Protocolo & Enmiendas

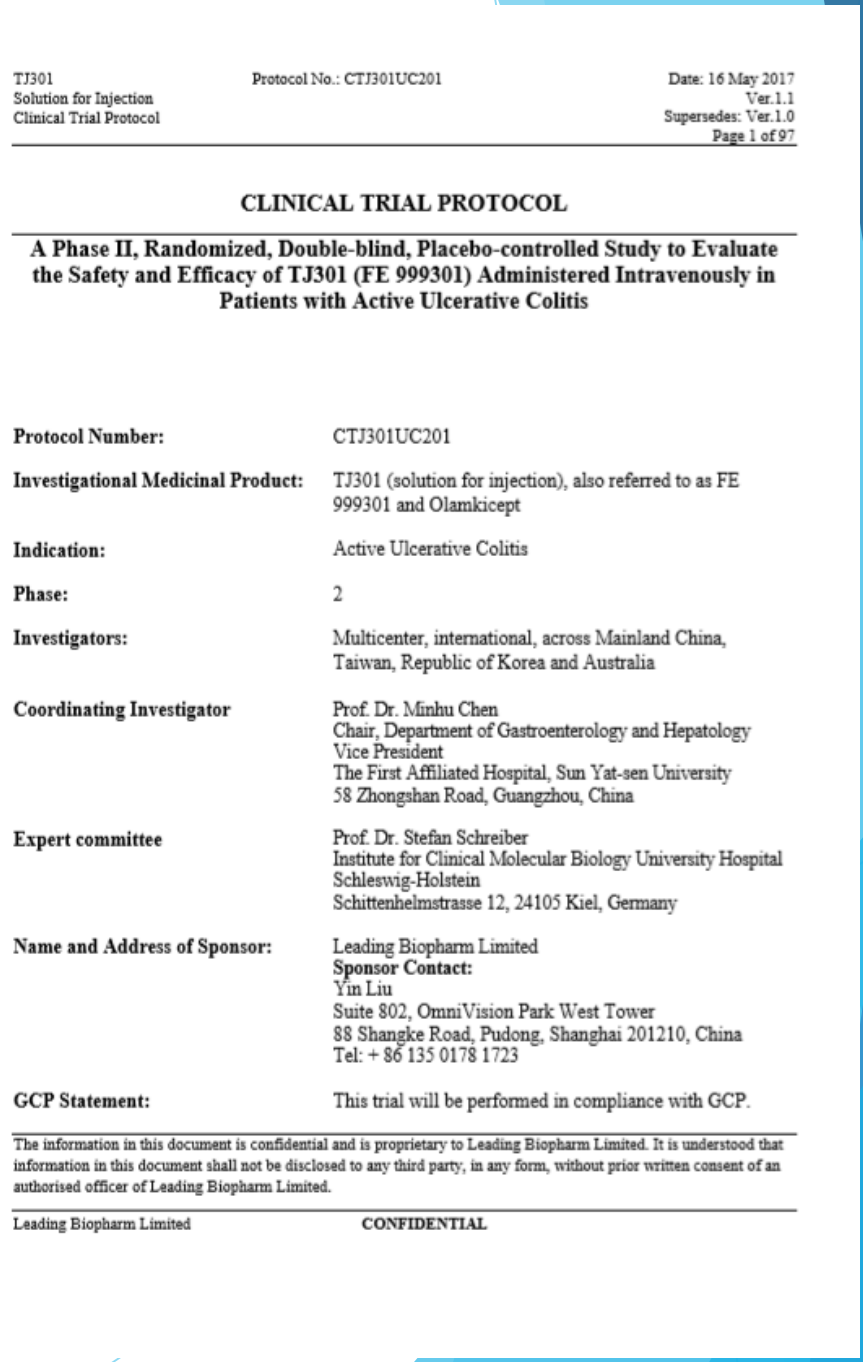
Guía Armonizada Tripartita – Guía para Buena Práctica Clínica

E6(R2)

Protocolo

1. Información General

- Título del protocolo, número de identificación del protocolo y fecha. Cualquier enmienda(s) deberá(n) llevar también el(los) número(s) de enmienda y la(s) fecha(s).
- Nombre y dirección del patrocinador y monitor (si fuera otro diferente al patrocinador).
- Nombre y título de la(s) persona(s) autorizada(s) por el patrocinador para firmar el protocolo y enmienda(s) del protocolo.
- Nombre y título, dirección y número(s) telefónico(s) del experto médico del patrocinador (o dentista cuando sea el caso) para el estudio.



TJ301
Solution for Injection
Clinical Trial Protocol

Protocol No.: CTJ301UC201

Date: 16 May 2017
Ver.1.1
Supersedes: Ver.1.0
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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.

Protocolo

1. Información General

- Nombre y título del (de los) investigador(es) responsable(s) de conducir el estudio y la dirección y número(s) telefónico(s) del (de los) sitio(s) donde se realizará estudio.

- Nombre y título, dirección y número(s) telefónico(s) de los médicos calificados (o dentistas, si aplicara) responsables de todas las decisiones médicas (o dentales) relacionadas con el lugar donde se realiza el estudio (si fuera otra personal diferente al investigador).

- Nombre(s) y dirección(s) de (de los) laboratorio(s) clínico(s) y otro(s) departamento(s) médico(s) y/o técnico(s) y/o instituciones involucradas en el estudio.

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2. Antecedentes

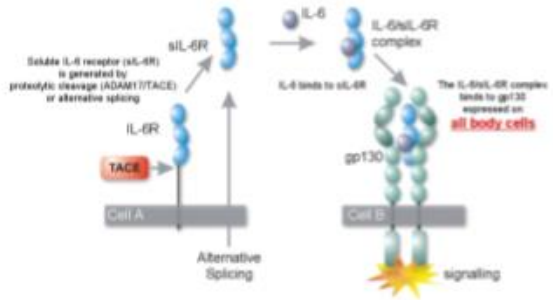
- Nombre y descripción de (de los) producto(s) en investigación.
- Resumen de los hallazgos de los estudio no clínicos que potencialmente tienen significancia clínica y de estudios clínicos que son relevantes para el estudio.
- Resumen de los riesgos y beneficios conocidos y potenciales, si los hubiere, para los seres humanos.
- Descripción y justificación de la vía de administración, dosis, esquema de dosis y período(s) de tratamiento.
- Una declaración de que el estudio será conducido en conformidad con el protocolo, la BPC y (los) requerimiento(s) regulatorio(s) aplicable(s).
- Descripción de la población que se va a estudiar.

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

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3. Objetivos y Propósitos del Estudio

- Objetivos
- Propósitos

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).

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4. Diseño del Estudio

La integridad científica del estudio y la credibilidad de los datos del estudio dependen substancialmente del diseño del mismo.

Incluye:

- Una exposición de los puntos de evaluación primaria y secundaria, si los hubiere, que se medirán durante el estudio.
- Una descripción del tipo diseño de estudio que se va a conducir y un diagrama esquemático del diseño, procedimientos y etapas de estudio.
- Una descripción de las medidas tomadas para minimizar/evitar sesgo, incluyendo:
  a. Asignación Aleatoria.
  b. Cegamiento.

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).

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4. Diseño del Estudio

- Una descripción de (de los) tratamiento(s) del estudio y la(s) dosis y esquema(s) de dosis del (de los) producto(s) en investigación.
- También incluir una descripción de la forma de dosis, empaque y etiquetado de (de los) producto(s) en investigación.
- La duración esperada de la participación de los sujetos y una descripción de la secuencia y duración de todos los períodos del estudio, incluyendo el seguimiento, si lo hubiera.
- Una descripción de las "reglas para suspender" o de los "criterios para descontinuar" sujetos individualmente, parte del estudio y el estudio completo.
- Procedimientos contables para el (los) producto(s) en investigación, incluyendo placebo(s) y comparador(es), si lo(s) hubiera.
- Mantenimiento de los códigos de la asignación aleatoria al tratamiento del estudio y los procedimientos para abrir los códigos.
- La identificación de cualquier dato que se registrará directamente en los FRCs (Formatos de Reporte de Caso), sin ningún registro de datos escrito o electrónico previo) y que se considerará como data fuente.

AVANZAR

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5. Selección y Retiro de los Sujetos

a) Criterios de inclusión de los sujetos.

b) Criterios de exclusión de los sujetos.

c) Criterios y procedimientos de retiro de los sujetos (por ejemplo), terminación del tratamiento del producto en investigación/tratamiento del estudio) especificando:

- Cuando y como retirar a los sujetos del estudio/tratamiento con el producto en investigación.
- El tipo de datos y el momento en que éstos se recolectarán de los sujetos retirados.
- Si los sujetos se reemplazarán y como se reemplazarán.
- El seguimiento para los sujetos retirados del tratamiento con el producto en investigación/tratamiento del estudio.

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6. Tratamiento de los Sujetos

- El(los) tratamiento(s) que se administrará(n), incluyendo el nombre(s) de todos los productos, la dosis, el esquema de dosis, la(s) vía(s), forma(s) de administración y el (los) período(s) de tratamiento, incluyendo el(los) períodos(s) de seguimiento de los sujetos por cada tratamiento con el producto en investigación/grupo de tratamiento del estudio/brazo del estudio.
- Medicamento(s)/tratamiento(s) permitido(s) incluyendo medicamento alternativo) y no permitido(s) antes y/o durante el estudio.
- Procedimientos para monitorizar el cumplimiento del sujeto.

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

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7. Procedimientos para monitorizar el cumplimiento del sujeto.

- Especificación de los parámetros de eficacia.
- Métodos y tiempos para evaluar, registrar y analizar los parámetros de eficacia.

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).

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8. Evaluación de Seguridad

- Especificación de los parámetros de seguridad.
- Métodos y tiempos para evaluar, registrar y analizar los parámetros de seguridad.
- Procedimientos para elaborar informes y para registrar y reportar eventos adversos y enfermedades intercurrentes.
- El tipo y duración del seguimiento de los sujetos después de la ocurrencia de eventos adversos.

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

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9. Estadística

- Descripción de los métodos estadísticos que se emplearán, incluyendo el momento en que se realizará algún análisis intermedio planeado.
- El número de sujetos que se planea incluir. En estudios multicéntricos, se deberá especificar el número proyectado de sujetos a incluir para cada sitio en donde se realizará el estudio. Razón por la cual se eligió el tamaño de muestra, incluyendo explicaciones sobre (o cálculos de) la potencia del estudio y justificación clínica.
- El nivel de significancia que se va a usar.
- Criterios para la terminación del estudio.

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.

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9. Estadística

- Procedimiento para explicar datos faltantes, sin usar y falsos.

- Procedimientos para reportar cualquier desviación o desviaciones del plan estadístico original deberán describirse y justificarse en el protocolo y/o en el informe final, según sea el caso.

- La selección de los sujetos que se incluirán en el análisis (por ejemplo todos los sujetos asignados de manera aleatoria, todos los sujetos a los que se les administró alguna dosis, todos los sujetos, sujetos evaluables).

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10. Acceso Directo a los Datos/Documentos fuente

El patrocinador deberá asegurarse de que esté especificado en el protocolo o en cualquier otro acuerdo escrito que el (los) investigador(es)/institución(es) permitirá(n) monitoreos, auditorías, revisión del CRI/EC e inspecciones regulatorias referentes al estudio, permitiendo el acceso directo a los datos/documentos fuente.

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

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11. Control de Calidad y Aseguramiento de la Calidad.

12. Ética.

Descripción de las consideraciones éticas relacionada con el estudio.

13. Manejo de Datos y Custodia de Registros.

14. Financiamiento y Seguro.

Financiamiento y seguro si es que no se ha especificado en un acuerdo por separado.

15. Política de Publicación.

Política de publicación si no se ha especificado en un acuerdo por separado.