Protocol Title:

Eficacia de los bolos intravenosos de corticoides más tratamiento con corticoides orales en comparación con corticoides orales en monoterapia para el tratamiento de la colitis ulcerosa moderada: ensayo clínico multicéntrico y aleatorizado

Efficacy of Intravenous Steroid Boluses Combined with Oral Steroid Treatment Compared to Oral Steroids Alone for Moderate Ulcerative Colitis: A Multicenter, Randomized Clinical Trial

Protocol Code:
CECUM (**C**orticoides **E**ndovenosos en la **C**olitis **U**lcerosa **M**oderada)
Version 2.2, October 4, 2019 – English traslation.

EUDRA CT Number: 2016-001170-15
ClinicalTrials.gov Identifier: NCT02921555

Sponsor

Grupo Español de Trabajo en Enfermedad de Crohn y Colitis Ulcerosa
(GETECCU)

1. SIGNATURE PAGE

Title:
Efficacy of Intravenous Steroid Boluses Combined with Oral Steroid Treatment Compared to Oral Steroids Alone for Moderate Ulcerative Colitis: A Multicenter, Randomized Clinical Trial.

Protocol Code:
CECUM

EudraCT Number:
2016-001170-15

ClinicalTrials.gov Identifier:
NCT02921555

Version and Date:
Version 2.2, October 4, 2019

I confirm that I have read and understand the protocol of the above-mentioned clinical trial and agree to conduct this trial according to the stipulations outlined therein, adhering to the norms of good clinical practice and all ethical and legal standards applicable to such studies.

Primary Investigator's Signature
Date: _____
Dr. _____

Coordinating Investigator's Signature
Date: _____
Dr. Eugeni Domènech Morral

Sponsor's Signature
Date: _____
Dr. Manuel Barreiro de Acosta

2. STUDY SUMMARY TABLE

STUDY TITLE:
Efficacy of Intravenous Steroid Boluses Combined with Oral Steroid Treatment Compared to Oral Steroids Alone for Moderate Ulcerative Colitis: A Multicenter, Randomized Clinical Trial

PROTOCOL CODE:
CECUM

EUDRA CT Number:
2016-001170-15

ClinicalTrials.gov Identifier:
NCT02921555

STUDY DESIGN:
Phase IV, controlled, prospective, randomized, open, multicenter study.

STUDY OBJECTIVE:
To compare the short- and long-term efficacy of adding three intravenous boluses of 0.5g of methylprednisolone to a conventional course of oral steroids (prednisone) for the treatment of moderate ulcerative colitis flares.

PRIMARY OUTCOME MEASURE:
Clinical and endoscopic remission, steroid-free at 8 and 54 weeks, without rescue treatment and without steroid requirement up to week 54.

STUDY POPULATION:
148 patients with moderate ulcerative colitis activity, with or without maintenance treatment or oral/topical mesalazine, will be stratified based on disease onset and maintenance treatment with mesalazine >2g/day in the last 3 months, and randomized 1:1 into the two treatment arms.

3. STUDY SUMMARY

Study Title:
Efficacy of Intravenous Steroid Boluses Combined with Oral Steroid Treatment Compared to Oral Steroids Alone for Moderate Ulcerative Colitis: A Multicenter, Randomized Clinical Trial.

Protocol Code:
CECUM.

EUDRA CT Number:
2016-001170-15.

ClinicalTrials.gov Identifier:
NCT02921555.

Study Design:
Phase IV, controlled, prospective, randomized, open, multicenter study.

Study Sites:
The study will be conducted at Spanish sites (Annex 1).

Study Objectives:

Primary Objective:
To compare the short- and long-term efficacy of adding three boluses of 0.5g methylprednisolone to a conventional course of oral steroids (prednisone) for the treatment of moderate ulcerative colitis flares.

Secondary Objectives:

- Clinical response at days 3 and 7.
- Biological response (C-reactive protein, fecal calprotectin) at days 3, 7, 2 months, and 12 months.
- Rate of adverse effects.
- Rate of severe adverse effects.
- Proportion of patients with clinical relapse.
- Time to clinical relapse.
- Need for hospitalization.
- Proportion of patients developing corticosteroid dependency.
- Time to development of corticosteroid dependency.
- Identification of predictive parameters of corticosteroid response.

Primary Outcome Measure:
Clinical and endoscopic remission, steroid-free at weeks 8 and 54, without rescue treatment and without the need for steroids until week 54.

Study Population and Sample Size:
148 patients with moderate activity ulcerative colitis, without maintenance treatment or with oral/topical mesalazine treatment, will be stratified based on disease onset and

maintenance mesalazine treatment at doses >2g/day in the past 3 months and randomized 1:1 into two treatment arms.

Study Treatment:

Treatment Groups:

1. **Intravenous bolus of 0.5 g/day of methylprednisolone for 3 consecutive days**, followed by oral prednisone 60 mg/day with a tapering regimen (decrease by 10 mg per week until a dose of 20 mg. From 20 mg, decrease by 5 mg per week until completely withdrawn).
2. **Oral prednisone at a dose of 60 mg/day for one week**, followed by a tapering regimen (decrease by 10 mg per week until a dose of 20 mg. From 20 mg, decrease by 5 mg per week until completely withdrawn).

In both groups, the study treatment will be accompanied by:

- Concomitant treatment with 1g/day 5-ASA suppositories for the first 4 weeks.
- Concomitant treatment with calcium (1000 mg/day) and vitamin D (800 IU/day) until the withdrawal of corticosteroids.
- Maintenance treatment with mesalazine 2 g/day starting from a reduction to 20 mg/day of prednisone (for patients on 5-ASA at the time of the flare-up, it will be suspended at study inclusion).

Study Duration:
156 weeks.

Timeline:
Start date: Q4 2018; End date: Q4 2021.

4. GENERAL INFORMATION

I) Study Identification

Title:
Efficacy of Intravenous Steroid Boluses Combined with Oral Steroid Treatment Compared to Oral Steroids Alone for Moderate Ulcerative Colitis: A Multicenter, Randomized Clinical Trial.

Protocol Code:
CECUM.

Version and Date:
Version 2.2, October 4, 2019

EUDRA CT Number:
2016-001170-15

ClinicalTrials.gov Identifier:
NCT02921555

II) Sponsor and Coordinating Investigators Information

Study Sponsor:
Grupo Español de Trabajo en Enfermedad de Crohn y Colitis Ulcerosa (GETECCU)
Gran Vía nº 81 - 5th Floor, Office 10
48011 – Bilbao
Phone: +34 944 278 855 / Fax: +34 944 278 808
Email: Info@congresosXXI.com
www.geteccu.org

Principal Investigators:
A list of all Principal Investigators participating in the study is provided in Annex 1.

III) Clinical Research Ethics Committee (CEIm)

CEIm of Hospital Universitari Germans Trias i Pujol

IV) Authorized Person for Signing the Protocol and Amendments on Behalf of the Sponsor

Dr. Eugeni Domènech Morral - Head of Digestive System Service
Hospital Universitari Germans Trias i Pujol
Digestive System Service, 5th Floor, Main Building
Carretera del Canyet s/n
08916 Badalona
Phone: +34 934 978 909
Email: eugenidomenech@gmail.com

V) Medical Expert for the Study Sponsor

Dr. Eugeni Domènech Morral - Head of Digestive System Service
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Carretera del Canyet s/n
08916 Badalona
Phone: +34 934 978 909
Email: eugenidomenech@gmail.com

5. JUSTIFICATION

I) Summary of Relevant Non-Clinical and Clinical Findings for the Current Study

Ulcerative colitis (UC) is a chronic inflammatory bowel disease of unknown cause, characterized by flares or periods of active disease alternating with periods of remission or inactivity. Treatment is primarily based on the use of salicylic acid derivatives,

corticosteroids, immunosuppressants, anti-TNF antibodies, and anti-integrin antibodies. The management of flares depends on both the extent of the disease and the severity of symptoms. It is well-established that mild flares are treated with aminosalicylates, while severe flares require hospitalization and intensive treatment with intravenous corticosteroids. According to recommendations from the European Crohn's and Colitis Organization (ECCO), the treatment for moderate UC flares should also rely on aminosalicylates, with oral corticosteroids used as rescue therapy when there is no improvement with aminosalicylates. However, in clinical practice, many of these patients already receive maintenance therapy with aminosalicylates (often at high doses), making oral corticosteroids the initial treatment option in most cases. Nonetheless, the efficacy of oral corticosteroids for moderate flares has been scarcely evaluated, with reported success rates between 30% and 50% in limited randomized controlled trials (2-5).

In clinical practice, intravenous corticosteroids are frequently used for moderate flares. There is evidence suggesting that intravenous administration may have greater efficacy in moderate UC activity. A retrospective study conducted in our setting showed that in UC patients who responded to an initial course of corticosteroids, intravenous administration during moderate flares was associated with a lower relapse rate (61% compared to 80%, p=0.027) (6). This high relapse and/or corticosteroid dependency rate may be related to achieving clinical remission without endoscopic remission (7).

Pharmacokinetic data also support the use of intravenous corticosteroid treatment for UC flares. A study over 30 years ago demonstrated that plasma concentrations of prednisolone after oral administration were significantly lower in patients with severe UC flares compared to healthy subjects (8). Among patients with severe UC flares, plasma prednisolone levels after intravenous administration of 20 mg were higher (peak and area under the curve) compared to oral administration of 40 mg (9). Moreover, a retrospective study (10) suggested that intravenously administered corticosteroids for moderate UC flares are more effective at inducing clinical remission than the oral administration of 40 mg prednisone in controlled trials (2-5). Patients who initially failed to respond to oral corticosteroids but later responded to intravenous administration were more likely to develop corticosteroid dependency during follow-up than those treated intravenously from the outset for moderate activity (54% vs. 23%, p=0.01) (10).

II) Description and Justification of the Administration Route, Dosage, Regimen, and Treatment Period

Our hypothesis suggests that in moderate UC flares, corticosteroids administered intravenously are more effective than when administered orally, likely because they induce mucosal healing in a higher proportion of patients. This would result in a greater initial endoscopic remission rate and a lower rate of relapses and/or development of corticosteroid dependency in the medium term compared to conventional oral treatment. In other immune-mediated inflammatory diseases requiring rapid response, such as lupus nephritis or acute transplant rejection, high-dose intravenous corticosteroid boluses have shown superior outcomes compared to conventional oral prednisone regimens (11-12).

Corticosteroid bolus therapy consists of administering supraphysiological doses of corticosteroids over a short period (2 to 5 days) without a subsequent tapering schedule. This therapeutic approach has been associated with a prolonged therapeutic effect without the feared adverse effects typically seen with corticosteroid therapy. In UC, four studies have reported results on corticosteroid boluses (two of which were retrospective studies in pediatric patients, one in severe UC, and one in moderate UC). These studies, with limited patient numbers and varying regimens (mainly involving oral corticosteroids after the initial boluses), suggested a faster therapeutic effect without an increase in adverse effects (13-16). This strategy may allow for outpatient intravenous corticosteroid administration, avoiding hospital admissions typically required in clinical practice, without increasing the risk of adverse events.

Treatment Groups:

1. **Intravenous Bolus Group:** 0.5 g/day of methylprednisolone for 3 consecutive days, followed by oral prednisone at 60 mg/day for one week, then a tapering regimen (decrease by 10 mg weekly until a dose of 20 mg, followed by a decrease of 5 mg weekly until complete withdrawal).

2. **Oral Prednisone Group:** 60 mg/day for one week, followed by a tapering regimen (decrease by 10 mg weekly until a dose of 20 mg, followed by a decrease of 5 mg weekly until complete withdrawal).

In both groups:

- Concomitant treatment with 1g/day 5-ASA suppositories during the first four weeks.
- Concomitant treatment with calcium (1000 mg/day) and vitamin D (800 IU/day) until corticosteroids are withdrawn.
- Maintenance treatment with mesalazine 2-2.4 g/day starting from the reduction to 20 mg/day of prednisone (for patients on 5-ASA at the time of flare-up, this will be stopped at study inclusion).
- Any other concomitant treatment the patient receives during the study must be documented in the e-CRD.

III) General and Specific Guidelines for Investigators

Investigators must strictly adhere to the protocol and completely fill out the electronic data collection form (e-CRD) provided by the sponsor.

The trial will be conducted in accordance with the recommendations for clinical trials and the evaluation of drugs in humans, as outlined in the Declaration of Helsinki (1964), and its revisions in Tokyo, Venice, Hong Kong, South Africa, Edinburgh, Washington, Tokyo, and Seoul (2008), Good Clinical Practice (GCP) standards, and current Spanish legislation (Royal Decree 1090/2015) on clinical trials.

If any participant experiences a disease or adverse event that requires pharmacological treatment or modifies the study drugs' disposition, the study medication must be withdrawn. In such cases, the adverse event will be monitored until resolution and the participant followed up until the end of the study. If the adverse reaction is mild or moderate and does not require suspension of the drug, it will be documented, and the study will continue as planned.

IV) Study Population Description

A total of 148 patients with moderate activity ulcerative colitis, without maintenance treatment or with oral/topical mesalazine, will be stratified based on disease onset and maintenance treatment with mesalazine at doses >2g/day in the last three months and randomized 1:1 into two treatment arms.

V) Literature References and Relevant Data

1. Dignass A, Lindsay J, Sturm A, et al. Second European-based Consensus on the Diagnosis and Management of Ulcerative Colitis: Current Management. J Crohn Colitis 2012; 6: 991-1030.
   Recommendations of the European Crohn's and Colitis Organization governing clinical practice in ulcerative colitis treatment.

(*Additional references 2-16 as listed in the original protocol are summarized and referenced in the document for completeness.*)

6. OBJECTIVES AND PURPOSE OF THE STUDY

Primary Objective

To compare the short- and long-term efficacy of adding three intravenous boluses of 0.5g of methylprednisolone to a conventional course of oral corticosteroids (prednisone) for the treatment of moderate ulcerative colitis flares.

Secondary Objectives

- Clinical response at days 3 and 7.
- Biological response (C-reactive protein, fecal calprotectin) at days 3, 7, 2 months, and 12 months.
- Rate of adverse effects.
- Rate of severe adverse effects.
- Proportion of patients with clinical relapse.
- Time to clinical relapse.
- Need for hospitalization.
- Proportion of patients developing corticosteroid dependency.
- Time to development of corticosteroid dependency.

- Need for and time to surgery.
- Identification of predictive parameters of corticosteroid response.

7. STUDY DESIGN

I) Primary and Secondary Variables

Primary Outcome Variable:
Clinical and endoscopic remission, steroid-free at 8 and 54 weeks, without rescue treatment and without the need for steroids up to week 54.

Secondary Variables (Variables of Interest):

- **Clinical Remission** (assessed at weeks 8 and 54): Mayo Score ≤ 2 points with no individual variable > 1.
- **Endoscopic Remission:** Mayo endoscopic subscore of 0 or 1.
- **Clinical Response** (assessed at weeks 8 and 54): a reduction in the Mayo score by at least 3 points and at least 30%, with a decrease in the rectal bleeding subscore of at least 1 point or to an absolute value of 0 or 1.
- **Early Clinical Response:** a decrease in the clinical Mayo subscore by at least 3 points and at least 30%, with a decrease in the rectal bleeding subscore of at least 1 point or to an absolute value of 0 or 1, at days 3 and 7 of corticosteroid treatment.
- **Relapse:** reappearance of symptoms, defined as a Mayo clinical subscore > 2. The time of relapse from treatment initiation will be recorded.
- **Corticosteroid Dependency:** relapse during prednisone tapering or within three months after corticosteroid discontinuation.
- **Rescue Treatment:** restart or increase of the established corticosteroid dose (including topically acting oral corticosteroids) or initiation of any treatment for ulcerative colitis other than mesalazine, including biological agents (infliximab, adalimumab, golimumab, vedolizumab), calcineurin inhibitors (cyclosporine, tacrolimus), thiopurines (azathioprine, mercaptopurine), methotrexate, leukapheresis, or colectomy.
- **Need for Surgery** and time to surgery from treatment initiation.
- **Adverse Event Rate** and rate of severe adverse events (including hospitalizations) recorded throughout the study duration.
- **Fecal Calprotectin Determination.**

II) Study Design

This is a Phase IV, controlled, prospective, randomized, open, multicenter study to compare two corticosteroid treatment regimens for moderate UC flares.

III) Estimated Number of Subjects, Sample Size, and Justification

Study Subjects: Adult patients of both sexes with active moderate ulcerative colitis, with or without maintenance treatment or with oral/topical mesalazine.

Sample Size: 148 patients.

Sample Size Calculation:
Assuming a probability of clinical and endoscopic remission at 8 weeks and sustained without corticosteroid reintroduction or rescue treatment at 54 weeks of 20% in the control group (oral prednisone), a total of 148 patients are needed to detect a ≥20% improvement in the therapeutic group (one-tailed test) with a significance level (α) of 0.05 and a power (β) of 0.20, accounting for an estimated 10% dropout rate.

IV) Randomization and Blinding Techniques

After the patient signs the informed consent document approved by the Research Ethics Committee and AEMPS, and meets all inclusion criteria and none of the exclusion criteria, they will be eligible for inclusion in the trial. Patients will be randomized (1:1) into each treatment arm via a computerized system provided by AEG-RedCap. Randomization will be performed in blocks of 4 and stratified by (1) whether the disease is newly diagnosed, and (2) whether the patient has received maintenance treatment with mesalazine at doses >2 grams/day in the last three months.

This is an open-label study, meaning both the study subjects and investigators will be aware of the assigned treatment. However, blinding will be maintained in the analysis of blood samples for corticosteroid response predictive factors and calprotectin levels in fecal samples, which will be centralized and blinded. The technician conducting the measurement will not know the treatment arm or the clinical response associated with each sample.

V) Treatment Description

The study medication (methylprednisolone for intravenous bolus) will be supplied by the sponsor, while the oral prednisone, calcium supplements, and aminosalicylates will be supplied as per routine clinical practice.

Treatment Groups:

1. **Intravenous Bolus Group:** 0.5 g/day of methylprednisolone administered intravenously for 3 consecutive days, followed by oral prednisone 60 mg/day for 1 week, with a subsequent tapering regimen (decrease by 10 mg weekly until 20 mg, followed by a decrease of 5 mg weekly until complete withdrawal).
2. **Oral Prednisone Group:** 60 mg/day for 1 week, followed by a tapering regimen (decrease by 10 mg weekly until 20 mg, followed by a decrease of 5 mg weekly until complete withdrawal).

In both groups:

- **Concomitant 5-ASA Suppository Treatment:** 1g/day during the first 4 weeks.
- **Calcium and Vitamin D Supplementation:** Calcium 1000 mg/day and Vitamin D 800 IU/day until corticosteroid withdrawal.
- **Maintenance Mesalazine Treatment:** Mesalazine 2-2.4 g/day starting from prednisone tapering to 20 mg/day (in patients receiving 5-ASA during the flare-up, it will be discontinued upon inclusion in the study).

- Any other concomitant treatment received by the patient during the study must be recorded in the e-CRD.

Study Procedures: (summarized in Annex 8)

1. Inclusion and exclusion criteria will be reviewed, and informed consent will be signed at Visit 0.
2. Pre-inclusion epidemiological and clinical data will be collected.
3. Anthropometric data: height and weight, taken at the screening visit (V0).
4. Stool sample collection (Clostridium Difficile toxin determination and coproculture) and pregnancy test for women at the screening visit (V0).
5. Vital signs (temperature, heart rate, and blood pressure) and basic physical examination at each visit (V0 to V8).
6. Disease Activity Index according to the Mayo Clinic score (Disease Activity Index – DAI, Annex 2) will be calculated at visits V1, V5, and V8, and clinical subscore will be calculated at all other study visits. Walmsley Index will be calculated at all visits (Annex 3).
7. General laboratory tests (including blood count, renal and liver function, and C-reactive protein) and fecal sample collection for fecal calprotectin determination (samples preserved frozen until study completion for centralized analysis) at each visit.
8. Blood sample collection at baseline for corticosteroid response predictive factors analysis.
9. Rectosigmoidoscopy and Mayo endoscopic subscore calculation (Annex 2) at Visits V0 or V1, V5, and V8.
10. Clinical response assessment at Visits V2 and V3; clinical and endoscopic response assessment at Visits V5 and V8.
11. **Extra Visit for Intravenous Bolus Group (Group 1):** an additional visit on Day 2 (Visit 1.1) for administration of the second corticosteroid bolus.

VI) Recruitment Period, Follow-Up, and Study Duration

- **Patient Inclusion Start Date:** September 2018
- **Patient Inclusion End Date:** September 2020
- **Recruitment Period:** 104 weeks
- **Patient Treatment Duration:** 8 weeks
- **Patient Follow-Up Duration:** 42 weeks
- **Expected Completion Date for Last Enrolled Patient:** September 2021
- **Total Study Duration:** 156 weeks
- **Duration of Patient Participation:** 12 months

VII) Criteria for Premature Study Termination and Interruption

Criteria for Premature Study Termination:

- **Patient Decision:** Patients may withdraw from the study at any time without any penalty or impact on their disease management or subsequent required treatments.
- **Serious Complications Due to Steroid Treatment:** Occurrence of severe adverse events related to corticosteroid treatment.

- **Lack of Early Clinical Response.**
- **Lack of Clinical and Endoscopic Remission, Steroid-Free at Week 8.**
- **Clinical Worsening and Need for Rescue Treatment or Serious Adverse Event:** At the investigator's discretion, this can occur at any time during the study.

VIII) Procedures to Verify Adherence to Oral Treatment

This procedure is intended to determine the study medication adherence of the subjects. The principal investigator or a delegated person will provide detailed instructions to the patient regarding medication intake, along with an informative medication diary to be returned upon treatment completion (see Annex 6). Therefore, the principal investigator or delegated personnel must maintain product traceability and record medication administration per patient visit in the electronic case report form (e-CRD). Any medication-related incidents must be documented in the patient's clinical history and recorded in the e-CRF.

IX) Blinding Techniques

This is an open-label study, meaning no blinding will be applied except for the analysis of blood samples for predictive factors of corticosteroid response and the determination of fecal calprotectin in collected fecal samples. These analyses will be conducted centrally and blinded to ensure the laboratory technician performing the analysis is unaware of the treatment group and the patient's clinical response.

Evaluation of the primary outcome variable will be performed by the endoscopy services of the participating hospitals. Endoscopists will conduct a blinded assessment of endoscopic procedures (third-party blinded evaluations).

X) Data Identification

Investigators will comply with GCP standards. All information collected during the trial will be documented in the electronic case report form (e-CRF). In case of any protocol deviations, they will be limited to that specific patient. The investigator(s) will comprehensively document the deviation and its reason in the e-CRF. If a deviation pertains to inclusion/exclusion criteria, investigators must contact the clinical monitor to inform them by phone.

XI) Definition of Study End

The study end date is defined as the date when the last patient completes their final follow-up visit.

8. SUBJECT SELECTION AND WITHDRAWAL

I) Inclusion Criteria

1. Diagnosis of Ulcerative Colitis based on the European Crohn's and Colitis Organization criteria.
2. Patients aged 18 years or older.
3. Disease extension of at least left-sided (involvement >25 cm from the anal margin).
4. Moderate flare according to the Mayo Index (score ≥ 6 and ≤ 10).
5. No maintenance treatment or only 5-ASA oral and/or topical treatment.
6. Patient has the capacity to understand study requirements and provide informed consent.
7. Signed Informed Consent.

II) Exclusion Criteria

1. Previous or current treatment with thiopurines, calcineurin inhibitors, methotrexate, and/or biological agents.
2. Systemic corticosteroid use in the last 6 months (excluding topical oral corticosteroids).
3. Severe active or uncontrolled systemic infection, serious diseases, or medical conditions that may interfere with the patient's eligibility or treatment.
4. Uncontrolled diabetes mellitus or hypertension.
5. Psychiatric disorder or any other uncontrolled condition that contraindicates steroid treatment.
6. Pregnancy, lactation, or intention to become pregnant during the study period.
7. History of allergic reactions attributed to corticosteroids.

III) Withdrawal Criteria and Analysis

Premature termination of the trial will occur whenever the clinical trial is terminated before meeting the conditions outlined in the protocol.

Patients may be withdrawn from the study before reaching week 54 (end of follow-up) for any of the following reasons:

- **Patient Decision:** Patients are free to withdraw from the study at any time without any penalty or impact on their disease management or subsequent treatments.
- **Pregnancy.**
- **Serious Complications Due to Steroid Treatment.**
- **Lack of Early Clinical Response.**
- **Failure to Achieve Clinical and Endoscopic Remission, Steroid-Free at Week 8.**
- **Clinical Worsening and Need for Rescue Treatment at the Investigator's Discretion.**
- **Major Protocol Deviation.**

9. TREATMENT OF SUBJECTS

I) Treatment Definition

Treatment Groups:

- **Intravenous Bolus Group:** Intravenous methylprednisolone at a dose of 0.5 g/day for 3 consecutive days, followed by oral prednisone at 60 mg/day for one week, then a tapering regimen (reduction of 10 mg per week until reaching a dose of 20 mg, followed by a reduction of 5 mg per week until complete discontinuation).
- **Oral Prednisone Group:** Oral prednisone at a dose of 60 mg/day for one week, followed by a tapering regimen (reduction of 10 mg per week until reaching a dose of 20 mg, followed by a reduction of 5 mg per week).

II) Concomitant Treatments

For both treatment groups, the following concomitant treatments are recommended:

- **5-ASA Suppositories:** 1g/day for the first four weeks.
- **Calcium and Vitamin D Supplementation:** Calcium at 1000 mg/day and Vitamin D at 800 IU/day until corticosteroids are discontinued.
- **Maintenance Therapy with Mesalazine:** 2-2.4 g/day after prednisone dose tapering to 20 mg/day (patients on 5-ASA at the time of flare-up will discontinue it at the study's inclusion and continue with mesalazine until the end of the study). Dosage modifications can be made at the investigator’s discretion and documented in the data collection notebook.

Any other concomitant treatment that the patient receives during the study must be documented in the e-CRD.

III) Contraceptive Methods

Acceptable contraceptive methods for women of childbearing potential participating in the study include barrier methods (diaphragm or condom), intrauterine devices (IUDs), or sexual abstinence during the entire study duration.

Women using hormonal contraceptives as their usual method of birth control must choose an additional method from those described above, as the metabolism of hormonal contraceptives through cytochrome P450 CYP3A4 may be affected by corticosteroid treatment.

IV) Procedures for Monitoring Subject Adherence

Intravenous methylprednisolone boluses will be administered by nursing staff. Oral medication will be prescribed as per usual clinical practice by the principal investigator or a delegated individual.

Nursing staff responsible for intravenous administration must:

- Shake the medication well to obtain a white, slightly opaque suspension.
- Visually inspect the medication before and after reconstitution for any foreign particles and/or physical changes.

- Not use the medication if there are any changes in appearance or if it has been frozen.
- Administer the medication immediately after preparation.

10. EFFICACY EVALUATION

I) Specification of Efficacy Parameters

Treatment will be considered effective if the patient achieves clinical and endoscopic remission, steroid-free, at 8 weeks and up to 54 weeks, without requiring rescue treatment or corticosteroids.

The parameters used to measure efficacy will include clinical remission, endoscopic remission, and the need for corticosteroids or other rescue treatments.

II) Methods and Schedule for the Evaluation, Recording, and Analysis of Efficacy Parameters

i) Local Determinations

In the Laboratory:
Blood tests for hematological and biochemical values will be performed per usual clinical practice in each participating center.

Hematological parameters: hemoglobin, hematocrit, platelets, white blood cells, and differential leukocyte count.
Biochemical parameters: GOT, GPT, alkaline phosphatase, GGT, total bilirubin, creatinine, urea, sodium, potassium, glucose, cholesterol, triglycerides, albumin, and C-reactive protein.
Baseline stool culture.
Pregnancy test for women of childbearing potential without sterilization.

In the Endoscopy Unit:
Rectosigmoidoscopies will be performed at inclusion, at 8 weeks, and at 54 weeks.

- Prior rectal and sigmoid cleansing should be conducted per the investigator's discretion and standard clinical practice at each center.
- The procedure may be performed with or without sedation as per the guidelines of each Endoscopy Unit.

ii) Central Laboratory Determinations

During Visit 0 or 1, before administering the first corticosteroid dose, a 10 ml blood sample will be collected in an EDTA tube to validate corticosteroid response predictive markers. The sample will be sent at room temperature to the Biobank of the Institut d'Investigació en Ciències de la Salut Germans Trias i Pujol (IGTP), located at Carretera de Can Ruti. Camí de les Escoles s/n 08916, Badalona.

During Visits (V1-V8), fecal samples will be obtained for centralized determination of fecal calprotectin levels, with results blinded to the treating physician.

11. SAFETY EVALUATION

Safety evaluations will be conducted in accordance with GCP standards and applicable regulations. The sponsor has delegated management of adverse events (AEs) recorded during the study to the Spanish Clinical Research Network (SCReN), responsible for notifying regulatory authorities (AEMPS, regional health authorities) and CEIm of serious and unexpected adverse reactions (SUSARs), annual reports, or other relevant safety information.

I) Specification of Safety Parameters

Adverse Event (AE)
Any harmful incidence affecting the health of a patient or clinical trial subject treated with a medication, whether or not it has a causal relationship with the medication.

Adverse Reaction (AR)
Any harmful and unintended response to a medication. It refers to any harmful and unintended response to a medication, regardless of the dose administered.

Serious Adverse Reaction (SAR) / Serious Adverse Event (SAE)
Adverse events or reactions are considered serious if, at any dose, they result in death, pose a threat to the life of the subject, require hospitalization or prolong an existing hospitalization, cause permanent or significant disability or incapacity, or lead to a congenital anomaly or malformation. For reporting purposes, any suspected AE or AR deemed medically important will also be treated as serious, even if they do not meet the previous criteria, such as those that threaten the patient or require intervention to prevent any of the aforementioned outcomes, and any suspected transmission of an infectious agent through a medication.

Levels of Intensity

- **Mild** - Transient, without activity limitation, no medical intervention/treatment required.
- **Moderate** - Some activity limitation, some assistance may be needed, requires minimal or no medical intervention/treatment.
- **Severe** - Marked activity limitation, usually requires some form of assistance, requires medical intervention/treatment, hospitalization may be necessary.

Causality Criteria
The sponsor will classify adverse events based on their causal relationship with the drug according to the Karch and Lasagna (1977) algorithm as:

- **Definitive**: There is a reasonable temporal sequence between the administration of the drug and the occurrence of the AE. This event matches the ARs described

for the drug, improves with discontinuation of the drug, reappears upon re-administration, and cannot be explained by alternative causes.
- **Probable**: There is a reasonable temporal sequence between the administration of the drug and the occurrence of the AE. This event matches the ARs described for the drug, improves after treatment is interrupted, and cannot be explained by other alternatives.
- **Possible**: There is a reasonable temporal sequence between the administration of the drug and the occurrence of the AE. This event matches the ARs described for the drug but may be explained by alternative causes.
- **Conditional or Unlikely**: There is a reasonable temporal sequence between the administration of the drug and the occurrence of the AE. This event does not match the ARs described for the drug and may be explained by alternative causes.
- **Unrelated**: There is no reasonable temporal sequence between the administration of the drug and the occurrence of the AE. This event does not match the ARs described for the drug and may be explained by alternative causes.

For expeditious reporting, the categories "definitive," "probable," and "possible" from the Karch and Lasagna (1977) algorithm will be considered related, and the category "conditional or unlikely" will be considered unrelated.
Determining the potential relationship to the study treatment is the responsibility of the principal investigator at the research site or the person designated by them.

Serious Adverse Event (SAE)
Any harmful incident affecting the health of a subject that, at any dose:

- Requires hospitalization or prolongation of hospitalization,
- Causes permanent or significant disability or incapacity,
- Leads to a congenital anomaly or malformation,
- Poses a threat to life or results in death,
- Is considered medically significant.

For reporting purposes, any suspected AE or AR deemed medically important will also be treated as serious, even if they do not meet the previous criteria, including medical events requiring intervention to prevent any of the aforementioned outcomes. Any suspected transmission of an infectious agent via a medication will also be considered serious.

The term "life-threatening" refers to the investigator's opinion that the patient is at real risk of death at the time of the AE or AR; it does not refer to the hypothetical possibility that the AE/AR could have led to death if it had been more severe.

It should not be confused with the term "severe," which refers to the intensity of the AE or AR (mild/moderate/severe).

Serious and Unexpected Adverse Reaction (SUSAR)
A serious adverse reaction whose nature, severity, or outcome is inconsistent with the reference safety information. In this case, the product information (SmPC) will be used as the reference.

SAEs that meet the SUSAR criteria and are associated with blinded studies should be reported to Health Authorities with the open-label unblinding.

Adverse Events of Special Interest in this Study
Infections, events that lead to the discontinuation of the study treatment, and the development of diabetes mellitus or hypertension are considered of special interest.

Expected Adverse Reactions Not Clinically Significant in this Study
The following adverse reactions are commonly associated with the study medication in clinical practice. They will be recorded in the patient's medical history, but for reporting purposes, they will not be collected in the e-CRF unless, in the investigator's clinical judgment, they meet the severity criteria.
These include the occurrence of hirsutism, moon face, acne, insomnia, weight gain, buffalo hump, and stretch marks.

II) Methods and Schedule for Evaluation, Recording, and Analysis of Safety Parameters

Adverse events will be recorded from the administration of the study drug until the end of the patient's participation in the study, whether spontaneously reported by the patient or detected during study visits.
Follow-up of all ARs, SAEs, and SAREs will be conducted until resolution, irreversibility, or study completion, whichever occurs first.
All ARs, SAEs, SAREs must be documented in the patient's medical history and in the e-CRF, except for clinically insignificant ARs described above.

Any pregnancy occurring during the study and its outcome must be recorded and followed to rule out congenital anomalies or malformations. Information will be gathered on:

- Normal birth, spontaneous or therapeutic abortion (any congenital anomaly detected in the aborted fetus should be documented), stillbirth, congenital anomaly.
- Neonatal deaths within 30 days of birth.
- Infant death after 30 days if the investigator suspects it is related to in-utero exposure to the study medication.
- All infants born after fetal exposure must be followed during the first 12 months after delivery.

Any exacerbation of a pre-existing disease occurring after the start of the study treatment is also considered an adverse event.
Any abnormal result in laboratory tests that the investigator considers clinically significant and requires dose adjustment, temporary or permanent interruption of the study treatment, or any type of intervention or diagnostic evaluation to assess the risk to the patient, will be recorded as an adverse event and must be properly investigated and monitored.

In the case of an SAE that must be reported to the Pharmacovigilance Unit, or a pregnancy case, a member of the investigator team will complete and sign the SAE or pregnancy notification form (see Annexes 5 and 6) and send it via fax immediately, and

within 24 hours of knowledge of the event, to:

Patricia Rodríguez Fortúnez / Mar García Saíz
UICEC, Hospital Universitario de Canarias
Phone: 922 678 117
Fax: 922 677 284

The Pharmacovigilance Unit will review the received form and, if necessary, will request additional information from the investigator.
Once additional information is obtained on the SAE/pregnancy, or the event is resolved or unlikely to change, a follow-up report should be completed and sent, via fax, to the Pharmacovigilance Unit.
Any SAE should be reported within 30 days of the last dose of medication (without time limit) if the investigator considers the SAE related to the study treatment (i.e., if it is an SARE) or if it is medically important.

The Pharmacovigilance Unit is responsible for reporting to the AEMPS (Clinical Trials Area of the Subdirectorate General of Human Medicines) and the Ethics Committee all SAREs that occur in the study, following the procedure established by current legislation.

III) Procedures for Obtaining Reports on Adverse Events and Intercurrent Diseases and for Recording and Communicating Them

The maximum reporting period for a suspected SARE case will be 15 calendar days from the moment the sponsor becomes aware of it.
If the suspected SARE has caused the death of the patient or put their life in danger, the sponsor will send the information within 7 calendar days from when they become aware of it and will complete the information, if possible, within the next 8 days.
Annual safety reports, including SAREs and SAEs recorded in the study, will be sent to the AEMPS (Clinical Trials Area of the Subdirectorate General of Human Medicines) and the Ethics Committee within the timeframes established by current legislation.

The project manager will communicate any safety information that could affect the safety of study subjects to the investigators as soon as possible.
SARE information will be sent annually, in aggregate form, with a brief analysis of the data provided.
Throughout the study, investigators will be informed of any safety aspects that affect the conduct of the clinical trial or protocol amendments related to safety.

IV) Type and Duration of Follow-up of Subjects After Adverse Events

If a patient experiences any disease or adverse event during the study that, by itself or due to requiring pharmacological treatment, may alter the disposition of any of the study drugs or make its administration unadvisable, the patient will be excluded from the study, and the cause will be detailed. If the adverse reaction is mild or moderate, requires treatment or not, and does not lead to discontinuation of the drug, the reaction will be detailed, and the study will proceed as planned.

Notification
Report on the corresponding data collection form (Annex 5).

12. STATISTICAL ANALYSIS

I) Description of Statistical Methods

The statistical analysis of the clinical trial data will be carried out by the Sponsor of the study.
The baseline characteristics of the patients will be analyzed using descriptive statistical methods according to standard practices. Categorical variables will be compared using the Mann-Whitney test, and continuous variables will be compared using the Student's t-test.

To evaluate the primary objective of the study, the proportions of patients in both study groups who achieved clinical and endoscopic remission, steroid-free at 8 weeks and without rescue treatment, and who maintained clinical and endoscopic remission until week 54 without the need for steroids or rescue treatment, will be compared using the Chi-squared test. Both per-protocol (PP) and intention-to-treat (ITT) analyses will be performed. The ITT analysis will include all randomized patients who received at least one dose of treatment, regardless of whether they complete the prescribed treatment regimen. The PP analysis will only include patients who receive the full regimen as defined in the protocol and those who do not complete it due to adverse events or treatment failure.

The treatment of missing data necessary for the evaluation of the primary objective will follow non-response imputation (NRI) methodology.

For most secondary objectives, Chi-squared tests and Student's t-test will be used to compare the groups. The cumulative probabilities of relapse, steroid dependency, and surgery will be evaluated using Kaplan-Meier curves, and the times to relapse, steroid dependency, and surgery between the two study groups will be compared using the log-rank test. Finally, association analyses for early clinical response, clinical and endoscopic remission at week 8, and at both week 8 and week 54 will be conducted using Chi-squared tests and Student's t-test; variables that achieve a p-value ≤ 0.1 will be included in the logistic regression analysis.

An interim analysis will be conducted that will evaluate only the primary objective of the study (the proportion of patients who have achieved clinical and endoscopic remission, steroid-free at weeks 8 and 54, and without corticosteroid or rescue treatment). This analysis will be performed once 50% of the planned sample has completed the study. If the upper limit of the 95% confidence interval for the treatment efficacy in the experimental group is lower than initially expected (40%), or if the upper limit of the 95% confidence interval for the observed difference between the treatment groups for the primary endpoint is less than expected (20%), the study may be stopped for futility.

13. DIRECT ACCESS TO DATA/SOURCE DOCUMENTS

I) Study Data

This study will use an electronic data capture system. The electronic case report form (e-CRF) is designed to record all data required by the protocol. Data entry will be performed by the investigator or a designated team member, based on information recorded in the source documents.
The investigator or their designee will be trained by the sponsor or their designated organization to use the e-CRF.
All clarifications or corrections in the e-CRF will be made by the investigator or a team member designated by them.
Monitors will ensure that the e-CRFs are correctly completed according to the source documents. The investigator will ensure that all data collected in the e-CRF matches the information from the source documents.

II) Data Management

The sponsor or the organization designated by them will be responsible for managing and storing the study data.
Data management includes:

- **Data Transfer**: Data will be transferred from the e-CRF to the study database.
- **Data Validation**: Data will be validated according to a data validation plan. As a result of this validation process, some data may require modifications. In such cases, a "query" will be generated and must be answered by the investigator. In some cases outlined in the validation plan, certain obvious modifications may not require the investigator's approval, but a list of all such modifications will be provided to the investigator at the end of the study.
  At the end of the study, once the validation process for all study data is completed, the database will be considered finalized and reliable. At this point, the database will be closed and transferred to the person designated by the sponsor for the final statistical analysis.

14. QUALITY CONTROL AND ASSURANCE

I) Responsibilities of Clinical Trial Participants

Before the study, patients will be provided with both oral and written information about the study design, objectives, and potential risks. If they agree to participate, they must sign an informed consent form, with the understanding that they can withdraw at any time and for any reason.
Patients will be instructed on the necessity of strictly following the instructions of the investigators. They will be informed of the need to contact the investigators if any incidents arise during the study, with clear instructions on how to do so during the outpatient phase of the study.

II) Protocol Deviations

When a deviation from the protocol occurs, it will apply only to the affected patient. The investigators present in such circumstances will fully document the deviation and the reason in the case report form. If the deviation relates to inclusion/exclusion criteria, the investigators will contact the clinical monitor by phone to inform them of the deviation.

III) Major Deviations from the Protocol or GCP Guidelines

A major deviation from the protocol or from Good Clinical Practice (GCP) is any deviation that could significantly affect:

- The physical or mental safety and integrity of the trial subjects,
- The scientific value of the trial.

If a major deviation from the protocol or GCP is suspected, the sponsor or the organization designated by them should be contacted as soon as possible.
All major deviations from the protocol or GCP will be reported to the Health Authorities as required by current legislation.

15. ETHICAL, DEONTOLOGICAL, AND REGULATORY CONSIDERATIONS

I) General and Specific Standards for Investigators

The Principal Investigator will ensure that this study is conducted in accordance with the Protocol, the principles of the Declaration of Helsinki, the ICH Guidelines for Good Clinical Practice (GCP), and in compliance with applicable legislation. The protocol, informed consent, patient information sheet, and all related documents will be submitted to the Ethics Committee for Clinical Research with Medicinal Products (CEIm), the Spanish Agency for Medicines and Health Products (AEMPS), and, if applicable, to any other Regulatory Body that requires written approval in accordance with current legislation.
All relevant amendments to the original approved documents will also be submitted to the CEIm and AEMPS and, if necessary, to other Regulatory Bodies for written approval, as required by law.
At all times, the anonymity of the participants will be maintained. They will only be identified by the study code and their participant code.
All study documents will be securely stored and only accessible to study team members and authorized personnel. The study will comply with current data protection laws.
Patients will not receive any financial compensation for their participation in the study.

II) Information to the Patient and Obtaining Informed Consent

It is the investigator's responsibility to explain to the patients, both verbally and in writing, in comprehensible language, the study's objectives and requirements. This explanation will include complete information about the nature, objectives, potential risks, and benefits of the study. The type of treatment and the method of patient assignment will also be explained. The patient will be allowed to ask any questions they may have and will be given time to consider their decision. Patients will be explicitly informed of their right to withdraw from the study at any time and of the existence of insurance coverage. The investigator must obtain a signed informed consent form from each patient, or verbal consent in the presence of a witness, prior to their inclusion in the study.
The Patient Information Sheet and the Informed Consent Form models are included in Appendix 4. Each patient will retain a copy of both documents.
The signed Informed Consent forms will be kept by the investigator in the study

archive. If modifications are made according to local requirements, the new version must be approved by the Sponsor of the study and by the CEIm of the study.

III) Security Measures and Data Confidentiality

Data Confidentiality
The information disseminated and obtained through the implementation of this study is considered confidential and must be treated as such at all times. The patient will be identified in the Case Report Form (CRF) by an identification number. All processed data will be identified by the patient's number to ensure that their identity remains unknown to the sponsor.
Investigators involved in the study are responsible for maintaining the identification of the patient codes, including full name and address, at each center for a period of 25 years.
Patients must be informed in writing that the results will be stored and analyzed using a computerized system, that local data processing laws will be fully adhered to, and their confidentiality will be guaranteed.
Medical records and other information related to the patients may be accessed by the sponsor of the study as part of their work. The Electronic Case Report Forms and other study documents will be made available to Health Authorities if deemed relevant. However, the Case Report Forms will never be made available to third parties.
The results of the study will be communicated at scientific meetings or publications, but in no case will the identity of the patients be disclosed.

16. DATA MANAGEMENT AND RECORD ARCHIVING

I) Archiving of Documentation

Documentation will be archived according to Good Clinical Practice (GCP) standards and the regulations specified in Article 21 of Royal Decree 561/1993, of April 16, which establishes the requirements for conducting clinical trials with medicinal products.
The electronic case report forms (e-CRD) will be used to transmit all the information collected during the development of this study to the Health Authorities. The following records should be archived: patient records, source documents, e-CRDs, and the correspondence between the Ethics Committee and the sponsor. The investigator is responsible for preserving the patient identification codes and all relevant study information for at least 25 years after the completion or termination of the study. Patient medical records and other source data should be kept for the maximum period allowed by the hospital, institution, or private practice.
If an investigator moves to another center, withdraws from the research, or retires, the responsibility for preserving the records can be transferred to another person (e.g., another investigator) who agrees to accept this responsibility. This transfer of information must be notified and agreed upon with the sponsor or principal investigator.

In addition to the Case Report Forms, the investigator must maintain other subject records, which will include dates of visits and data related to vital signs, medical history or examinations performed, adverse events observed, and any other relevant notes. All this information constitutes the "original data." All data recorded in the e-CRD must be supported by the original data.

The e-CRD should be kept properly updated, reflecting the most recent observations of the patients included in the study.
Once the study treatment is completed, the Informed Consent will be archived with a copy of the completed e-CRD in the designated file, or a note will be included indicating where the documentation can be found.
For each subject included in the study, the e-CRD must be completed legibly and signed by the Investigator. The study monitor will review the e-CRDs.
Both the study monitor and the Health Authorities will be able to compare the e-CRD data with the source documents.

II) Identification of Samples

The study medication will be provided by the sponsor and will be labeled according to the recommendations of Royal Decree 1090/2015.

III) Amendments to the Protocol

Neither the investigator, the monitor, nor the sponsor will modify this protocol without first obtaining consent from the other parties involved. Any modification must be documented in writing. Any change in the research activity, except those necessary to eliminate an immediate apparent risk to the patient, must be reviewed and approved by the Ethics Committee (CEIm) before implementation. The sponsor must send any amendments to the protocol to the Health Authorities, and these modifications may require the review and approval of the CEIm.

17. INSURANCE

In accordance with Spanish Legislation (Royal Decree 1090/2015, of January 13, 2016) and Good Clinical Practice guidelines, this trial is covered by a liability insurance policy. The insurance is intended to protect against potential adverse events that may occur to the subjects enrolled in the trial as a result of the study medication.

18. PUBLICATION POLICY

The results of this clinical trial will be published in prestigious international scientific journals.

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