Clinical Study Protocol

OPTIM

OPTIMAL CARE WITH GUSELKUMAB IN CROHN'S DISEASE

GETAID-2025-03
EUCT Number: 2025-524573-16-00
Protocol Version: V1.2 – 26-MAR-2026

Sponsor: Groupe d´Etude Thérapeutique dans les Affections Inflammatoires Digestives (GETAID)
GETAID, 50 Rue Richer 75009

E-mail address: projet@getaid.org

Coordinating Investigator **Pr Mathurin FUMERY, MD PhD** CHU d'Amiens – Picardie 1 Rue du Professeur Christian Cabrol 80000 AMIENS E-mail: fumery.mathurin@chu-amiens.fr	**Methodologist** **Pr Eric VICAUT** GETAID, 50 rue Richer 75009 Paris E-mail: Eric.vicaut@aphp.fr
Pr David LAHARIE, MD PhD CHU de Bordeaux – Hôpital Haut L'Eveque 1 avenue Magellan 33600 PESSAC E-mail: david.laharie@chu-bordeaux.fr	**Project Director** **Mme Julie MUSSOT** GETAID, 50 Rue Richer 75009 E-mail: jmussot@getaid.org

TABLE OF PROTOCOL VERSIONS

Reference	Version	Date	Status
Initial protocol	V1.2	26-MAR-2026	

STUDY INFORMATION

Title:	**OPTIMAL CARE WITH GUSELKUMAB IN CROHN'S DISEASE**
Protocol version:	1.1
Date of last version of the protocol:	26-MAR-2026
EUCTR	2025-524573-16-00
Active substance (INN common name):	Guselkumab (Tremfya®)
Pharmaco-therapeutic group (ATC Code):	L04AC16
Medicinal product(s):	Guselkumab (Tremfya®)
Product reference:	Guselkumab (Tremfya®)
Name of Marketing Authorization Holder(s)	Janssen Research & Development, LLC
Research question and objectives	What is the real-world effectiveness of GUS under optimal conditions of use with dose intensification in CD ? The primary objective is to evaluate the one-year effectiveness of GUS in CD in real-world setting.
Country(-ies) of study	France
Author	Pr David LAHARIE (GETAID president), Pr Mathurin FUMERY (GETAID)

PROTOCOL SIGNATURE PAGE

Sponsor
Groupe d'Etude Thérapeutique des Affections Inflammatoires Digestives (GETAID)
President: Pr David LAHARIE

Date_____ Signature _____

Coordinator Investigator : Pr Mathurin FUMERY

Date_____ Signature _____

Site Investigator
I will conduct the trial in compliance with GCP, with the relevant regulatory requirement(s) and with the protocol agreed to by the sponsor and given approval/favorable opinion by the IRB/IEC; I agree to comply with procedure for data recording/reporting, especially to report all SAEs to GETAID and, if applicable to my National Sponsor within 24H of awareness. I agree to allow and facilitate monitoring, auditing and inspection and to retain the trial related essential documents until the sponsor informs me/institution these documents are no longer needed.
I will conduct this trial according to the timelines provided.
I understand that all information concerning the study supplied to me by GETAID in connection with this trial and not previously published is considered confidential information.
I agree that documents and other data pertinent to this trial are property of GETAID.
I understand that any changes in the protocol must be approved in writing by GETAID and the IRB/IEC and local competent authorities before implementation.
By my signature below, I hereby attest that I have read, understood and agree to abide by all conditions, instructions and restrictions contained in the protocol.

Investigator

Name _____

Date_____ Signature _____

LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
CD	Crohn's Disease
CRF	Case Report Form
DSMB	Data and Safety Monitoring Board
FAS	Full Analysis Set
ECCO	European Crohn and Colitis Organization
eDC	electronic Data Capture
EU CTR	European Union Clinical Trials Regulation
FC	Fecal Calprotectin
GCP	Good Clinical Practice
GETAID	Group d'Etude Thérapeutique dans les Affections Inflammatoires Digestives
GMP	Good Manufacturing Practice
GUS	Guselkumab
IBD	Inflammatory Bowel Disease
ICH	International Conference on Harmonization
ICF	Informed Consent Form
IEC/IRB	Independent Ethics Committee/ Independent Review Board
IL	anti-interleukin
IMP	Investigational Medicinal Product
IUS	Intestinal Ultrasound
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
PP	Per Protocol
PQC	Product Quality Complaint
PRO	Patient-Reported Outcome
QP	Qualified Person
qXw	every X weeks
SAE	Serious Adverse Event
SAS	Safety Analysis Set
SC	Subcutaneous
SES-CD	Simple Endoscopic Score for Crohn Disease
SFCR	Steroid Free Clinical Remission
TNF	Tumor Necrosis Factor

TABLE OF CONTENTS

1. SYNOPSIS

Title	**OPTIMAL CARE WITH GUSLEKUMAB IN CROHN'S DISEASE / OPTIM study** A prospective open label interventional, multicenter study
EUCT number	2025-524573-16-00 (GETAID 2025-03)
Protocol version	V1.2 – 26-MAR-2026
Study Rationale	Crohn's disease (CD) is a chronic and destructive inflammatory disease of the gastrointestinal tract characterized by phases of relapse and remission. Tumor necrosis factor (TNF) antagonists, anti-integrins and anti-interleukin (IL) 12/23 are the main therapeutic agents to obtain deep remission and prevent disability. Despite the significant advances these biologics represent in treating inflammatory bowel disease (IBD), many patients experience suboptimal responses, including primary non-response or a loss of effectiveness over time, often leading to treatment discontinuation. For all these medications, a dose-response relationship has been demonstrated and an increase in dose or dosing frequency is recommended. Dose escalation is now an essential therapeutic approach necessary in 30 to 50% of CD patients treated with biologics. This strategy, supported by international guidelines, allows for long-term efficacy to be maintained without compromising safety. Guselkumab (GUS) is a monoclonal antibody targeting the p19 subunit of IL-23. In a recent phase III trial (GALAXI), GUS demonstrated superiority of both subcutaneous (SC) maintenance doses (200 mg every 4 weeks [q4w] and 100 mg every 8 weeks [q8w]) compared to placebo and ustekinumab. These two dosing regimens provide important flexibility by enabling therapeutic intensification for patients who are unresponsive to induction therapy or who have lost response. In the GALAXI phase III program, at least 30% of patients did not achieve clinical response after a 12-week intravenous induction, and almost 20% experienced a loss of response by week 44. In these patients, the benefit of an intensified dose of GUS (200 mg q4w) maintenance remains to be determined to guide clinicians in optimizing its use in clinical practice. We aimed to evaluate the one-year effectiveness of GUS in CD in real-world settings and under optimal conditions allowing dose intensification.
Primary Objective	To evaluate the one-year effectiveness of GUS in CD in real-world setting.
Secondary Objectives	- To evaluate the effectiveness of GUS intensification from 100 mg q8w to 200 mg q4w in patients with loss of response, - To evaluate the effectiveness of an intensified GUS 200 mg q4w maintenance therapy in patients who are primary non-responders to GUS SC induction at 12 weeks; - To assess the factors associated with GUS intensification effectiveness.

Study Endpoints	<u>Primary endpoint</u> - Steroid free clinical remission (SFCR) associated with fecal calprotectin < 250 ug/g at W48. <u>Secondary endpoints</u> - Morphological remission at W48 assessed using the same tool that was used for the patient's inclusion : endoscopy, MRI or IUS (major secondary endpoint), - SFCR associated with fecal calprotectin < 250 ug/g at W12, W24 and W48, - Clinical remission at W12, W24, and W48, - Clinical response at W12, - Biomarker remission at W12, W24, and W48, - Need for GUS dose intensification (W12, W24, W48), - Serum levels of GUS (W12, W24, and W48), - Neutralizing antibodies to GUS (W12, W24, and W48), - CD-related hospitalization during study period (W12, W24, and W48), - CD-related surgery during study period (W12, W24, and W48), - Change in Short IBD-Q (quality of life index) from baseline (W12, W24, and W48), - GUS persistence Among patients with GUS intensification over the study period: - SFCR associated with fecal calprotectin < 250 ug/g at +12 weeks after GUS intensification, - Clinical remission and response at +12 week after GUS intensification, - Biomarker remission at +12 week after intensification, - Serum levels of GUS and neutralizing antibodies + 12 weeks after GUS intensification), - CD-related hospitalization and surgery + 12 weeks after GUS intensification), - Change in Short IBD-Q (quality of life index) + 12 weeks after GUS intensification), Factors associated with the effectiveness of GUS intensification
Study Design	This is a prospective open label interventional, multicenter study to document the optimal use of GUS for the treatment of CD in a clinical practice setting.
Study population	Adult patients with active Crohn's disease.
Eligibility criteria	**Inclusion criteria** - Patients with a diagnosis of CD according to ECCO guidelines, - 18 years of age or older at the time of informed consent, - Absence of contraindication to guselkumab, - Active disease according to PRO2 (abdominal pain > 1 or stool frequency > 3), and faecal calprotectin > 250 ug/g, - Objective active disease documented within ≤ 2 months by endoscopy or by MRI when not contraindicated, orby IUS), - Not currently participating in any interventional research. - Patient naïve or exposed to one or more advanced therapy, in accordance with the approved indication for guselkumab in Crohn's disease. - Females of childbearing potential must have a negative serum pregnancy test at the baseline Visit.

<table>
<tr><td></td><td>Exclusion criteria
- Patient under legal protection,
- Previous exposure to an anti-IL23
- Combination of advanced therapy with GUS,
- Patient with ostomy,
- Pregnant or breastfeeding woman,
- Patient with perianal CD predominant disease.
- Active clinically significant infection or HIV, Hep B, Hep C, or active tuberculosis</td></tr>
<tr><td>Study treatment</td><td>Study treatment
All eligible patients will receive SC GUS 400 mg q4w induction at weeks (W) 0-4-8.

• Primary responders according to PRO 2 (decrease ≥ 30%) and FC (decrease ≥ 25%) at W12 will receive GUS 100 mg q8w maintenance therapy. In case of loss of response, defined by a FC increase (> 25% with a minimal cut-off of 250 ug/g) between W12 and W48 or by a FC > 250 µg/g at W24, or disease activity confirmed by IUS/MRI/endoscopy patients will be intensified to GUS 200 mg q4w.
• Primary non-responders according to PRO 2 (absence of decrease ≥ 30%) or to FC (absence of decrease ≥ 25%) at W12 will receive GUS 200 mg q4w maintenance therapy.</td></tr>
<tr><td>Study Duration</td><td>Duration of study participation for each individual patient: 48 weeks +/- 12 weeks. The extension of the 3 months of follow-up is justified by the monitoring of patients who will receive therapeutic intensification between W32 and W48.</td></tr>
<tr><td>Number of subjects</td><td>A total of 210 patients will be enrolled.</td></tr>
<tr><td>Study timelines</td><td>
<table>
<tr><td>Milestone</td><td>Planned date</td></tr>
<tr><td>First patient inclusion</td><td>Q2 2026</td></tr>
<tr><td>End of recruitment</td><td>Q4 2027</td></tr>
<tr><td>End of follow-up (last patient)</td><td>Q3 2028</td></tr>
<tr><td>Final report of study results</td><td>Q1-2029</td></tr>
</table>
</td></tr>
</table>

2. INTRODUCTION

2.1. RATIONALE AND BACKGROUND

Crohn's disease (CD) is a chronic and destructive inflammatory disease of the gastrointestinal tract characterized by phases of relapse and remission (1). Overarching therapeutic goals are to eliminate symptoms, avoid disease complications and optimize the patient's quality of life. By reaching certain therapeutic targets – according to a "treat-to-target" approach - it is believed that the chances of achieving these therapeutic goals are markedly improved. Recently, the STRIDE II guidelines recommend to consider symptomatic control as a early target and then the normalization of objective biomarkers of inflammation and endoscopic healing with the aim of modifying the disease course.

Tumor necrosis factor (TNF) antagonists, anti-integrins and anti-interleukin (IL) 12/23 are the main therapeutic agents to obtain deep remission and prevent disability (2). Despite the significant advances these biologics represent in treating CD, approximatively 10 to 20% of patients will not respond after the induction phase, defined as primary non-response, and another 30 to 40% may lose response over time (secondary loss of response) or may be intolerant to the treatment (3,4). In patients with a suspicion of primary non response or loss of response to advanced therapy, it is first recommended to objectively assess active disease. For all these medications, a dose-response relationship has been demonstrated and an increase in dose or dosing frequency is recommended. For certain drugs as anti-TNF, therapeutic drug monitoring (TDM) determines drug serum concentrations and the presence of anti-drug antibodies (ADAbs) and can help guide treatment optimization to improve patient outcomes. Early optimization of a patient's current treatment and maintenance of clinical remission is also important to avoid a rapid progression through therapeutic options. Finally, dose escalation is now an essential therapeutic approach necessary in 30 to 50% of CD patients treated with biologics. This strategy, supported by international guidelines, allows for long-term efficacy to be maintained without compromising safety (2, 5).

Guselkumab (GUS) is a novel monoclonal antibody targeting the p19 subunit of IL-23. In two recent phase III trials (GALAXI and GRAVITI), GUS IV and SC induction demonstrated superiority to placebo to induce clinical response and remission at W12 (6,7). The GALAXI trial demonstrated that both subcutaneous (SC) maintenance doses (200 mg every 4 weeks [q4w] and 100 mg every 8 weeks [q8w]) was superior to placebo and ustekinumab as maintenance therapy. These two dosing regimens provide important flexibility by enabling therapeutic intensification for patients who are unresponsive to induction therapy or who have lost response. In the GALAXI phase III program, at least 30% of patients did not achieve clinical response after a 12-week intravenous induction, and almost 20% experienced a loss of response by week 44. In these patients, the benefit of an intensified dose of GUS (200 mg q4w) maintenance remains to be determined to guide clinicians in optimizing its use in clinical practice.

2.2. KNOWN AND POTENTIAL RISKS AND BENEFITS

Guselkumab has demonstrated efficacy in phase 3 studies in adult patients with moderately to severely active Crohn's disease, including improvement in clinical and endoscopic outcomes. Its safety profile is generally consistent with that established from approved indications. Known and potential risks associated with guselkumab include infections, including tuberculosis, hypersensitivity reactions, malignancies, liver enzyme elevations, and precautions related to live vaccines.

In accordance with the SmPC, appropriate precautions and safety monitoring are implemented in this study, with tuberculosis assessment, vaccination recommendations, and liver function monitoring. Considering the approved indication of guselkumab in Crohn's disease, the available efficacy and safety data, and the low-interventional nature of the study, the expected benefits of participation are considered to outweigh the potential risks.

The OPTIM study is expected to provide clinically relevant real-world data on the one-year effectiveness of guselkumab and on the effectiveness of dose intensification strategies in patients with inadequate response or loss of response.

3. RESEARCH QUESTION AND OBJECTIVES

3.1. Research Question

What is the real-world effectiveness of GUS under optimal conditions of use with dose intensification in CD?

3.2. Objective(s) and Outcome(s)/Measure(s) of Interest

The **primary objective** of the OPTIM study is to evaluate the one-year effectiveness of GUS in CD in real-world setting.

- To evaluate the effectiveness of GUS intensification from 100 mg q8w to 200 mg q4w in patients with loss of response,
- To evaluate the effectiveness of an intensified GUS 200 mg q4w maintenance therapy in patients who are primary non-responders to GUS SC induction at 12 weeks;
- To assess the factors associated with GUS intensification effectiveness.

3.3. Endpoints

Primary endpoint

- Steroid free clinical remission (SFCR) associated with fecal calprotectin < 250 ug/g at W48.

Secondary endpoint

- Morphological remission at W48 assessed using the same tool that was used for the patient's inclusion: endoscopy, MRI or IUS (major secondary endpoint),
- SFCR associated with fecal calprotectin < 250 ug/g at W12, W24 and W48,
- Clinical remission at W12, W24, and W48,
- Clinical response at W12,
- Biomarker remission at W12, W24, and W48,
- Need for GUS dose intensification (W12, W24, W48),
- Serum levels of GUS (W12, W24, and W48),
- Neutralizing antibodies to GUS (W12, W24, and W48),
- CD-related hospitalization during study period (W12, W24, and W48),
- CD-related surgery during study period (W12, W24, and W48),
- Change in Short IBD-Q (quality of life index) from baseline (W12, W24, and W48),
- GUS persistence

Among patients with GUS intensification over the study period:

- SFCR associated with fecal calprotectin < 250 ug/g at +12 weeks after GUS intensification,
- Clinical remission and response at +12 weeks after GUS intensification,
- Biomarker remission at +12 weeks after intensification,
- Serum levels of GUS and neutralizing antibodies + 12 weeks after GUS intensification),
- CD-related hospitalization and surgery + 12 weeks after GUS intensification),
- Change in Short IBD-Q (quality of life index) + 12 weeks after GUS intensification),
- Factors associated with the effectiveness of GUS intensification.

4. RESEARCH METHODS

4.1. Study Design

This is a prospective open label interventional, multicenter study to document the optimal use of GUS for the treatment of CD in a clinical practice setting.

Prior to data collection, all potential participants must sign a participation agreement/informed consent form (ICF) allowing source data verification in accordance with local requirements and sponsor policy.

All eligible patients will receive SC GUS 400 mg q4w induction at weeks (W) 0-4-8.

- Primary responders according to PRO 2 (decrease ≥ 30%) **and** FC (decrease ≥ 25%) at W12 will receive GUS 100 mg q8w maintenance therapy. In case of loss of response, defined by a FC increase (> 25% with a minimal cut-off of 250 ug/g) between W12 and W48 or by a FC > 250 µg/g at W24, or disease activity confirmed by IUS/MRI/endoscopy patients will be intensified to GUS 200 mg q4w.

- Primary non-responders according to PRO 2 (absence of decrease ≥ 30%) **or** to FC (absence of decrease ≥ 25%) at W12 will receive GUS 200 mg q4w maintenance therapy.

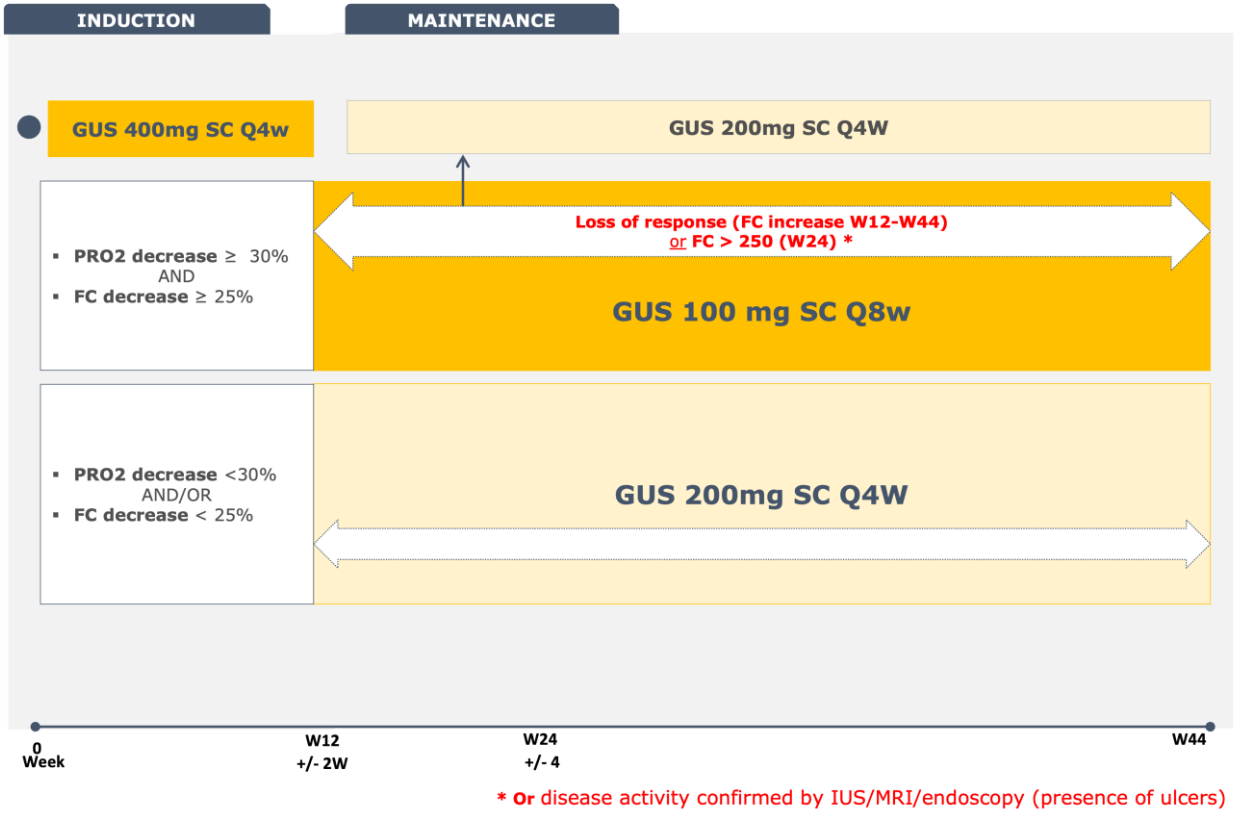

Figure 1: Study design

Treatment with guselkumab (Tremfya®) will be provided by the Janssen Pharmaceutical company as per the EMA approved product label and regulations for the prescription of medicinal products for patients with moderate to severe CD. **Patients can be treated whatever the line of advanced therapy (L1 and other).**

The study will start when the first patient provides their consent to participate in data collection. The study will end when data collection for the last patient is completed. The overall duration of the study will be 48 weeks +/- 12 weeks.

4.1.1. Rationale for Study Design Elements

Study Design

The prospective open label interventional study design facilitates collection of a sufficient quantity of defined variables, where available in clinical practice, to address the research question.

To avoid potential bias in patient selection, each participating physician should enroll eligible patients in a consecutive manner (ie, in the order in which they are assessed for eligibility). All patients who meet the selection criteria should be offered enrollment in the study.

4.2. Setting and Study Population

4.2.1. Study Setting

Sites participating in this open label interventional study will be hospitals and private centers, members of the GETAID treating and managing patients with CD in routine clinical practice.

25 academic French centers will participate to the recruitment of patients in this study. All participating center belongs to the GETAID (www.GETAID.org), an independent network of French IBD centres involved in care and research on CD. The GETAID has designed and conducted numerous clinical trials since its creation in 1989 and provides access to a large population of CD patients, with local investigators with extensive clinical trial experience.

This study will be proposed to all CD patients in whom treatment with guselkumab is considered whatever the line of advanced therapy. We expect the recruitment of 8 patients/center over the 18-month recruitment period.

4.2.2. Patient Selection Criteria

At each site, the participating physician will determine the eligibility of patients for data collection in this study based on the inclusion and exclusion criteria described below. If there is a question about any of the selection criteria, the participating physician should consult with the appropriate sponsor representative before enrolling the patient. To avoid potential selection bias, all eligible patients should be offered enrollment for data collection in the study.

Inclusion Criteria

Each patient must satisfy the following criteria to be eligible for data collection in this study:

- Patients with a diagnosis of CD according to ECCO guidelines,
- 18 years of age or older at the time of informed consent,
- Absence of contraindication to guselkumab,
- Active disease according to PRO2 (abdominal pain > 1 or stool frequency > 3), and faecal calprotectin > 250 ug/g,
- Objective active disease documented within ≤ 2 months by endoscopy or, by MRI when not contraindicated or by IUS),
- Not currently participating in any interventional research.
- Patient naïve or exposed to one or more advanced therapy, in accordance with the approved indication for guselkumab in Crohn's disease.
- Females of childbearing potential must have a negative serum pregnancy test at the baseline Visit.

Exclusion Criteria

Patients who meet any of the following criteria will not be eligible for this study:

- Patients under legal protection,
- Previous exposure to an anti-IL23
- Combination of advanced therapy with GUS,
- Patient with ostomy,
- Pregnant or breastfeeding woman,
- Patient with perianal CD predominant disease.
- Active clinically significant infection or HIV, Hep B, Hep C, or active tuberculosis

MRI Contraindications :

Imaging will be performed according to standardized procedures in order to ensure a precise examination.

The risks associated with the magnet during MRI are the most common. The magnetic field (which is harmless) can attract and move certain metallic objects on or inside your body. Depending on the type of metal and the position of the object, the examination may or may not be carried out. Certain surgical clips in the brain and metallic fragments in the eyes contraindicate the exam. Likewise, electronic devices (particularly pacemakers) can be affected by the magnetic field.

There are also risks related to the injection of a contrast agent for MRI. As with any introduction of a pharmaceutical product into the body, adverse reactions may occur. Sometimes, at the time of

injection, a portion of the product may leak around the vein; simple local care is usually sufficient to limit this reaction.

An allergic reaction may occur, and it is impossible to predict. However, it is more common in people with allergies. Reactions can vary, from mild eye irritation to more serious consequences (cardiorespiratory arrest), although these are very rare. The staff, trained for such situations, have the necessary equipment readily available.

MRI may be challenging in individuals with claustrophobia; appropriate measures (e.g., patient counseling, open MRI, or sedation) should be considered to ensure patient comfort and safety."

Contraception

Woman in the age of childbearing potential must agree to use a highly method of contraception throughout the duration of the study and for up to 12 weeks after the last administration of guselkumab (Tremfya). Acceptable highly effective methods of contraception are those with a failure rate of less than 1% per year when used correctly, in accordance with current CTFG recommendations for example, intrauterine device, hormonal contraception, true abstinence. Female subjects of nonchildbearing potential do not need to use birth control.

Tuberculosis assessment

In accordance with the SmPC, patients must be evaluated for tuberculosis infection prior to initiation of guselkumab treatment. Patients with active tuberculosis tuberculosis are not eligible for study participation. Patients receiving guselkumab will be monitored for signs and symptoms of active tuberculosis during and after treatment. Anti-tuberculosis treatment should be considered prior to initiation of guselkumab in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed.

4.2.3. Duration of Study Period(s) and Follow-Up

- Start of data collection : W0 (baseline), date of GUS initiation.
- Duration of study participation for each individual patient 48 weeks +/- 12 weeks. The extension of the 3 months of follow-up is justified by the monitoring of patients who benefited from therapeutic intensification between W32 and W48.
- End of study : W48 (+/- 12 weeks for patients with GUS intensification between W32 and W48)

4.2.4. Study visits, assessments and treatment strategy

The study consists of an induction period followed by a maintenance period, with mandatory visits and additional visits scheduled according to treatment response and disease activity.

Study treatment
All eligible patients will receive subcutaneous guselkumab (GUS) 400 mg every 4 weeks during the induction period at Weeks 0, 4, and 8.
At Week 12, treatment response will be assessed based on patient-reported outcomes (PRO2) and fecal calprotectin (FC):

- **Primary responders**, defined as a decrease ≥ 30% in PRO2 and ≥ 25% in FC, will receive GUS 100 mg every 8 weeks as maintenance therapy.
- In case of **loss of response** between Weeks 12 and 48—defined as an increase in FC > 25% with a minimum cutoff of 250 µg/g, or an FC value > 250 µg/g at Week 24, or objective disease activity confirmed by IUS, MRI, or endoscopy—patients will be intensified to GUS 200 mg every 4 weeks.
- **Primary non-responders**, defined as the absence of a ≥ 30% decrease in PRO2 or a ≥ 25% decrease in FC at Week 12, will directly receive GUS 200 mg every 4 weeks as maintenance therapy.

This response-driven treatment strategy explains the need for additional visits during the maintenance period.

Visit 1 – Baseline (Week 0)

At baseline, written informed consent is obtained, and eligibility criteria are confirmed. Demographic data, medical history, and disease history are collected. Disease activity is assessed through clinical examination, PRO2, quality of life (SIBDQ), inflammatory biomarkers (CRP and fecal calprotectin). Assessment of infection or HIV, Hep B, Hep C, or active tuberculosis, blood samples for chemistry and hematology tests and pregnancy test (for women of childbearing potential only). Concomitant medications and adverse events are recorded. Objective disease activity is assessed using endoscopy, MRI, or intestinal ultrasound (IUS) performed within 2 months prior to baseline. Guselkumab induction therapy is initiated.

Visit 2 – Follow-up (Week 12)

This mandatory visit includes clinical assessment, PRO2, blood samples for chemistry and hematology tests, inflammatory biomarkers (CRP and fecal calprotectin), quality of life evaluation, and review of adverse events and concomitant medications and pregnancy test (for women of childbearing potential only). Pharmacokinetic sampling is performed. Treatment response is evaluated at this visit to define the maintenance regimen (standard maintenance or intensified therapy).

Visit 3 – Follow-up (Week 24)

Assessments performed at Week 12 are repeated, including clinical examination, PRO2, blood samples for chemistry and hematology tests, inflammatory biomarkers evaluation (CRP and fecal calprotectin) quality of life, adverse events, and concomitant medications and pregnancy test (for women of childbearing potential only). Pharmacokinetic sampling is performed. Disease activity at this visit may contribute to the identification of loss of response and the need for treatment intensification.

Additional visit – Loss of response (any time during the maintenance period)

If a loss of response is suspected during the maintenance period, an additional visit may be scheduled. This visit includes clinical assessment, PRO2, blood samples for chemistry and hematology tests, inflammatory biomarkers evaluation (CRP and fecal calprotectin) and review of adverse events and concomitant medications and pregnancy test (for women of childbearing potential only). Objective disease activity may be reassessed using IUS, MRI, or endoscopy, as clinically indicated, to support the decision to intensify treatment.

Additional visit – Post-intensification treatment adjustment (+12 weeks)

Twelve weeks after treatment intensification, an additional follow-up visit may be performed to assess response to the intensified regimen. Assessments include clinical examination, PRO2, blood samples for chemistry and hematology tests, inflammatory biomarkers evaluation (CRP and fecal calprotectin) quality of life evaluation, pharmacokinetic sampling, and optional objective disease activity assessment and pregnancy test (for women of childbearing potential only).

Visit 4 – End of Study (Week 48 ± 12 weeks)

The end-of-study visit includes a final clinical examination, PRO2 assessment, blood samples for chemistry and hematology tests, inflammatory biomarkers evaluation (CRP and fecal calprotectin), quality of life assessment, review of adverse events and concomitant medications, pharmacokinetic sampling and pregnancy test (for women of childbearing potential only), and completion of the end-of-study form.

Laboratory assessments

Hematology and clinical chemistry tests will be performed according to the schedule of assessments and will include, as applicable, hematocrit, hemoglobin, red and white blood cell

counts with differential, platelet count, creatinine, total bilirubin, ALT, AST, and alkaline phosphatase.
A serum pregnancy test will be performed at screening for women of childbearing potential. Subjects with a positive pregnancy test will not be eligible for inclusion. In case of a borderline result, the test may be repeated to confirm eligibility. In addition, a pregnancy test will be performed at each visit to ensure that the female participant remains not pregnant throughout the study.
Documentation of prior negative HIV, HBV, HCV and tuberculosis screening performed before treatment initiation will be verified at screening. Subjects with evidence of active tuberculosis will not be eligible.
Additional assessment of faecal calprotectin will be performed according to the schedule of assessments.

Blood collection should be performed, as per clinical practice, and prior to study treatment administration during the visit

Disease activity assessment

Disease activity will be assessed throughout the study using a combination of clinical, biomarker and morphological evaluations.
Clinical activity will be evaluated based on clinical remission and response, while biomarker activity will be assessed using faecal calprotectin.
Morphological assessment will be performed using the same modality as that used for inclusion (endoscopy, MRI or IUS), to ensure consistency over time. These assessments will be used to evaluate the effectiveness of guselkumab, including after dose intensification when applicable.

Safety monitoring

Investigators are required to evaluate participants for any signs or symptoms of infection at scheduled visits. If a patient develops a clinically important or serious infection or is not responding to standard therapy, the patient should be monitored closely and treatment should be discontinued until the infection resolves.
In accordance with the SmPC, liver transaminases (ALT and AST) will be monitored during thestudy according to the schedule of assessments. Any clinically significant elevation will be documented and managed as appropriate.

Study Completion, Discontinuation of Treatment, and Withdrawal from Study Data Collection

When an enrolled patient completes or withdraws from the study, the participating physician will complete an end-of-study form for the individual patient and provide a specific date for the end-of-study observation. When a patient withdraws before completing the study, the reason for withdrawal is to be documented in the CRF and in the source document. Patients who withdraw will not be replaced.
If a patient is lost to follow-up, every reasonable effort should be made (within clinical practice) by personnel at the participating site to contact the patient and determine the reason for discontinuation. The measures taken to follow up should be documented. In the event that the status of the patient cannot be determined and the patient is considered to be lost to follow-up,

an end-of-study form for the individual patient will be completed and a specific date for the last observation will be provided.
A patient will be withdrawn from further documentation in this study for any of the following reasons:

- Withdrawal of consent
- Lost to follow-up
- Death
- Patient permanently stops receiving the treatment being observed (GUS)

All treatment decisions will be made at the discretion of the treating physician. Starting or stopping therapies for CD during the observation period will not impact data collection for this study. If a patient discontinues treatment before the end of the observational period, the end-of-treatment and follow-up assessments should be documented.
Additionally, a patient will be withdrawn from further documentation in this study for any of the following reasons:

- The participating physician (or treating physician where different) believes that it is in the best interest of the patient to stop treatment (eg, for safety reasons such as an adverse event)
- They develop a medical condition that requires concomitant therapy with a drug listed as prohibited in the respective product information

If a patient discontinues treatment before the end of the observational period, an end-of-study form should be completed.
Patients who are subsequently enrolled in another non-Janssen-sponsored non-interventional study do not need to be withdrawn, if this study do not impact the respect of the protocol of the current study.
The study is considered completed with the last data collection time point (W48 +/- 3 months) for the last patient participating in the study. Participating sites will be closed upon study completion.

4.3. Investigational Medical Product

Description of identification

Drug Name	Tremfya® /Guselkumab
Pharmaceutical form	Solution for injection
Strength	100 mg or 200mg
Presentation	Prefilled syringe or prefilled pen
Route of admisnitration	Subcutaneous

The investigational medicinal product (IMP), guselkumab will be supplied by Janssen. The product batches provided for this study are manufactured and released for clinical trial use. These batches are not commercial lots and are intended exclusively for use within the framework of this clinical study.

Formulations

- Guselkumab 100 mg for injection (SC)

100mg in 1ml solution per prefilled syringe
Active substance : Guselkumab (INN)

- Guselkumab 200mg for injection (SC

200mg in 2ml solution per prefilled pen
Active substance : Guselkumab (INN)

Packaging and distribution
Packaging, labelling, quality control testing, batch certification and release of the clinical trial supplies will be performed by CLINIGEN in accordance with applicable GMP requirements. Batch release will be carried out by a Qualified Person (QP) in compliance with Regulation (EU) No 536/2014.
Clinical trial supplies will be distributed to study sites under appropriate conditions to ensure traceability, accountability, and compliance with regulatory requirements.

4.4. Concomitant medications

4.4.1. Permitted medications

In case of prior study treatment with either azathioprine (AZA), 6-Mercpatopurine (6-MP) or methotrexate (MTX) maintenance of therapy will be allowed at the same dose during the study process.
A steroid course will be permitted to treat flares of luminal disease during the study with a starting dose of 40 mg tapered over a maximum of 12 weeks.

4.4.2. Prohibited medications

- Any current or previous use of the following before the first trial agent injection: anti-IL 23: risankizumab (Skyrizi®) or mirikizumab (Omvoh®)
- The following treatments must be discontinued prior to first trial injection : anti-TNF biologic agents or other agents intended to suppress or eliminate TNF: infliximab (Inflectra®, Remicade®, Remsima®, Flixabi®), golimumab (Simponi®) and adalimumab (Humira®, Amgevita®, Amsparity® ,Hulio®, Hyrimoz®, Hukyndra®, Lybmiris®, Idacio®, Imraldi®), anti-IL 12/23: ustekinumab (Stelara®, Otulfi®, Pyzchiva®, Steqeyma®, Uzpruvo® and Wezenla®), and anti-integrin: vedolizumab (Entyvio®) and Janus Kinase inhibitors (JAKi): tofacitinib (Xeljanz®), upadacitinib (Rinvoq®) or filgotinib (Jyseleca®).
- Oral corticosteroids at a dose > 40 mg prednisone or its equivalent per day.
- The introduction of other IBD treatments is prohibited throughout the duration of participation in the study.

4.4.3. Vaccines

Although not mandated by the protocol, vaccinations recommended by local guidelines should be considered. Live vaccines should not be administered concurrently with guselkumab treatment. Before live viral or live bacterial vaccination, guselkumab should be withheld for at least 12 weeks after the last dose and may be resumed at least 2 weeks after vaccination.

Inactivated (non-live) vaccines may be administered before or during the study, according to local practice guidelines.

4.5. Variables

The Data Collection Overview that follows the abstract summarizes the expected frequency and timing of data collection in this study. Data will be collected from all patients who receive at least one administration of the product under study within the protocol-defined data collection period.

DATA COLLECTION OVERVIEW

	Induction period	**Maintenance period**				
Nb visit Type/name	**V1** **Baseline**	**V2** **Follow Up**	**V3** **Follow Up**	**V (Optional 1)** **Loss of response visit**	**V (Optional 2) Post-intensification treatment adjustment visit**	**V4** **End of Study**
Week (W)	W0	W12	W24	Anytime during the maintenance period	+ 12W after GUS intensification	W48 (+/- 12W)
Patient consent[a]	X					
Selection criteria	X					
Tuberculosis, HIV, Hep B, Hep C tests	X					
Demographics	X					
Medical history	X					
Disease history	X					
Current disease status	X					
Physical examination	X	X	X	X	X	X
Guselkumab dose / intervals	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X
Adverse events[b]	X	X	X	X	X	X
PRO2	X	X	X	X	X	X
Blood sampling[e]	X	X	X	X	X	X
Biomarkers (CRP /calprotectin)	X	X	X	X	X	X
Quality of life (SIBDQ)	X	X		X	X	X
Pharmacokinetics	X	X	X	X	X	X
Objective disease activity assessment (endoscopy / MRI / IUS)	X (≤ 2 months)[c]			X		X
End-of-study form						X[d]

[a] Before the start of data collection in this study, all patients must sign a participation agreement/ICF allowing source data verification in accordance with local requirements; the participation agreement/ICF may be obtained at or before baseline..

[b] All adverse events and special situations following exposure to a product under study are to be recorded in the CRF, regardless of seriousness or causality. Adverse event collection should start with the first use within the study of a product under study and will apply to all adverse events that occur within the study

[c] Disease activity may be assessed using endoscopy, MRI, or IUS performed up to 2 months prior to the baseline visit

[d] When an enrolled patient completes or withdraws from the study, or is lost to follow-up, the participating physician will complete the end-of-study form for the individual patient and provide a specific date for the end-of-study observation(s).

PRO, Patient Reported Outcome; MRI, magnetic resonance imaging; IUS, intestinal ultrasound; S-IBDQ, Short IBD quality of life questionnaire

[e] blood sampling for chemistry and hematology tests

4.5.1. Guselkumab and others IBD therapies

After a signed participation agreement/ICF is obtained, details of relevant CD therapies taken since diagnosis will be documented retrospectively. This will include all IBD medications taken since the CD diagnosis.

During the study from baseline to the end of the study, the following data will be documented at each visit:

- Guselkumab therapy, dose and mode of administration,
- Start/stop dates and reason for discontinuation,
- All IBD therapies will be collected taking in consideration :
  - azathioprine and methotrexate are authorized medication at stable dose
  - infliximab, adalimumab, vedolizumab, ustekinumab, upadacitinib, risankizumab, mirikizumab are prohibited during the study.
  - A reduction in steroids aimed at stopping corticosteroids at W12 will be systematically proposed

4.5.2. Evaluation of Effectiveness and Patient-Reported Outcomes

Clinical endpoint will be assessed according to STRIDE II guidelines.

Primary endpoint

- Steroid free clinical remission (SFCR) associated with fecal calprotectin < 250 ug/g at W48.

Secondary endpoint

- **Morphological remission** at W48 assessed using the same tool that was used for the patient's inclusion : endoscopy, MRI or IUS (major secondary endpoint),
- **Clinical response** (W12 and , + 12 weeks after GUS intensification),
- **Clinical remission** (W12, W24, W48 and , + 12 weeks after GUS intensification),
- **Steroid-free clinical remission (SFCR)** (W12, W24, W48 and , + 12 weeks after GUS intensification),
- **Need for guselkumab dose intensification** (W12, W24, W48),

- **Change in Short IBD-Q** (quality of life index) from baseline (W12, W24, W48 and , + 12 weeks after GUS intensification),
- **Biomarker remission** (fecal calprotectin) (W12, W24, W48 and , + 12 weeks after GUS intensification),
- **Morphological response** at W48 assessed using the same tool that was used for the patient's inclusion : endoscopy, MRI or IUS,
- **Serum levels of guselkumab** (W12, W24, W48 and , + 12 weeks after GUS intensification),
- **Neutralizing antibodies to guselkumab** (W12, W24, W48 and , + 12 weeks after GUS intensification),
- **CD-related hospitalization during study period** (W12, W24, W48 and , + 12 weeks after GUS intensification),
- **CD-related surgery during study period** (W12, W24, W48 and , + 12 weeks after GUS intensification),
- **GUS persistence**

Definitions

- **Clinical response**: decrease of at least 50% in PRO2 (abdominal pain and stool frequency),
- **Clinical remission**: abdominal pain ≤ 1 and stool frequency ≤ 3,
- **Steroid-free clinical remission**: abdominal pain ≤ 1 and stool frequency ≤ 3 without steroids for at least one week,
- **Biomarker remission** (fecal calprotectin < 250 ug/g),
- **Morphological remission** (assessed using the same tool that was used for the patient's inclusion : endoscopy, MRI or IUS)
    - Endoscopy: SES-CD <3 points or
    - IUS: bowel wall thickness ≤3 mm without color doppler signal, or
    - MRI : bowel wall thickness ≤3 mm without contrast enhancement.
- **Morphological response** (assessed using the same tool that was used for the patient's inclusion : endoscopy, MRI or IUS)
    - Endoscopy: decrease in SES CD ≥ 50%
    - IUS: decrease in bowel wall thickness ≥ 50%
    - MRI: decrease in bowel wall thickness ≥ 50%

4.5.3. Evaluation of Safety

Adverse Events and Adverse Drug Reactions

All adverse events and special situations following exposure to a product under study are to be recorded in the CRF for the protocol-defined data collection period and in the patient's source records, regardless of seriousness or causality.

Adverse event collection should start with the first use within the study of a product under study and will apply to all adverse events, regardless of seriousness, that occur within the study

Section 6 provides further details of safety data collection and reporting procedures.

The sponsor assesses the safety of each experimental drug on an ongoing basis throughout the research. It shall establish a system and written procedures to ensure the quality of the collection, documentation, evaluation, validation, archiving and reporting of cases of serious adverse events and serious adverse effects as well as of the new facts referred to in Article R. 1123-46 of the French Public Health Code.

The sponsor assesses any adverse event notified by the investigators regarding its seriousness. For each serious adverse event, the sponsor assesses it relatedness to the experimental drug, concomitant drugs, study procedure as well as the unexpected character of the event. Whenever the investigator and the sponsor disagree on the relatedness of the experimental drug to the serious adverse event, both causalities have to be indicated on the declaration to the relevant authorities as mentioned in article R. 1123-54 of the French Public Health Code.

The sponsor/vigilance unit must declare any unexpected serious adverse event and new data observed during the study to Clinical Trials Information System (CTIS) according to the EU Clinical Trial Regulation (EU CTR)) according to the following timetable:

- without delay after being informed for life threatening or fatal serious adverse effects,
- no later than 15 calendar days after being informed for all other serious adverse effects.

If necessary a follow up will be uploaded to CTIS within 8 calendar days of the initial declaration regardless of the seriousness.

The sponsor/vigilance unit must record all unexpected serious adverse events related to the experimental drug in the EudraVigilance database:

- no later than 7 calendar days after being informed for life threatening or fatal serious adverse effects,
- no later than 15 calendar days after being informed for all other serious adverse effects.

If necessary a follow up will be recorded in the EudraVigilance database within 8 calendar days of the initial declaration.

4.5.4. Sample Collection and Handling

- CRP and fecal calprotectin will be collected at baseline, W12, W24, W48 and , + 12 weeks after GUS intensification) and evaluated locally A fecal sample (stool container) will be asked to patient at each visit for local fecal calprotectin dosage.

- Trough serum levels and antibodies to guselkumab (W12, W24, W48 and , + 12 weeks after GUS intensification): a blood sample of 9 ml (in a dry tube with red cap or a tube with lithium heparinate with green cap) will be collected locally. A laboratory manual will be available to define the sending procedures of the biological's samples (in accordance to the procedures of the central lab). Each sample will be tagged with the name of the study, the number of patients and the date of the visit. Stockage and then analysis will be performed centrally.

4.6. Data Sources

The primary data source for this study will be the medical record of each participating patient. Source documentation should be in patients' records for all data entered into the CRF. To confirm data collected in the CRF for this study, source documentation should also be available for the following: patient identification, eligibility and study identification; date of signed participation agreement/ICF; date of study completion and reason for early discontinuation of treatment or withdrawal from the study (if applicable). The author of any entry in the source documents should be identifiable.
The type and level of detail of source data available for a patient should be consistent with that commonly recorded at the participating site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the participating physician before the study.

The following data will be recorded directly into the CRF and will be considered source data:

- Inclusion/exclusion criteria,
- Date of visit,
- Data of Birth,
- Gender,
- Height and weight,
- Smoking status,
- Date of diagnosis,
- Montreal classification (with maximal disease extension and disease complication),
- Disease extension and phenotype at baseline,
- Previous and current (including dose and interval for current medication) IBD medications,
- PRO (abdominal pain, and stool frequency),
- Short IBDQ,
- CD Intestinal resection,
- CD related hospitalization,
- Endoscopy results (SES-CD, presence of ulcers),
- IUS results (bowel wall thickness, color doppler signal, complication),
- MRI results (bowel wall thickness, contrast enhancement, T2 hypersignal, complication),
- Fecal calprotectin and CRP levels,
- Reason for guselkumab intensification, reason for guselkumab withdrawal,
- AE and SAE.

4.7. Data Suitability Assessment

4.7.1. Study Size

A sample size of N= 200 eligible patients (active disease according to PRO2 (abdominal pain > 1 or stool frequency > 3), and faecal calprotectin > 250 ug/g) treated during the induction phase, this population will allow to estimate the primary criterion with a precision (based on two-sided 95%CI) of ± 7% or better. Since it is estimated that approximately 50 % /50% will be

responders/non responders at W12 under these hypotheses the primary criterion will be estimated in each group with a precision (based on two-sided 95%CI) of ± 10% or better. Considering a 5% attrition during the induction phase a total of N= 210 patients will be included.

4.7.2. Data Collection and Management

Participating sites will enter data into the case report form (CRF) using electronic data capture (eDC) via an internet browser-based interface named CLEANWEB®. The CRF will direct the site regarding which data are required for collection. Participating sites will be trained on the use of the eDC system. Data collected should be recorded accurately, legibly and promptly for each patient during the study. Further details of CRF completion procedures are presented in CW-063-USM-FR Guide Investigateur.

The PRO questionnaires will be provided to patients in the local language by local investigators. Completed PRO questionnaires will be reported by local investigators into the study database.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a site visit log that will be kept at the participating site. Further details of monitoring procedures are presented in Monitoring Plan.

4.8. Data Analysis

Statistical analyses will be performed by or under the authority of the sponsor. A general description of the planned statistical methods to be used to analyze the data collected in this study is presented in the following subsections. Additional details will be provided in a statistical analysis plan

4.8.1. Data Sets Analyzed

The Full Analysis Set (FAS):

Considering the type of study, the FAS will include all subjects included who received at least one dose of GUS

Note however, that a description of any patient included that would not receive GUS will be presented with the reasons of non administration of GUS

The Per-Protocol Analysis Dataset (PP):

The PP population will include all subjects
who received GUS

and

who have at least one post-randomization assessment of primary criterion available

and

who did not meet any major protocol deviations which may affect primary assessments (see specific paragraph for details).

The exclusion of subjects from the PP population will be determined in a final data review meeting blinded of any information regarding the results of the treatment. Reason(s) for exclusion will be documented for each subject

The primary efficacy analysis will be considered on the FAS population; the PP population will provide an additional sensitivity analysis.

The Safety Analysis Set (SAS):

The safety population will include all subjects who received at least one unit of GUS(i.e. similar definition as FAS in this study)

4.8.2. Safety Analyses

Adverse Events

The verbatim terms used by physicians to document adverse events in the CRF will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All documented adverse events will be included in the analysis. For each adverse event, the percentage of patients who experience at least 1 occurrence of the given event will be summarized.
Where appropriate, additional summaries, listings, datasets, or narratives may be provided, as appropriate, for those patients who die, who discontinue treatment due to an adverse event, or who experience a severe or a serious adverse event.

4.8.3. Statistical Methods

This is a non-comparative descriptive study without any formal hypothesis to be tested.

4.8.3.1. Descriptive Analysis

The qualitative variables will be expressed by numbers and percentages and 95% two-sided confidence intervals. Qualitative variables will be expressed by means, standard error, medians and interquartile intervals. The normal feature of the distribution of quantitative variables will be checked. Time to event data will be described by survival curves and Kaplan-Meier estimates.

4.8.3.2. Estimands

In accordance with addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials E9(R1)

Main estimands

The primary objective of the OPTIM study is to evaluate the one-year effectiveness of GUS in CD in real-world setting.

In order to assess at best the effectiveness of GUS, two main estimands will be considered.
The corresponding estimands for the primary objective and primary endpoint have the following attributes:

1: Treatment policy Estimands

i) Population: Adult with a diagnosis of CD according to ECCO guidelines and corresponding to the inclusion/exclusion criteria mentioned above.
ii) Variable: The main criterion for efficacy is the percentage of patients with steroid free clinical remission (SFCR) associated with fecal calprotectin < 250 ug/g at W48
iii) Intercurrent events:
- Death
- Inability to collect information at W48 due to lost to Follow-up or missing data
- Treatment interruption, or changes in the treatment attributed by the design .
The handling of consequences of intercurrent events will be based on a *"treatment policy approach"* :
-In case of death, the patient will be considered as a failure (ie, no remission)
- Even if the patient did not follow the treatment scheme assigned by the protocol its value at W48 will be used.
-in case of missing value at W48 a multiple imputation method (MCMC) will be used.
iv) Population summary measure:
Percentage and 95% CI
v) Interventions:
Administration of GUS as described in paragraphs and figures above.

2: While on Treatment Estimands
Attributes of the estimands will be the same with the exception of the handling of the consequences of treatment interruption or changes from the assigned scheme.
In these cases the last value observed when the patient was on treatment according to the protocol will be used.

Sensitivity estimands

Since Multiple Imputation method (MCMC) for missing data is a base on a missing at random hypothesis (MAR), a sensitivity analysis using worse case scenario for missing value at W48 will be used.

Secondary endpoints

Estimands attributes will be the same as those described for main endpoint.

4.8.3.3. Statistical Evaluation

Analysis of the primary endpoint

The main efficacy analysis will calculate the percentage of patients with steroid free clinical remission (SFCR) associated with fecal calprotectin < 250 ug/g at W48 described with its 95%CI. This percentage will be calculated according to the whole population and to the status of the patients after induction (ie Responder/Non responder).

Analyses of the secondary endpoints

The percentage of patients with Clinical response at W12 will be calculated with its 95% CI

The percentages and 95%CI of patients with

- SFCR associated with fecal calprotectin < 250 ug/g ,
- Clinical remission at W12, W24 and W48, will be calculated at each time
- Biomarker remission at W12, W24, and W48,
- Morphological remission at W48, (assessed using the same tool that was used for the patient's inclusion : endoscopy, MRI or IUS),
- Morphological response at W48, (assessed using the same tool that was used for the patient's inclusion : endoscopy, MRI or IUS),
- Need for GUS dose intensification (W12, W24, W48),
- GUS persistence
- CD-related hospitalization during study period (W12, W24, and W48),
- CD-related surgery during study period (W12, W24, and W48),

will be calculated at each time.
In addition, a survival analysis for these events will be performed and Kaplan Meier estimates will be calculated.

Changes from baseline in Serum levels of GUS, Neutralizing antibodies to GUS in Short IBD-Q (quality of life index) from baseline (W12, W24, and W48), will be described at different times by their mean, SD, median and upper and lower quartiles.

GUS persistence will be described by survival curves and summarized using Kaplan-Meier estimates

All these populations will be calculated according to the whole population and to the status of the patients after induction (i.e. Responder/Non responder).

For quantitative parameters, graphs will also be provided (curves of evolution during the 48 weeks of the study).

Exploratory Analyses

Univariate and multivariate (if condition of validity are fulfilled) logistic regressions models will be used to identify the factors associated with GUS intensification effectiveness.

Sub-group Analyses

Similar analyses will be performed in order:

- to evaluate the effectiveness of GUS intensification from 100 mg q8w to 200 mg q4w in patients with loss of response,
- To evaluate the effectiveness of an intensified GUS 200 mg q4w maintenance therapy in patients who are primary non-responders to GUS SC induction at 12 weeks;

No comparison will be made between the group GUS 100 mg q8w and GUS 200 q4w maintenance therapy.

Multiplicity adjustment

No tests will be performed in this study and multiplicity control is not relevant for the study.

Missing Values

See estimands paragraph.

4.8.4. Interim Analyses

No interim analyses will be performed in this study.

4.9. Quality Control

Procedures to ensure the accuracy and reliability of data will include the selection of qualified physicians and appropriate participating sites using the GETAID network, review of data collection procedures with the participating physician and site personnel before the study, and periodic monitoring visits and/or remote monitoring by the sponsor (see Section 9.12). Written instructions for the handling, storage, and shipments of samples obtained in clinical practice will be provided where appropriate.

Guidelines for CRF completion will be provided and reviewed with the participating site personnel before the start of the study (see CW-063-USM-FR Guide Investigateur) The sponsor will review CRFs for accuracy and completeness during on-site monitoring visits (where applicable); any discrepancies will be resolved with the participating physician or designee, as appropriate. After uploading the data into the study database, they will be verified for accuracy and consistency with the data sources.

The participating physician and/or site will maintain all CRFs and source documentation that support the data collected for each patient, as well as all study documents specified by the applicable regulatory requirement(s). The participating physician and/or site will take measures to prevent accidental or premature destruction of these documents. Essential documents must be retained for at least 25 years after the completion of the final study report but will be retained for a longer period if required by applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the participating physician and/or site as to when these documents no longer need to be retained.

Representatives of the sponsor may visit the participating site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and/or company policy. Similar procedures may also be conducted by a regulatory body.

4.10. Strengths and Limitations of the Research Methods

The study benefits from standardized procedures, qualified sites via the GETAID network, and monitoring to reduce data entry errors. However, as a prospective open label interventional study design, residual confounding and selection bias may persist. Random error from practice variability is possible. Efforts such as training and monitoring should minimize information bias.

Any remaining errors are likely non-differential, reducing precision rather than introducing major distortion.

5. PROTECTION OF HUMAN SUBJECTS

This study will be undertaken only after having obtained approval from the EU CTR, of the final protocol, any applicable amendments, and the participation agreement/ICF, and the sponsor has received a copy of this approval).

Prior to data collection, all patients must sign a participation agreement/ICF allowing source data verification in accordance with local requirements and sponsor policy. Potential participants will be told that their consent to allow collection of information within the context of this study is entirely voluntary and may be withdrawn at any time. Patients will be informed of the prospective open label interventional study nature of the study, that the sponsor only intends to collect information and follow the course of treatment in the clinical practice setting, and that their participation in the study does not involve invasive procedures outside of the recommendations in the local label. Only patients who are fully able to understand the nature of the study and provide their consent voluntarily will be enrolled.

Personal data collected from patients enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study and must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations .

6. COLLECTION AND REPORTING OF SAFETY DATA AND COMPLAINTS

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of patients, physicians, and the sponsor, and are mandated by regulatory agencies worldwide. All studies conducted by the sponsor or its affiliates will be conducted in accordance with established procedures and regulatory requirements worldwide to ensure appropriate reporting of safety information.

General procedures for the collection and reporting of any adverse events, adverse reactions, special situations, and product complaints within the study are described in the following sections. Definitions, classifications and related criteria for safety events and complaints are described in section 9.16.

6.1. General Procedures

In this study, GUS is the Janssen product(s) under study. Safety information and PQCs for these medicinal products will be collected and reported during the study as described in the following sections.

The sponsor will provide appropriate pharmacovigilance training to the participating site personnel. The sponsor assumes responsibility for appropriate reporting of (serious) adverse events and significant safety information originating from the data collected for Janssen medicinal products to the regulatory authorities. All collected adverse events will be summarized in the final study report.

The names (and corresponding contact details) of the individuals who should be contacted regarding product safety issues and/or quality issues are listed on the contact information page(s), which is/are provided separately.

6.2. Prospective Study Period

6.2.1. All Adverse Events

Solicited Adverse EventsAs mentioned in the informed consent, the patient should inform the investigator if signs or symptoms of clinically important chronic or acute infection occur in order to have a medical advice.

All adverse events and special situations following exposure to a product under study are to be systematically recorded in the CRF for the protocol-defined data collection period and in the patient's source records, regardless of seriousness or causality.

Adverse event collection should start with the first use of a product under study and will apply to all adverse events, regardless of seriousness, that occur within the study within 30 days after a patient's last use within the study of a product under study.

All adverse events following exposure to a product under study should be assessed by the participating physician to document the causal relationship of the adverse event, which must be recorded in the CRF. An adverse event will be considered as an ADR if there is at least a reasonable possibility of a causal relationship (see Section 9.16).

All adverse events and special situations following exposure to a product under study are to be systematically collected.

These adverse events may be subject to spontaneous reporting procedures as described below.

All adverse events should be followed-up in accordance with clinical practice, regardless of seriousness. This follow-up should be recorded in the patients' source records [and documented in the CRF].

Expedited Reporting of Adverse Events

Any event that meets the definition of a serious adverse event (see Section 9.16) should be reported as a serious adverse event according to the requirements in Section 9.16.

Adverse Events of Special Interest

Additionally, for the Janssen product under study, the following medical concepts require expedited reporting to the sponsor to meet regulatory reporting requirements:

- Active tuberculosis (TB)
- Malignancy
- Elevation of liver transaminases

All adverse events for a Janssen product under study that fall under these medical concepts should be recorded in the CRF and reported to the local sponsor as soon as possible according to the process for serious adverse event reporting (9.16), even though they would not necessarily be considered a serious adverse event.

Spontaneous Adverse Events

For adverse events and special situations that are not systematically collected (eg, for a medicinal product other than the product under study, and where the participating physician considers there is at least a reasonable possibility of a causal relationship to a medicinal product (i.e., spontaneous ADRs), the participating physician is requested to report the event as soon as possible, as indicated below:

- For ADRs and special situations related to a non-studied Janssen product (ie, any Janssen product used within the study period other than the product under study), report the event directly to the local sponsor.
- For ADRs and special situations related to any other medicinal product, notify the manufacturer of the medicinal product or the appropriate regulatory/competent authority through the national spontaneous reporting system.

Where available, reports of spontaneous ADRs will be summarised in the clinical study report.

6.2.2. Serious Adverse Events

All serious adverse events following exposure to a Janssen product under study should be reported directly by the participating physician, within 24 hours of them becoming aware, to the local sponsor (GETAID) using a Serious Adverse Event Report Form (or local equivalent).
For reports of hospitalization, it is the sign, symptom or diagnosis which led to hospitalization that is the serious event for which details must be provided.
Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility).
- Surgery or procedure(s) planned before entry into the study (should be documented in the CRF). Note: Hospitalizations that were planned before the start of data collection, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.

The cause of death of a patient in a study, whether or not the event is expected or associated with the product under study, is considered a serious adverse event.]

6.2.3. Pregnancy

Any report of exposure to a product under study during pregnancy involving maternal or paternal exposure to the product under study is to be documented by the participating physician, recorded in the AR form of the eCRF as a special situation, and documented in the patient's source records.
All reports of pregnancy involving maternal or paternal exposure occurring with exposure to a Janssen product under study must be reported to the sponsor by the participating site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form.
Abnormal pregnancy outcomes (eg, spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using a Serious Adverse Event Form.
Any patient who becomes pregnant during the study must be promptly withdrawn from the study.
Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant should be obtained where possible.

6.3. Product Quality Complaints

A PQC may have an impact on the safety and effectiveness of the product.
All initial PQCs involving a Janssen product must be reported to the local sponsor by the participating site personnel within 24 hours after being made aware of the event using the appropriate product quality complaint form.
If the defect for a Janssen product is combined with a serious adverse event, the study-site personnel must report both the SAE and the PQC to the sponsor.
A sample of the suspected product should be maintained under the correct storage conditions until a shipment request is received from the sponsor.

7. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results of the study will be reported in a clinical study report generated by the sponsor, which will contain data collected from all study sites that participated in the study. The sponsor will register and/or disclose the existence of and the results of clinical studies as required by law.

Patient identifiers will not be used in the publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the participating physician) shall be the property of the sponsor as author and owner of copyright in such work.

8. REFERENCES

1. Dolinger L, Torres J, Vermeire S. Crohn's disease. Lancet. 2024;403:1177-1191.
2. Feuerstein JD, Ho EY, Shmidt E, et al. AGA Clinical Practice Guidelines on the Medical Management of Moderate to Severe Luminal and Perianal Fistulizing Crohn's Disease. Gastroenterology. 2021;160:2496-2508.
3. Singh S, Murad MH, Fumery M, Sedano R, Jairath V, Panaccione R, et al. Comparative efficacy and safety of biologic therapies for moderate-to- severe Crohn's disease: a systematic review and network meta-analysis. Lancet Gastroenterol Hepatol. 2021;6:1002–14.
4. Peyrin-Biroulet L, Danese S, Argollo M, Pouillon L, Peppas S, Gonzalez-Lorenzo M, et al. Loss of response to vedolizumab and ability of dose intensification to restore response in patients with Crohn's disease or ulcerative colitis: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2019;17:838–846.
5. Gordon H, Minozzi S, Kopylov U, et al. ECCO Guidelines on Therapeutics in Crohn's Disease: Medical Treatment. J Crohns Colitis. 2024;18:1531-1555.
6. Panaccione, R et al. Efficacy and safety of guselkumab therapy in patients with moderately to severely active Crohn’s disease: results of the GALAXI 2 & 3 phase 3 studies. Oral presentation (Abstract #1057b) at Digestive Disease Week (DDW) 2024. May 2024.
7. Panaccione R, Hart A, Steinwurz F et al. S1052 Efficacy and Safety of Subcutaneous Guselkumab Induction Therapy in Patients With Moderately to Severely Active Crohn’s Disease: Results Through Week 48 From the Phase 3 GRAVITI Study. *Am J Gastroenterology* 119(10S):p S740-S741, October 2024.

9. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

9.1. Regulatory and Ethical Considerations

Investigator Responsibilities

The investigator is responsible for ensuring that the study is conducted in accordance with the approved protocol, the current ICH Good Clinical Practice guideline ICH E6(R3), and all applicable national, European, and international regulatory requirements.

Good Clinical Practice constitutes an internationally accepted ethical and scientific quality standard for designing, conducting, documenting, and reporting clinical studies involving human participants. Compliance with these principles ensures the protection of participants' rights, safety, and well-being, and the reliability and credibility of the data generated. These principles are aligned with the Declaration of Helsinki.

Within the European Union, the study must comply with Regulation (EU) No 536/2014, under which all clinical trial applications are submitted, assessed, and decided upon through the Clinical Trials Information System (CTIS). Although the scientific and ethical assessment in France involves both the Comité de Protection des Personnes (CPP) and the Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM), a single harmonized decision is issued via CTIS, in accordance with the Regulation.

In France, the study must also comply with the relevant provisions of the French Public Health Code (Code de la Santé Publique) governing research involving human participants. The CTIS-issued decision constitutes the formal national authorization, even though the CPP and ANSM contribute to the assessment process.

The processing of personal data must comply with the General Data Protection Regulation (GDPR – Regulation (EU) 2016/679) and the applicable French data-protection requirements, particularly the Méthodologie de Référence MR-001, which applies to research involving human participants in the context of clinical trials.

The investigator must ensure that all procedures related to participant information and consent, confidentiality, safety monitoring, and reporting of adverse events are carried out in accordance with these ethical and regulatory frameworks.

Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the participants, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involve only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

In situations where a departure from the protocol is unavoidable during the study, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact must be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country/territory, if applicable. A study may not be initiated until all local regulatory requirements are met.

Required Pre-study Documentation

The following documents must be provided to the sponsor before shipment of study intervention to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, participant compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the participants)
- IB (or equivalent information) and amendments/addenda

- Sponsor-approved participant recruiting materials
- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant compensation programs, and the sponsor has received a copy of this approval. This letter of approval must be dated and must clearly identify the IEC/IRB and the documents being approved.

Approval for the collection of optional samples for research and for the corresponding ICF must be obtained from the IEC/IRB. Approval for the protocol can be obtained independent of this optional research component.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to participants
- If applicable, new or revised participant recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study intervention
- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data, or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study.

9.2. Financial Disclosure

Investigators and sub investigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study.

9.3. Informed Consent Process

Each participant must give consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the participant can read and understand. The informed consent must be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study site personnel must explain to potential participants the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive. Finally, they will be told that the investigator will maintain a participant identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the participant is authorizing such access. It also denotes that the participant agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations, if needed the physician may also recontact the participant for the purpose of obtaining consent to collect information about his or her survival status.

The participant will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent must be appropriately recorded by means of the participant's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant.

9.4. Recruitment Strategy

Refer to Recruitment and Informed Consent Procedure Template for details.

9.5. Data Protection

Privacy of Personal Data

The collection and processing of personal data from participants enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.
These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of participants confidential.
The informed consent obtained from the participant includes information about, and where required per applicable regulations, explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. The informed consent also provides information to address the lawful transfer of the data to other entities and to other countries/territories.
The participant has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that is not correct or complete, or make requests concerning his or her personal data in accordance with applicable data protection law. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.
In the event of a data security breach, the sponsor will apply measures to adequately manage and mitigate possible adverse effects taking into consideration the nature of the data security breach as necessary to address other obligations such as notifying appropriate authorities in accordance with applicable data protection law.

9.6. Storage, Use, Transfer, and Retention of Data and Samples

Study samples will be coded at all times in accordance with the informed consent and will not be labeled with personal identifiers.
Investigator and study site will only store, use, transfer and retain data and study samples, including optional study samples, in accordance with the informed consent and applicable law, and in accordance with any separate written agreement with sponsor. Other than what is specified in a separate written agreement with sponsor, study site and investigator shall not conduct or facilitate any research by a third party not required by the protocol (i) on participants if such research interferes with the conduct of the study or (ii) on samples collected from study participants during the study, including optional samples, if the research relates to OPTIM or (iii) on data collected from study participants during the study if the research relates to OPTIM.
Sponsor may store, use, transfer or retain the data and study samples, including optional study samples, for uses not specified by the protocol, including compatible research, in compliance with the informed consent and applicable law.

9.7. Committees Structure

A DSMB will be established to ensure the continuing safety of the participants enrolled in this study. The DSMB consists of members with expertise in Crohn's Disease trials and biostatistics; committee membership responsibilities, authorities, and procedures will be documented in its charter. After the review, the DSMB will make recommendations regarding the continuation of the study.

9.8. Use of Information and Publication

All information, including but not limited to information regarding OPTIM, supplied by the sponsor to the study site or investigator and not previously published, and any data or analysis generated as a result of this study, are considered confidential and remain the sole property of the sponsor. Study site and investigator shall not use this information except in the performance of this study and shall not disclose this information to anyone except to persons involved in the study that need such information to assist in conducting the study, and then only on like terms of confidentiality and non-use.

Study site and investigators shall not publish study results except as required by law or as specified in a separate, written agreement between the sponsor and the study site or investigator. The Sponsor will register the study and publish the study results in compliance with applicable law and may register the study or publish study results when not required.

Authorship of any peer-reviewed publications will be determined by mutual agreement in line with International Committee of Medical Journal Editors authorship guidelines.

In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the interim results of clinical studies as required by law. The disclosure of the study results will be performed after the end of study.

9.9. Data Quality Assurance

Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study site personnel before the study, and periodic monitoring visits by the sponsor. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for CRF completion will be provided and reviewed with study site personnel before the start of the study. The sponsor may review the CRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After uploading the data into the study database they will be verified for accuracy and consistency with the data sources.

9.10. Case Report Form Completion

CRFs are prepared and provided by the sponsor for each participant in electronic format. All data relating to the study must be recorded in the CRF. All CRF entries, corrections, and alterations must be made by the investigator or authorized study site personnel. The investigator must verify that all data entries in the CRF are accurate and correct.

The study data will be transcribed by study site personnel from the source documents onto an electronic CRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the participant's source documents. Data must be entered into the CRF in English. The CRF must be completed as soon as possible after a participant visit and the forms must be available for review at the next scheduled monitoring visit.

If necessary, queries will be generated in the eDC tool. If corrections to a CRF are needed after the initial entry into the CRF, this can be done in either of the following ways:

- Investigator and study site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study site personnel.

9.11. Source Documents

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of the assessment by the investigator of all AEs and follow-up of AEs; concomitant medication; intervention receipt/dispensing/return records; study intervention administration information; and date of study completion and reason for early discontinuation of study intervention or withdrawal from the study, if applicable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

An eSource system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If eSource is utilized, references made to the CRF in the protocol include the eSource system but information collected through eSource may not be limited to that found in the CRF.

9.12. Monitoring

The sponsor will use a combination of monitoring techniques remote, or on-site monitoring to monitor this study.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor may compare the data entered into the CRF with the source documents (eg, hospital/clinic/physician's office medical records); a sample may be reviewed. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and study site personnel and are accessible for verification by the sponsor study site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study site personnel. The sponsor expects that, during monitoring visits, the relevant study site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study site personnel will be available to provide an update on the progress of the study at the site.

9.13. On-site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Participant privacy must, however, be respected. The investigator and study site personnel are responsible for being present and available for consultation during routinely scheduled study site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator must immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

9.14. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRF and all source documents that support the data collected from each participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing

applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained. For trials performed under Regulation [EU] No. 536/2014, the sponsor and the investigator shall archive the content of the clinical trial master file for at least 25 years after the end of the clinical trial.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

9.15. Study and Site Start and Closure

First Act of Recruitment

The first subject screened is considered the first act of recruitment and it becomes the study start date.

Study/Site Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator

9.16. Definitions and Classifications of Safety Events, Product Complaints, and Criteria

9.16.1. Adverse Event Definitions

Adverse Event

An adverse event is any untoward medical occurrence in a patient administered a medicinal product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can be any unfavorable and unintended sign (including an abnormal finding or lack of expected pharmacological action), symptoms, or disease temporally associated with the use of a medicinal product, whether or not related to that medicinal product.

This includes any occurrence that is new in onset or aggravated in severity from the baseline condition, or abnormal results of any diagnostic procedures that are conducted per clinical practice.

For combination products with a device constituent, adverse events include those resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the device. It includes any adverse event resulting from use error or from intentional misuse of the device.]

Adverse Drug Reaction

An adverse drug reaction (ADR) is defined as a response to a medicinal product that is noxious and unintended. The phrase “response to a medicinal product” means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. The phrase “a reasonable possibility” means that there are facts, evidence, or arguments to support a causal association with the medicinal product.

An ADR, in contrast to an adverse event, is characterized by the fact that a causal relationship between the medicinal product and the occurrence is suspected. All adverse events are judged by either the reporting physician or the sponsor as having a reasonable causal relationship to a medicinal product qualify as ADRs.

Serious Adverse Event

A serious adverse event, based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use, is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product

- Is medically important*

* Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above.

Unexpected Adverse Events

An adverse event is considered unexpected if the nature or severity is not consistent with the applicable product reference safety information. The expectedness of an adverse event will be determined by whether or not it is listed in the applicable reference safety information

9.16.2. Product Quality Complaint Definition

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, reliability, or performance of a distributed product, including its labeling, drug delivery system, or package integrity. A PQC may have an impact on the safety and efficacy of the product. In addition, it includes any technical complaints, defined as any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or the drug delivery system.

This definition includes any PQC related to a device constituent in a combination product, including those used in the administration of the product. A device deficiency is an inadequacy of a device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate labeling.]

9.16.3. Attribution Definitions

Assessment of Causality

Assessment of the causal relationship between a medicinal product and an adverse event should be performed for all adverse events. The causal relationship can be one of the following:

Related

There is a reasonable causal relationship between administration of the medicinal product [or the product under study] and the adverse event.

Not Related

There is not a reasonable causal relationship between administration of the medicinal product [or the product under study] and the adverse event.

The term "reasonable causal relationship" means there is evidence to support a causal relationship.

9.16.4. Severity Criteria

Where applicable, an assessment of severity grade will be made using the following general categorical descriptors:

Mild

Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate

Sufficient discomfort is present to cause interference with normal activity.

Severe

Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.
The participating physician should use clinical judgment in assessing the severity of events not directly experienced by the patient (eg, laboratory abnormalities).