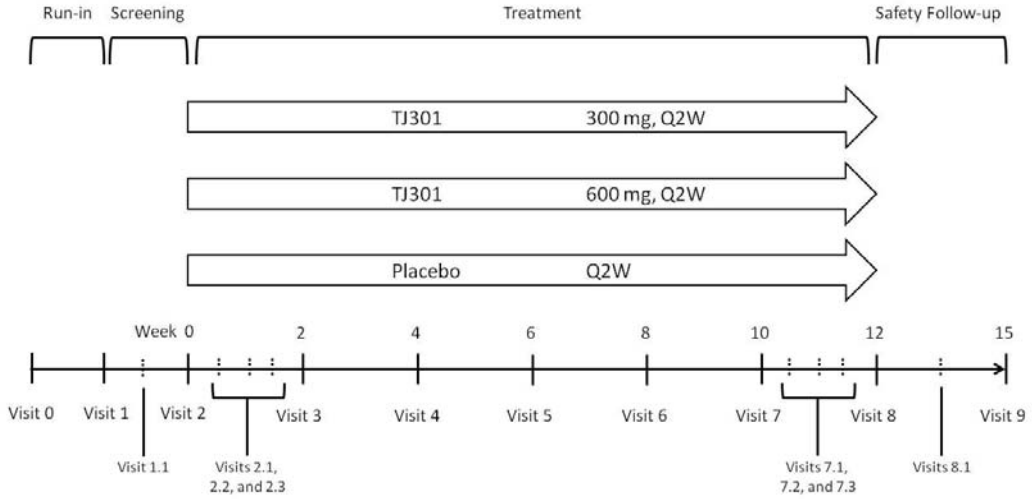
The trial includes a Run-in Period (if stable conventional treatment needed), a 4-week Screening Period, a 12-week Treatment Period, and a 3-week Safety Follow-up Period to Day 105.

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

During the treatment period and the follow-up period, patients should be on stable conventional treatment for UC in double-blind. 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 per day (or equivalent), and/or with medications containing 5-aminosalicylates (5-ASA), and/or with azathioprine (AZA)/mercaptopurine (6-MP) /methotrexate (MTX).

Figure 1 Study Flowchart



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

- Visit 0: Run-in period: is 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 per day (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 0.75 mg/kg/day or mercaptopurine (6-MP) at no less than 0.5 mg/kg/day for at least 6 months and stable for at least 6 weeks prior to Randomization, or MTX no less than 12.5 mg/week and stable for at least 12 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.

Conventional Therapy	Dose Requirement	Duration for stable treatment
Corticosteroids	No more than 20 mg prednisone (or equivalent)	Stable for at least 2 weeks prior to Randomization
5-ASA	No less than 2 g 5-ASA per day	Treatment for at least 3 months and stable for at least 4 weeks prior to Randomization
AZA	No less than 0.75 mg/kg/day	Treatment for at least 6 months and stable for at least 6 weeks prior to Randomization
6-MP	No less than 0.5 mg/kg/day	Treatment for at least 6 months and stable for at least 6 weeks prior to Randomization
MTX	No less than 12.5 mg/week	Stable for at least 12 weeks prior to Randomization

- Visit 1: Screening Visit, start of Screening Period (Days -28 to -6 prior to Visit 2)
- Visit 1.1: Randomisation Visit (Baseline)
- Visit 2: 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 1.1

(Randomisation Visit, baseline), 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).

Blood samples for ADA analysis will be collected as follows:

At the 1st , 2nd , 3rd and 5th administrations: blood samples will be collected pre-dose (within 1 hour prior to dosing on Days 0, 14, 28 and 56), and on Days 84 and 105.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 h (Day 10) 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. In addition, TJ301 serum concentration (PK) will be measured using backups from ADA samples taken before administration on days 14, 28, 56, and 84 in the non-PK subgroup.

For patients completing the12-week treatment period, a Safety Follow-up Visit will be scheduled on Day 105 (Week 15). For patients not completing the12-week treatment period, a Safety Follow-up Visit will be scheduled 35 days (5.8 - 6.6 half-lives of TJ301) after the last dose of IMP.

4.2 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.

The sample size calculation of the TJ301 groups and placebo group is based on the clinical response rate at week 12, with a 1-sided test at the 0.05 significance level. The enrolment of 27 patients per treatment group will provide at least 70% power estimated by PASS 16 software, assuming the clinical response rate of the TJ301 treatment group achieving best efficacy is 60% and that of placebo treatment group is 30% according to previous studies. Considering the dropout rate of 10%, 30 patients will be randomized in each treatment group (90 in total).

4.3 Randomisation

After all applicable screening assessments have been performed at the Randomisation Visit (Visit 1.1), patients who have met all inclusion criteria and none of the exclusion criteria will be centrally, dynamically, randomised in a 1:1:1 ratio to each of the three arms, namely placebo, 300 mg TJ301, or 600 mg TJ301, and will receive a unique computer-generated subject number by validated Interactive Web Response System (IWRS). Randomisation will be stratified by prior corticosteroids treatment (yes/no) and prior biologic treatment(yes/no) collected at Visit 1.

In addition, PK samples will be only collected from 8 patients in each of the three arms, placebo, 300 mg TJ301 and 600 mg TJ301, in Mainland China as PK sub-study.

4.4 Blinding

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 blind codes will not be available to any person involved in the conduct and evaluation of the trial until the trial is unblinded.

A central, computer-based randomisation procedure is used to eliminate selection bias.

4.5 Interim and Final Analyses

No interim analysis was planned and final analysis will be conducted after data base is locked.

5 Analysis Sets

Intention-to-Treat Analysis Set (ITT)

The Intention-to-treat (ITT) analysis set will include all randomised patients. Planned treatment group will be used in summary.

Full Analysis Set (FAS)

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. The primary analysis population for efficacy end points will be the Full Analysis Set (FAS). Planned treatment group will be used in summary.

Per Protocol (PP) Analysis Set

The PP analysis set will consist of FAS patients who had no major protocol deviations\violations that would impact efficacy analysis, without missing primary efficacy endpoint. The secondary analysis population for efficacy endpoints will be the Per Protocol Analysis Set (PPS). Actual treatment group will be used in summary.

Safety Analysis Set (SS)

The Safety analysis set will include all randomised patients who received at least one dose of IMP. The primary analysis population for safety endpoints will be the Safety Analysis Set (SS). Actual treatment group will be used in summary.

PK Analysis Set (PKS)

The PK analysis set will consist of all patients (excluding patients treated with placebo) who have at least one after-dose measurable plasma sample. The primary analysis population for PK endpoints will be the PK Analysis Set (PKS). Actual treatment group will be used in summary.

PD Analysis Set (PDS)

The PD analysis set will consist of patients in PD subgroup who have at least one after-dose measurable plasma sample. The primary analysis population for PD endpoints will be the PD Analysis Set (PDS). Actual treatment group will be used in summary.

Immunogenicity Analysis Set (IS)

The immunogenicity analysis set (IS) will consist of all randomised patients who received at least one dose of IMP and have measurable immunogenicity data after administration. The

primary analysis population for immunogenicity endpoints will be the immunogenicity Analysis Set (IS). Actual treatment group will be used in summary.

6 Statistical Analysis

6.1 Visit Windows

Scheduled visits will be used in analyses.

For Safety data, the unscheduled visits will not be included into the summaries, but will be considered when the worst results should be used, such as the shift table.

6.2 Data Conventions

6.2.1 Definitions of Full and Partial Mayo Score

The full Mayo score 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).

In parallel to the investigator scoring, endoscopic scoring (endoscopic component of the Mayo score) will be performed through centralised reading for efficacy assessment. 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). If the endoscopic qualifying score is missing, the investigator scoring will be the replacement for efficacy analysis.

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.

The scores for stool frequency and rectal bleeding will be calculated as an average based on scores

collected from the Patient daily Diary, the algorithm rule is: for up to 7, but at least 3 days prior to each applicable visit, if there are less than 3 days with valid score, the scores for stool frequency and rectal bleeding at each applicable visit will be missing; else if there are 3 three consecutive days with valid scores, the average score of the three scores will be used for each applicable visit; if there are no three consecutive days with valid scores, the three non-consecutive days with valid scores will be used. See Details in Table 1 . The scores for stool frequency and rectal bleeding are also collected from investigators side, who derive from the average of 3-5 diary days prior to each visit.

Table 1 Algorithm of Scores for Stool Frequency and Rectal Bleeding at Each Visit

Situation	Prior 7 days	Prior 6 days	Prior 5 days	Prior 4 days	Prior 3 days	Prior 2 days	Prior 1 day	Algorithm
1	a	b					g	(a+b+c)/3
2	a							missing
3	a						g	missing
4	a	b				f	g	(b+f+g)/3
5	a	b	c				g	(a+b+c)/3
6		b	c	d			g	(b+c+d)/3

If the scores for stool frequency and rectal bleeding calculated by programming is missing, the scores from investigators side will be the replacement. The scores from investigators side will be the primary analysis.

The physician's global assessment and endoscopic appearance scores will be collected in the e-CRF. 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 recorded as missing. In addition, the stool frequency and rectal bleeding subscore will be recorded as missing for the day of all endoscopies and the day after.

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 rectal 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 criterion. The Endoscopy subscore is modified so that a value of 1 does not include friability.

6.2.2 PK Data Conventions

6.2.2.1 BLQs

BLQ values will be imputed for tabular summaries according to the following rules:

- All BLQ values will be set to 1/2 LLOQ. When the sum of missing values and BLQ values exceeds 2/3 of the total numbers of measurement, only the statistics n, n >= LLOQ, Min and Max are presented. If Min or Max is BLQ, the BLQ will be listed.

BLQ values will be imputed in the PK concentration dataset used for the derivation of PK parameters. The following rules will be applied:

- BLQs before the T_{max} of a subject profile will be assigned to zero.
- BLQs after the T_{max} of a subject profile will be assigned to zero.
- Single BLQ which fall between two measurable concentrations will be set to missing.
- Consecutive BLQs which fall between measurable concentrations will be set to missing. Measurable concentrations following consecutive BLQs after the T_{max} of a subject profile will be set to missing.

BLQ values will be imputed for individual concentration-time plots according to the following rules:

- BLQs before the T_{max} of a subject profile will be assigned to zero.
- BLQs after the T_{max} of a subject profile will be assigned to zero.
- For concentration-time profile after each dose, single BLQ which fall between two measurable concentrations will be set to missing.
- For concentration-time profile after each dose, consecutive BLQs which fall between measurable concentrations will be set to zero and measurable concentrations following consecutive BLQs after the T_{max} will be retained.

The PK concentration data will be transferred after database lock. The processing of the other cases of BLQ can be discussed and determined through the PK data review meeting, if necessary.

6.2.2.2 Missing Data

For PK concentration data, missing values will not be included in the pharmacokinetic analysis and descriptive statistics, and only presented as "missing" in the listing.

For those PK parameters which cannot be calculated by PK concentration data, "Not Calculated (NC)" will be displayed in the listing, and be set to missing in the descriptive statistics and statistical model analysis.

6.2.3 Other Data Conventions

- The integer age (years) of a subject at time of informed consent will be derived from the date of birth and the date of informed consent using the following formula:

  $$Age = (infcons - dob + 1)/365.25$$

  where dob = subject's date of birth and infcons=date of informed consent.

- Body Mass Index (BMI) at baseline

  The body mass index (kg/m^2) of a subject at baseline will be derived using the following formula:

  $$BMI = \text{Weight at baseline in kgs} / (\text{Height at screening in meters})^2$$

- Study Day

  The study day will be calculated by referring the first dose date. Study day= date of interested-first dose date+1. In this case, the first dose date is day 1.

- The birth date will be used to calculate age. If the month and day is missing, then 01Jul would be used. 15 would be used if Only day is missing, No dealing with other partial dates.

- 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.

- Changes from baseline will be calculated as " value in post-baseline visit minus baseline value" provided when both baseline and post-baseline visit values exist for a subject; otherwise change from baseline value will be missing for that subject.
- Categorical variables: will be presented using non-missing observations and percentages. Denominators for calculation of percentages will be taken as the number of subjects with non-missing observations in the specified population and treatment group unless otherwise stated. Usually, percentages will be presented to 1 decimal place. No percentage for 0, and no decimal place when the percentage is 100.
- Continuous variables: will be presented using number of subjects with non-missing observations (n), mean, standard deviation (SD), median, minimum and maximum. In general, minimum and maximum will be presented to the same level of accuracy as the raw data; means, medians will be presented to one further decimal place; SDs will be presented to two further decimal places. However, all the decimal places should be no more than four decimal places.
- All statistical testing will be performed with 2-sided test and statistical significance will be claimed if p-value ＜0.1 (except as otherwise specified). P-value from treatment comparison is presented to 3 decimal places, “<.001” if it is less than 0.001, and “>.999” if it is more than 0.999.
- One Year is equal to 365.25 days, and one month is equal to 30.4375 days.
- All data will be summarized by different treatment groups, Placebo, and Total, unless otherwise stated.
- All data will be listed by individual patient and study visit.
- All the data analysis will be performed by SAS v9.4 or above, unless otherwise stated.
- PK Parameter will be calculated by WinNonlin v8.3.1 or above.

6.3 Patient Disposition, Demographics and Baseline Characteristics

6.3.1 Patient Disposition

All patients screened (who signed ICF), screen failed, the reason of screen failure will be summarized. The patients randomized, taking treatment drugs, completion and discontinuation of the study, as well as the reasons of discontinuation will be summarized by treatment groups.

The summary of the numbers and percentage of patients in various analysis sets will be presented based on ITT by treatment groups.

The patients who did not satisfy the inclusion criteria or satisfy the exclusion criteria will be listed for all screened subjects. The reason of discontinuation and the reason not in analysis sets will be listed for the randomized subjects. The details of informed consent, randomization, taking treatment drugs, status of study completion and status of analysis set for a subject also will be listed.

6.3.2 Demographics and Other Baseline Characteristics

Descriptive statistics of demographics and other baseline characteristics will be summarized and listed for all patients in the FAS, and SS by treatment group.

Demographic data included gender, age, height at baseline, weight at baseline, BMI at baseline, race, and ethnic origin, smoking and alcohol habits, etc.

6.3.3 Protocol Deviations

The criteria for major protocol deviations in which data will be excluded from the PPS will be determined prior to database lock and unblinding.

The major protocol deviations will be summarized by treatment groups and PD categories for all patients in the SS. All the major protocol deviations will be listed by the treatment groups in the SS.

6.3.4 Medical and Surgical History

Medical history will be coded according to System Organ Class (SOC) and Preferred Term (PT) using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA) and summarised and listed for all patients in the FAS and SS population by treatment groups. The number and percentage of patients with medical history conditions will be summarised by SOC and PT.

The diagnosis date of Ulcerative Colitis (UC) and duration till screening visit will be listed for all the SS population, and

Duration of UC till screening visit (in years) = (Informed consent date – UC diagnosis date) / 365.25.

If the UC diagnosis date is partially or fully missing, imputation will be used per the following rules.

Table 3 Imputation Rules for UC Diagnosis Date

Situations	Rules
Missing day (Both year and month are not missing)	Impute the day as "01"
Missing month and day (year is not missing)	Impute the month and day as 1st, Jan
Missing year	No imputation

6.3.5 Prior and Concomitant Medication

Prior medication is defined as the medication with ending date prior to date of informed consent.

Concomitant medication is defined as the medication but not the study treatment, which meet either of the two conditions:

1) Starts on or after the date of informed consent;

2) Starts before date of informed consent, and continues after date of informed consent.

If the ending date of medication is fully or partially missing, imputation will be performed per the

rules as follows:

Table 4 Rules for Prior and Concomitant Medication

Ending Date of Medication	Rules	Derivation
Missing day (Both year and month are not missing)	If the year and month of medication end date equals or is later than the year and month of Informed consent date	Concomitant Medication
	If the year and month of medication end date is prior to month of Informed consent date	Prior Medication
Missing month and day (year is not missing)	If the year of medication end date is equal or later than the year of Informed consent date	Concomitant Medication
	If the year of medication end date is prior to the year of Informed consent date	Prior Medication
Missing year (year, month, and day are all missing)	No imputation	Concomitant Medication
No date information	No imputation	Concomitant Medication

Prior and concomitant medication will be coded on ATC based on current version of WHO DD. The number and percentage of subjects with prior or concomitant medication will be summarized according to treatment groups, ATC and PT based on SS. The listing of detail of prior or concomitant medication will be presented.

6.3.6 Treatment Exposure

Based on SS, the number and percentage of subjects treated will be summarized according to treatment groups, and visit.

Based on SS, the actual injection times (times), treatment duration (days), treatment dosage (mg), treatment compliance (%) will be summarized, and the Statistics will include n, Mean, SD, Median, Min, and Max. Besides, the treatment compliance (%) will be also summarized:

- <80%
- 80-120% (both included),
- >120%.

Treatment duration (days) = last dose date – first dose date +1.

Treatment dosage (mg) = actual times of dose * treatment group dosage (300/600/0) mg. For Placebo group, treatment exposure = 0 mg.

Treatment compliance (%) = actual times of dose / planned times of dose (6 times) * 100.

The dosing information will be listed for the SS analysis set.

6.4 Efficacy Analyses

6.4.1 Primary Endpoints

The primary efficacy endpoint is the percentage of subject achieve clinical response per Full Mayo score (defined as 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. Full Mayo scores will be listed based on FAS.

Based on the FAS, the subject number and percentage of clinical responses for each treatment group will listed, and Clopper-Pearson's method will be used to estimate the 90% CI of the clinical response percentage. Normal Approximation method is applied to estimate the absolute treatment difference of clinical response rate, 90% CI and P-value. The Exact method will be used if the number of clinical responses is too small (for example, <=5).

This binary outcome (response status=yes/no) variable will be analysed by a logistic regression model with Week 12 clinical response status as response variable, treatment, the randomisation-stratification factors, and the baseline full Mayo score as covariates. The adjusted treatment difference of Week 12 clinical response rate between treatment groups will be derived, then the standard error of it will be calculated by Delta method, finally the adjusted treatment difference of clinical response rate and its 90% CI will be accurately estimated. The odds ratio, its 90% CI and

P-value will also be calculated. The method above is the primary analysis method for primary endpoint. The histograms of Week 12 clinical response will be graphed, displaying the clinical response rate, Logistic-model adjusted treatment difference of clinical response rate, and its 90% CI and P-value.

Cochran Mantel-Haenszel Chis-square test is considered, from which treatment difference and 90%CI, P-value will be adjusted by randomisation-stratification factors, also the relative risk and its 90% CI of the treatment difference of clinical response rate will be given.

A patient with missing data of primary efficacy endpoint at Week 12 will be assumed to be non-responder.

Sensitive Analyses are performed on PP analysis set, multiple imputation on missing data, excluded subjects significantly impacted by COVID-19, subjects from Chinese Mainland, and Mayo-sub score calculated by programming from Stool Frequency and Rectal Bleeding, etc.

6.4.2 Secondary Endpoints

Based on FAS and PPS, all dichotomised secondary endpoints will be analysed using the same methods that we did for primary endpoint, such as descriptive statistics, logistic regression model, Cochran Mantel-Haenszel method, and histogram graphs, etc. And it will be treated as non-remission or non-healing if there is a missing of a dichotomised secondary endpoint above.

- The percentage of subject achieve clinical remission per Full Mayo score (defined as a full Mayo score ≤2, no individual subscore >1, rectal bleeding subscore = 0) at Week 12.
- The percentage of subject achieve Mucosal healing (defined as Mayo endoscopic subscore = 0 or 1) at Week 12.
- The percentage of subject achieve FDA-defined remission (defined as per modified Mayo score, Stool frequency subscore≤1, Rectal bleeding subscore=0, and Endoscopy subscore =0 or 1) at Week 12.

The line chart of clinical response based on 9-partial Mayo score/ Clinical remission based on 9-partial Mayo score by each visit will be displayed.

Also, Generalized Estimating Equations (GEE) will be applied 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 PPS analysis set.

- The percentage of subject achieve clinical remission per Partial Mayo score (defined as a stool frequency subscore=0, rectal bleeding subscore = 0, and 9-point partial Mayo score ≤1) at Weeks 4, 6, 8, 10, and 12.
- The percentage of subject achieve clinical response per Partial Mayo score (defined as 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.

Based on FAS and PPS, for continuous endpoints of repeated measures, Mixed Model Repeated Measures model (MMRM) will be applied with the change from baseline as response variable, treatment, the randomisation-stratum, visit, and a treatment by visit interaction as factors, respective baseline score as covariate. No imputation will be performed on missing data.

Week 12 full and modified Mayo score change from baseline will be analysed by using an Analysis of Covariance (ANCOVA) model with treatment, baseline score as covariates. No imputation will be performed on missing data. The histograms of Week 12 full, partial and modified Mayo score change from baseline will be graphed, displaying the adjusted least square mean, difference of least square mean between treatment groups, and their 90% CI and P-value. Also the line chart of 9-point partial Mayo score by each visit will be displayed.

- 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.
- Change from Baseline to Weeks 4, 8, and 12 in exploratory biomarkers (erythrocyte sedimentation rate [ESR], C-reactive protein (CRP), IL-6, s-IL6R, IL-6/sIL-6R complex,

neutrophil and platelet count, faecal calprotectin).

6.4.3 Subgroup Analysis

For the FAS and PPS, patients in both the placebo and the treatment groups will be split into subgroups based on the baseline full Mayo score (<8, >=8), duration of disease diagnosis (<7 years, >=7years), the baseline level of IL-6/sIL-6R complexes, baseline calprotectin level, baseline randomisation-stratification factors. Comparison in primary endpoints will be made for different subgroups.

6.5 Safety Analyses

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

6.5.1 Adverse Events

A pre-treatment adverse event will be defined as an adverse event which occurs after the informed consent form had been signed 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 until the Safety Follow-up Visit (for patients completing the 12-week Treatment Period, a Safety Follow-up Visit will be scheduled on Days 105 (Week 15); for patients not completing the 12-week treatment period, a Safety Follow-up Visit will be scheduled 35 days after the last dose of IMP). If an adverse event on Day 1 occurs before administration of IMP, it will be recorded as a pre-treatment adverse event.

When calculating TEAE, the AE start date is compared with the first dose date. If the AE start date is fully or partial missing, imputation of date of TEAE will be performed as follows:

Table 5 TEAE Derivations When AE Start Date is Missing or Partially Missing

AE Start Date	Rules	Derivations

Missing day (Both year and month are not missing)	If the year and month of AE Start date is equal or later than the year and month of the first dose date	TEAE
	If the year and month of AE Start date is prior to month of the first dose date	If the severity increases after treatment, the AE will be considered as TEAE; else the AE will not be considered as TEAE.
Missing month and day (year is not missing)	If the year of AE Start date is equal or later than the year of the first dose date	TEAE
	If the year of AE Start date is prior to the year of the first dose date	If the severity increases after treatment, the AE will be considered as TEAE; else the AE will not be considered as TEAE.
Missing year (including, year, month, and day are missing)	If the AE End date is prior to the first dose date	Not TEAE, Pre-treatment AE
	No imputation	TEAE

Treatment-emergent adverse events will be tabulated by SOC and PT using the current MedDRA. The total number of patients (n) reporting an adverse event, the percentage of patients (%) with an adverse event, and the number of events (e) reported will be presented. If multiple AEs for one patient, the patient is only counted for one time when counting number of subjects (n) and percentage (%). The number of AEs will be counted for multiple times when counting number of AE incidence (e).

Summary tables will be prepared for:

- All adverse events
- All Treatment Emergent Adverse Events (TEAEs) by SOC and PT

- All Serious Adverse Events (SAEs) by SOC and PT
- Drug Related Adverse events (Causal Relationship to IMP=”Related”) by SOC and PT
- Adverse events leading to death by SOC and PT
- Adverse events leading to withdrawal by SOC and PT
- Treatment Emergent Adverse events by SOC and PT by most severe intensity
- Adverse Events of Special Interests (AESIs) by SOC and PT

A separate data listing will be provided for all TEAEs, all SAEs, AESIs and pre-treatment.

Based on the safety data observed in earlier clinical development of TJ301 and the safety concerns observed from other IL-6 blockers, the Sponsor have defined below events as adverse events of special interest in this study: severe infection (including opportunistic infections such as tuberculosis), gastrointestinal perforation/abscesses, infusion related reactions, malignancy, immunogenicity (presence of anti-TJ301 antibody), and moderate or severe of neutrophil count decreased, platelet count decreased, liver enzyme increased and serum lipid increased.

6.5.2 Vital Signs and Body Weight

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. Body weight will be measured at Visits 1.1, 4, 6 and 8.

The vital signs parameters, body weight and their changes from baseline will be summarized by treatment group and visits for each vital signs parameter.

Based on the normal ranges of vitals (Table 6), measurements of vital signs will be categorized as low, normal and high. For a subject with any abnormal measurement, the corresponding item with abnormal measurement for the subject will be listed at all visits.

Table 6 Normal Range of Vital Signs

Item	Normal Range	Unit
Pulse	60~100	bpm
Body Temperature	35.7~37.5	^{o}C

Item	Normal Range	Unit
Respiration	16~20	bpm
Systolic Pressure	90~140	mmHg
Diastolic Pressure	60~90	mmHg

6.5.3 Electrocardiogram

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

The ECG parameters and their changes from baseline will be summarized by treatment group and visits.

The Investigator will evaluate the clinical significance of the ECGs. Overall ECG will be summarized by treatment group at all the visits. A shift from baseline tables (vs. worst value) for overall ECG will also be summarized at baseline and post-baseline visits.

All ECG data will be listed, and all measurements for a patient also will be listed if any clinically significant abnormal evaluation is found.

6.5.4 Clinical Safety Laboratory Parameters

Laboratory parameters (haematology, clinical chemistry, coagulation, and urinalysis) will be measured at site according to the schedule in visits 1.1, 3, 4, 5, 6, 7, 8, 9 (follow-up).

For continuous variables, baseline, post-baseline and their changes from baseline will be summarized according to the descriptive statistics, in each treatment group and visit. For categorical variables, all the values at baseline and post-baseline will be summarized using the frequency and the percentage of patients (%), in each treatment group and visit.

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. This data will be presented in shift from baseline tables (vs. worst value) for each laboratory parameters.

For a subject with any clinically significant abnormal evaluation, the corresponding test's values for the subject will be listed at all visits.

For female subjects, a serum ß-HCG and a serum pregnancy test will be conducted at the Baseline Visit (Visit 1.1) and urine pregnancy tests will be conducted at visit 8 and follow-up visit. The subjects with pregnancy test positive during the trail will be listed.

6.5.5 Physical Examinations

A complete physical examination including general appearance, head, eyes, ears, nose, and throat (HEENT), neck, cardiovascular, thorax/lungs, breasts, abdomen, 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 assessments of physical examinations will be presented in shift from baseline tables (vs. worst value) for each item. All physical examination results will be listed. For any physical examination parameter, subjects with clinically significant abnormal findings will be listed for all visits.

6.5.6 Tuberculosis Related Examinations

Tuberculosis test, including QuantiFERON-TB Gold or T-spot test plus CT or chest X-ray, performed both at Screening period (Visit 1) and Safety follow-up visit (Visit 9). Symptoms of tuberculosis will be examined on visits 2, 3, 4, 5, 6, 7 and 8.

The same analysis will be performed on tuberculosis test as laboratory tests.

6.6 PK Analysis

6.6.1 Concentration of Study Drug

Statistical analysis and list of concentration-time data will be carried out based on PKS.

The concentration data of TJ301 will be summarized and listed according to dose group, planned day and planned blood collection time point. The descriptive statistics include n，n>=LLOQ，

Mean, SD, Median, Min, Max, CV%, GeoMean, CV_b%. When the total number of missing values and BLQ values exceeds 2/3 of the total, only the statistics n, n >= LLOQ, Min and Max are presented. If Min or Max is BLQ, the BLQ will be listed.

According to the dose group, the average blood concentration-time plot (linear and semi-logarithmic) of TJ301 is drawn according to the planned sampling time. The individual blood concentration time curve of TJ301 will graphed according to the actual sampling time (linear and semi-logarithmic).

6.6.2 PK Parameters

Summary and list of TJ301 PK parameters will be carried out based on PKS

According to the actual sampling time, the PK parameters will be calculated using the non-compartment model (NCA) of Phoenix WinNonlin 8.3.1 software.

The PK parameters of single dose include T_{max}, C_{max}, $AUC_{0\text{-}14day}$, $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, CL, V_z, $t_{1/2}$, and $MRT_{inf.}$ The PK parameters of multiple dose include $T_{max,ss}$, $C_{max,ss}$, C_{trough}, AUC_{τ}, $AUC_{0\text{-}t}$, CL, V_{ss}, $t_{1/2}$, $R_{ac,Cmax}$, $R_{ac,AUC}$ and MRT_{inf}.

Statistical analysis of PK parameters of single and multiple administration will be carried out according to the dose group. The statistics are shown in the table below.

	PK parameters	Statistics
Single dose	C_{max}, $AUC_{0\text{-}14day}$, $AUC_{0\text{-}t,}$ $AUC_{0\text{-}inf}$, CL, V_z, λ_z, $t_{1/2}$, and MRT_{inf}	n, Mean, SD, Min, Max, Median, %CV, GeoMean, $\%CV_b$
Multiple dose	$C_{max,ss}$, C_{trough}, AUC_{τ}, $AUC_{0\text{-}t,}$ CL, V_{ss}, $t_{1/2}$, $R_{ac,Cmax}$, $R_{ac,AUC}$ and MRT_{inf}	
Single dose	T_{max}	n, Median, Min, Max
Multiple dose	$T_{max,ss}$	n, Median, Min, Max

6.6.3 Dose Proportionality

Plot boxplot of TJ301 dose-normalized PK parameters and dose (single dose: C_{max}, $AUC_{0\text{-}14\ day}$, $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$; multiple dose $C_{max,\ ss}$, C_{trough}, AUC_{τ}, $AUC_{0\text{-}t}$). Dose-normalising will be carried out relative to 100 mg.

After logarithmic conversion of the dose-normalising PK parameters (dose-normalising will be carried out relative to 100 mg), the dose linearity will be evaluated by ANOVA. Point estimates and 90% confidence intervals of the difference between 600 mg dose group and 300 mg dose group will be calculated with dose group as a fixed effect. The point estimates and 90% confidence intervals of the ratio between 600 mg dose group and 300 mg dose group will be obtained after the inverse logarithmic conversion.

6.6.4 Steady-state Assessment Analysis

Based on PKS, to compare pre-dose concentration (C_{trough}) of the continuous 3rd, 4th, 5th and 6th dosing of TJ301 by the Mixed Model, then evaluating whether the drug concentration has reached steady-state. In this model, the log-transformed C_{trough} will be compared with all other log-transformed C_{trough} at different dosing timepoint, and the corresponding geometric mean ratios and 90% confidence intervals will be listed. The mean C_{trough} – time plot will be drawn according to the dose group (Mean±SD).

6.7 PD Analysis

Exploratory biomarkers (erythrocyte sedimentation rate [ESR], C-reactive protein (CRP), IL-6, s-IL6R, IL-6/sIL-6R complex, neutrophil and platelet count, faecal calprotectin) will be performed at Baseline, weeks 4, 8, and 12.

The baseline, post-baseline and their changes from baseline will be summarized for the patients in the PD population, according to the descriptive statistics, in each treatment group and visit.

6.8 Immunogenicity Analysis

Blood samples for ADA analysis will be collected at the pre-dose of 1st, 2nd, 3rd, and 5th

administrations of study drug (within 1 hour prior to dosing on Days 0, 14, 28 and 56), and on Days 84 and 105.

For any subject, if a positive ADA result was measured at any visits after treatment and during the treatment period, the overall ADA result for this subject will be Positive. ADA will be summarized by descriptive statistics for all the patients in the IS population by each treatment group and visit.

7 References

[1] Guidance of Data Management and Statistical Analysis Plan and Report for Clinical Trials (released by NMPA), 2016.

[2] Guidance of Biostatistics for Clinical Trials (released by NMPA), 2016.

[3] International conference on harmonization (ICH). Structure and Content of Clinical Study Reports.

[4] International conference on harmonization (ICH). Statistical Principles for Clinical Trials.

8 APPENDICES

Appendix 1 – Calculation of Worsening

For a given day from Visit 5 and onward, 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 5, 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, Day45 is between Visit 5 and Visit 6, then the delta in the daily score for rectal bleeding at the Day 45 will be calculated as the change in the daily score for rectal bleeding at Day 45 from the daily score for rectal bleeding at Visit 5.
- Assume that for a patient, Day 60 is between Visit 6 and Visit 7, then the delta in the daily score for rectal bleeding at the Day 60 will be calculated as the change in the daily score for rectal bleeding at Day 60 from the daily score for rectal bleeding at Visit 6.

Worsening will be defined as an increase from last visit in Mayo rectal bleeding subscore ≥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 – Clinical Safety Laboratory Parameters

The following laboratory parameters will be measured.

Laboratory parameters: urinalysis, 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. (If any of the following laboratory parameters can not be measured at local site(s) in Mainland China, samples will be sent to the central lab for measurement, including HIV (HIV-1/2 Antibodies), HBV(Hepatitis B Surface Antigen (HBsAg) and Hepatitis B Core Antibody (HBcAb), any patient who is $HBsAg^-$ and $HBcAb^+$ at screening will have quantitative serum HBV DNA test), HCV (Hepatitis C Antibody), TB (QuantiFERON-TB Gold), EBV[Viral capsid antigen (VCA)-IgM test and VCA-IgG test], *Clostridium difficile* (*Clostridium difficile* toxin assay) and Urine screening for drugs of abuse.)

IL-6, sIL-6R, IL-6/sIL-6R complex, faecal calprotectin test and the laboratory parameters that can not be measured at local site(s) in Mainland China will be analysed in central lab; Anti-TJ301 antibodies, neutralizing antibodies, and Pharmacokinetics TJ 301 will be analysed in PK 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)
- Aspartate transaminase (AST)
- Gamma glutamyl transferase (GGT)
- Alkaline phosphatase (AP)
- Bilirubin – total
- Bilirubin – direct (only if total bilirubin is outside the normal range)
- C-Reactive protein (CRP)
- Potassium
- Sodium
- Chloride
- Calcium
- Glucose

- HbA1c (only at baseline visit)
- Insulin (only at baseline visit)
- Albumin
- Creatinine
- Total cholesterol, LDL cholesterol, HDL cholesterol
- Triglycerides
- Protein - total

Coagulation Tests:

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

Urinalysis:

- Glucose
- Bilirubin
- Ketone
- Specific Gravity
- Blood

- pH
- Protein
- Urobilinogen
- Nitrite
- Leucocytes

Urinalysis (microscopic, if applicable):

- Sediment, including epithelial cells, casts, crystal and bacteria.

Pregnancy Tests:

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

Exploratory Biomarkers:

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

Pharmacokinetics:

- TJ301 in serum

Other Laboratory Assessments:

- Urine screening for drugs of abuse (e.g. cocaine, barbiturates, amphetamines, opiates, benzodiazepine, and cannabinoids)
- HIV (HIV-1/2 Antibodies)
- HBV (Hepatitis B Surface Antigen (HBsAg) and Hepatitis B Core Antibody (HBcAb), any patient who is HBsAg- and HBcAb+ at screening will have quantitative serum HBV DNA test)
- HCV (Hepatitis C Antibody)
- TB (QuantiFERON-TB Gold; or T-spot test plus CT or 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, neutralizing antibodies

Appendix 3 – 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~-1	0	*2*	*6*	*10*	14	28	42	56	70	72	76	80	84	90	105
Allowed window for visit (days)						*±1*	*±1*	±1	±2	±2	±2	±2			±1	-2	±2	±2
Visits	**Visit 0 Stabilization**	**Visit 1 Screening**	**Visit 1.1 Baseline**	**Visit 2**	***V 2.1***	***V 2.2***	***V2.3***	**V 3**	**V 4**	**V 5**	**V 6**	**V 7**	***V 7.1***	***V 7.2***	***V7.3***	**V 8 (EoT Visit)**	***V 8.1***	**V 9 (Safety Follow-up Visit)**
Informed consent	•	•[a]																
Inclusion/exclusion criteria	•	•	•[o]															
Stable conventional treatment	•	•	•	•				•	•	•	•	•				•		•
HIV, HBV, HCV, EBV, CMV (suspicion) test		•																
TB related examination[b]		•		•				•	•	•	•	•				•		•
Randomisation			•[o]															
Demographics	•	•																
Alcohol and tobacco habits		•																
Medical and surgical history		•																
UC medical history, confirmation of UC diagnosis, and previous UC therapy	•	•																
Urine screening for drug abuse		•																
Endoscopy[c] including biopsy sampling		•[d]														•[p]		
Diary dispensing		•	•					•	•	•	•	•						
Diary review[e]			•					•	•	•	•	•				•		
Efficacy evaluation (full Mayo score)			•													•		

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~-1	0	*2*	*6*	*10*	14	28	42	56	70	72	76	80	84	90	105
Allowed window for visit (days)						*±1*	*±1*	±1	±2	±2	±2	±2			±1	-2	±2	±2
Visits	**Visit 0 Stabilization**	**Visit 1 Screening**	**Visit 1.1 Baseline**	**Visit 2**	***V 2.1***	***V 2.2***	***V2.3***	**V 3**	**V 4**	**V 5**	**V 6**	**V 7**	***V 7.1***	***V 7.2***	***V7.3***	**V 8 (EoT Visit)**	***V 8.1***	**V 9 (Safety Follow-up Visit)**
Efficacy evaluation (9-point partial Mayo score)			•					•	•	•	•	•				•		
Blood sampling for PK assessments[f]				•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Faeces sampling for calprotectin[g]				•					•		•					•		
Blood sampling for biomarkers[h]				•					•		•					•		
Blood sampling for anti-TJ301 antibodies[i]				•				•	•		•					•		•
Clinical laboratory tests[j]			•					•	•	•	•	•				•		•
Pregnancy test[k]			•													•		•
Stool sample for *Clostridium difficile* assay		•																
Physical examination[l]		•	•						•		•					•		•
Vital signs[m]		•	•					•	•	•	•	•				•		•
12-lead ECG			•					•	•	•	•	•				•		•
Concomitant medications documented		•	•	•				•	•	•	•	•				•		•
Adverse events documented	←----------																	----------→
IMP administration[n]				•				•	•	•	•	•						

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

b. Tuberculosis test, including QuantiFERON-TB Gold or T-spot test plus CT or chest X-ray, performed both at Screening period (Visit 1) and Safety follow-up visit (Visit 9). Patients should be closely monitored for the development of symptoms of Tuberculosis during the treatment with TJ301 and performed further Tuberculosis tests.If necessary, TB can be tested. It is recommended to use the same test method for the same subject at each visit. For subjects who have been tested positive for TB in the 9th visit, retesting is recommended..

c. During the 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 -1 to -28 days (after signing the ICF) is acceptable. The biopsy sample is not necessary if UC is already confirmed.

d. The screening endoscopy should be performed at Day -28 to Day -6.

e. The scores for stool frequency and rectal bleeding will be calculated as an average based on scores collected from the Patient daily Diary, for 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.

f. 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 h (Day 10) 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.

g. Stool samples for faecal calprotectin tests will be available within 1 day prior to dosing.

h. Biomarkers erythrocyte sedimentation rate [ESR], C-reactive protein (CRP), neutrophil and platelet count tests will be analysed in local sites. The clinical laboratory inspection has been done at baseline. If all the biomarkers tested by the research center have been included, there is no need to repeat the test in V2. V4, V6, V8 biomarker detection items, if included in the clinical laboratory inspection, there is no need to repeat the test before administration IL-6, sIL-6R, IL-6/sIL-6R complex, and faecal calprotectin tests will be analysed in central lab. IL-6, sIL-6R, IL-6/sIL-6R complex blood sample collection time: blood samples were collected before 1st , 3rd and 5th administrations (ie within 1 hour before administrate on 0, 28, and 56 days) and also on day 84..

i. Blood samples for ADA analysis will be collected as follows: at the 1st , 2nd , 3rd and 5th administrations: blood samples will be collected pre-dose (within 1 hour prior to dosing on Days 0, 14, 28 and 56), and on Days 84 and 105.

j. Includes haematology, clinical chemistry, coagulation tests, and urinalysis assessments. Ensure the subject has fasted starting before or at midnight on the evening prior to this visit (including Visit 1.1, 3, 4, 5, 6, 7, 8 and 9).

k. Serum pregnancy test at Visit 1.1 and urine pregnancy test at Visits 8 and 9.

l. 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.

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

n. IMP administration should be the last procedure of each IMP administration visit. The infusion time will be 2 hours ±10 minutes.

o. On Day -1, PK subgroup subjects will be admitted to unit. Inclusion/exclusion criteria will be assessed, followed by randomization. IMP thawing will take place over night. Subjects will be discharged from the unit after the last PK sampling on Day 0 and other assessments.

p. The same endoscopy method (colonoscopy or sigmoidoscopy) as at Visit 1 (screening) is preferably used at Visit 8 (EoT), centrally read.