Clinical Study Protocol

EMINENT CD

Efficacy of MIrikizumab to achieve transmural healing in patiENTs with Crohn's Disease

GETAID-2025-02

EUCT Number: 2025-521889-95-00

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Sponsor: Groupe d´Etude Thérapeutique dans les Affections Inflammatoires Digestives (GETAID)

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TABLE OF PROTOCOL VERSIONS

Reference	Version	Date	CTIS approval	Status
Initial protocol	V1.1	14/01/2026	05/02/2026	Authorized
MS1	V2	09/03/2026	18/05/2026	Authorized

PROTOCOL SIGNATURE PAGE

Sponsor

Groupe d'Etude Thérapeutique des Affections Inflammatoires Digestives (GETAID)

President: Pr David LAHARIE

Date_____ Signature _____

Coordinator Investigator : Pr Anthony BUISSON

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

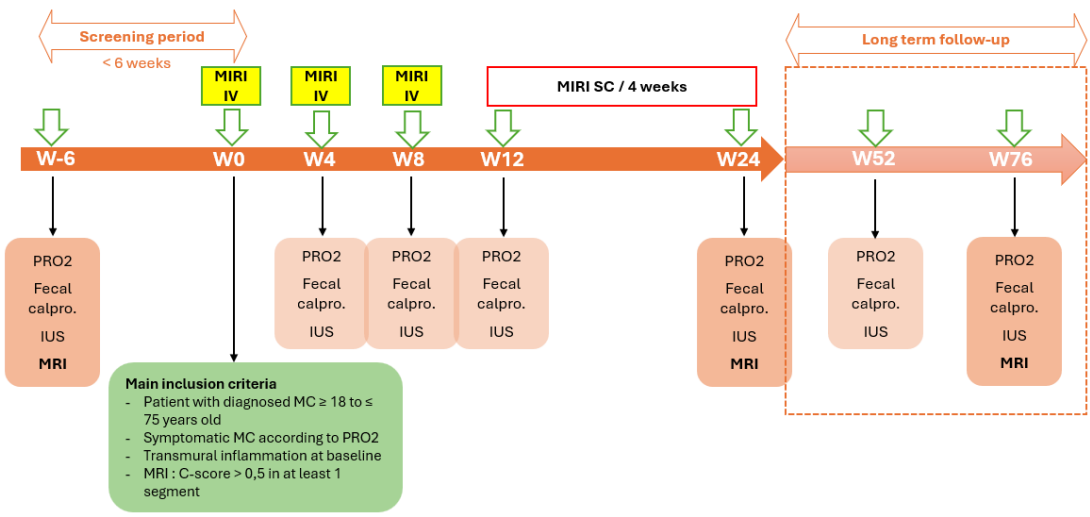
AE	Adverse Event
CD	Crohn's Disease
DO	Drop out
DSMB	Data and Safety Monitoring Board
e-CRF	Electronic Case Report Form
GCP	Good Clinical Practice
GETAID	Group d'Etude Thérapeutique dans les Affections Inflammatoires Digestives
IBD	Inflammatory Bowel Disease
ICH	International Conference on Harmonization
ICF	Informed Consent Form
IRB/IEC	Independent Review Board/ Independent Ethics Committee
ITT	Intent To Treat
PP	Per Protocol
SAE	Serious Adverse Event
SUSAR	Suspected Unexpexted Serious Adverse Reaction

TABLE OF CONTENTS

1. SYNOPSIS

Title	Efficacy of MIrikizumab to achieve traNsmural healing in patiENTs with Crohn's Disease: **EMINENT-CD study.**
Phase	Phase 4
Design	Therapeutic open-label prospective study
Sponsor	Groupe d'étude des affections inflammatoires digestives (GETAID) 50, rue Richer, 75009 Paris, France
Protocol number	GETAID-2025-02
EUCT number	2025-521889-95-00
Principal investigator	Pr Anthony BUISSON MD PhD CHU de Clermont-Ferrand, 58 rue Montalembert, 63000 Clermont-Ferrand
Protocol version	V2 dated 09/03/2026
Eligibility criteria	**Inclusion criteria** - Patients with CD - ≥ 18 years-old ≤ 75 years old - Symptomatic CD according to PRO-2 (stool > 3 or abdominal pain score > 1) - Transmural inflammation on baseline MRI (C-score > 0.5 in at least one segment) **Exclusion criteria** - Prior exposure to anti-p19 biological therapy - Exposure to more than 1 class of advanced therapies at a dose approved for the treatment of Crohn's disease (janus kinase [JAK] inhibitors, infliximab, adalimumab, certolizumab pegol, vedolizumab, ustekinumab, or approved biosimilars for these agents - Contra-indication to mirikizumab - Definitive ostomy - Colectomy with IPAA - Isolated or uncontrolled perianal lesions - Severe obstructive symptoms - Intra-abdominal abscess - Contra-indication to MRI - No health insurance - Pregnant or lactating women. Women of childbearing potential should use an effective method of contraception during treatment and for at least 10 weeks after treatment - Patients already included in biomedical research other than an observational study (*e.g.,* registry, cohort) - Concomitant *Clostridioides difficile* infection - HIV infection

	- Patient under guardianship, curatorship or safeguard of justice
Objectives	**Primary objective** To describe the efficacy of mirikizumab therapy to achieve transmural response in patients with CD. **Secondary objectives** To describe the efficacy of mirikizumab therapy to achieve the combination of clinical remission and transmural response in patients with CD. To describe the efficacy of mirikizumab therapy to achieve transmural healing in patients with CD. To assess the efficacy of mirikizumab on bowel urgency. To assess the kinetics of transmural response or healing in patients with CD treated with mirikizumab. To search for predictors of transmural healing/response in patients treated with mirikizumab. To assess clinical and biochemical efficacy of mirikizumab therapy. To assess the clinical and biochemical efficacy time of mirikizumab therapy. To assess drug retention over time. To evaluate the impact of mirikizumab therapy to prevent bowel damage progression. To evaluate the impact of mirikizumab therapy on disability. To evaluate the impact of mirikizumab therapy on quality of life. To evaluate the acceptability of mirikizumab therapy. To assess the safety of mirikizumab. To assess the correlation between PRO-2, bowel urgency, faecal calprotectin level, CRP, and transmural activity. **Exploratory objectives** To validate the "TRENCH" definition of transmural healing To assess modifications of intestinal microbiota
Endpoints	**Primary endpoint** Transmural response (TR25): decrease of at least (>=) 25% of C-score in each and all active segment from baseline to week 24 **Secondary endpoints** • Composite endpoint combining clinical remission and transmural response (TR25) at 6 months: ○ Clinical remission will be defined according to PRO-2 ○ Transmural response will be defined as a decrease of at least 25% of C-score in each active segment at baseline

	• Improvement or normalization of bowel urgency according to UNRS and Urgent score BU clinical meaningful improvement was defined as decrease of >=3 points • BU Remission was defined as UNRS =<2 • Transmural response (TR50): decrease of at least 50% of C-score in each active segment at baseline • Transmural healing: C-score < 0.5 in each active segment at baseline/TRENCH definition • Complete transmural healing: C-score = 0 in each active segment at baseline • MaRIA at 6 months • IUS transmural response/healing at week 4,8, 12 and 24 • Bowel damage (Lemann Index) at 6 and 18 months • Clinical response and remission at week 4,8, 12 and 24 • Biochemical remission at week 4,8, 12 and 24 • Drug retention • IBD-disability index, IBD disk • IBDQ • 10 points-Acceptability numerical scale (ANS) • Adverse events and severe adverse events **Other/Exploratory endpoints** • Alternative definitions of transmural healing/response • Microbiota modifications (α and β-diversity, metagenomic…)
Study treatment and procedure	Mirikizumab will be used as scheduled in the drug label: induction with IV infusions (900 mg) at week 0, week 4 and week 8 For clinical responders and non-responders: SQ injections (300 mg) at week 12 and every 4 weeks 

Number of subjects	No data is currently available on the expected rate of our primary endpoint (transmural response) in patients with CD treated with mirikizumab. However, in the DEVISE project, transmural response (TR25) was achieved in 47.8% in a cohort of 64 patients treated with anti-TNF agents (including 67.4% of bio-naïve patients). Owing to the promising results of mirikizumab in both bio-naïve and anti-TNF-exposed patients, we expect that the rate of TR25 in our study will be at least 40-50%. With 67 patients analyzed, the 95% confidence interval will be [28.5-53.0] if the primary endpoint was achieved in 40% of the patients. To consider potential loss of follow-up (< 10 %), we suggest enrolling 75 patients to ensure that approximately 67 patients complete week 24.
Study timelines	Study start: April 2026 Inclusion period: 12 months (April 2026 – April 2027) Study duration per participant: 18 months Follow-up period: - 1,5 years for primary endpoint - 2,5 years for long-term data Total study duration : 30 months. Planned study completion (LPLV): October 2028

2. BACKGROUND AND STUDY RATIONALE

2.1. Latest state of scientific knowledge

Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD) that can highly alter patients' quality of life[1] and lead to bowel damage[2,3] due to its transmural pattern. The current guidelines recommend using treat-to-target strategies to achieve the combination of steroid-free clinical remission and endoscopic remission[4]. However, the implementation of these strategies and endpoints are limited by the need for repeated colonoscopies, which dramatically reduced patients' acceptability and adherence to such a management[5].

Magnetic Resonance Imaging (MRI) could be an attractive alternative due to its better patients' acceptability than endoscopy[5]. MRI enables by itself a concomitant evaluation of both small bowel and colon, a transmural assessment of bowel inflammation, and the detection of CD-related complications (stricture, fistula). In the last decade, MRI showed its reliability and accuracy to detect disease activity[6]. Thus, the concept of transmural healing has emerged as a promising therapeutic target. It has been associated with longer time spent in steroid-free clinical remission, decreased risk of hospitalization, slower progression of bowel damage and reduced risk of subsequent surgery[7–13]. Furthermore, recent works suggested that transmural healing could lead to better outcomes, such as prevention of bowel damage progression, than endoscopic remission[8,11–13]. However, despite this accumulation of arguments, the recent international guidelines STRIDE 2 did not recommend its use in daily practice[4]. Based on statements from Sandborn and colleagues considering that the ideal treatment goal in any chronic disease was one that is clearly defined, achievable with medical or surgical therapy, predictive of long-term outcomes, affordable, non-invasive and relevant across disease subtypes, with a low test-to-test variability[14], we identified that the two main scientific missing characteristics to retain transmural healing as the best therapeutic target in CD were the lack of consensual definition and insufficient evidence of being reachable with the current medications.

Thanks to the DEVISE-CD project, we built and validated a dedicated score to assess transmural response (TR) and transmural healing (TH) in patients with CD, so-called C-score

(or modified Clermont score for assessing transmural therapeutic efficacy in Crohn's disease), and confirmed that these definitions of TR and TH are associated with improved outcomes. Moreover, we reported that more than 40 % of patients achieved transmural response after anti-TNF therapy. In parallel, the TRENCH project from GETAID aims to provide a consensual definition of transmural healing in CD.

Despite all this accumulated data, the potential of achieving transmural response or transmural healing with advanced therapy remains poorly investigated hitherto.

Mirikizumab is an anti-IL23 demonstrating a high level of efficacy in patients with CD compared to placebo or active comparator such as Ustekinumab. However, the efficacy of mirikizumab to achieve transmural response or transmural healing remains to be explored.

2.2. Statement of assumptions and objectives

No data is currently available on the expected rate of our endpoint (transmural response) in placebo patients with CD. However, in the DEVISE project, transmural response (TR25) was achieved in 47.8% in a cohort of 64 patients treated with anti-TNF agents (including 67.4% of bio-naïve patients)(1). As mirikizumab is a highly effective advanced therapy in patients with CD, we expect that our endpoint will be achieved by between 33% to 50% of patients treated with mirikizumab. The objective is to assess how frequently patients taking mirikizumab can achieve transmural response.

This clinical trial will be conducted per this present protocol, ICH, GCP and local regulatory requirements.

2.3. Summary of foreseeable and known benefits and risks for those undergoing research

Benefits:

Direct: Patients will have access to an anti-IL23 before its availability in daily practice in France.

Indirect: The data generated will improve scientific knowledge that could lead to better management of patients with CD.

Risks:

The safety profile of mirikizumab has been already investigated and no strong negative signal has been reported. However, the main adverse events are infections and mild elevation of liver enzymes.

3. STUDY OBJECTIVES

3.1. Primary objective

To describe the efficacy of mirikizumab therapy to achieve transmural response in patients with CD.

3.2. Secondary objectives

- To describe the efficacy of mirikizumab therapy to achieve the combination of clinical remission and transmural response in patients with CD.
- To describe the efficacy of mirikizumab therapy to achieve transmural healing in patients with CD.
- To assess the efficacy of mirikizumab on bowel urgency.
- To assess the kinetics of transmural response or healing in patients with CD treated with mirikizumab.
- To search for predictors of transmural healing/response in patients treated with mirikizumab.
- To assess clinical and biochemical efficacy of mirikizumab therapy.
- To assess the clinical and biochemical efficacy time of mirikizumab therapy.
- To assess drug retention over time.
- To evaluate the impact of mirikizumab therapy to prevent bowel damage progression.
- To evaluate the impact of mirikizumab therapy on disability.
- To evaluate the impact of mirikizumab therapy on quality of life.
- To evaluate the acceptability of mirikizumab therapy.
- To assess the safety of mirikizumab.

- To assess the correlation between PRO-2, bowel urgency, faecal calprotectin level, CRP, and transmural activity.

Exploratory objectives

- To validate the "TRENCH" definition of transmural healing
- To assess modifications of intestinal microbiota

4. TRIAL END POINTS

4.1. Primary end point

Transmural response (TR25): decrease of at least (>=) 25% of C-score in each and all active segments from baseline to week 24.

4.2. Secondary end points

- Composite endpoint combining clinical remission and transmural response (TR25) at 6 months
  - Clinical remission will be defined according to PRO-2
  - Transmural response will be defined as a decrease of at least 25% of C-score in each active segment at baseline
- Improvement or normalization of bowel urgency according to UNRS and Urgent score
- BU clinical meaningful improvement was defined as decrease of >=3 points; BU Remission was defined as UNRS =<2
- Transmural response (TR50): decrease of at least 50% of C-score in each active segment at baseline
- Transmural healing: C-score < 0.5 in each active segment at baseline/TRENCH definition
- Complete transmural healing: C-score = 0 in each active segment at baseline
- MaRIA at 6 months
- IUS transmural response/healing at week 4,8, 12 and 24
- Bowel damage (Lemann Index) at 6 and 18 months
- Clinical response and remission at week 4,8, 12 and 24

- Biochemical remission at week 4,8, 12 and 24
- Drug retention
- IBD-disability index
- IBDQ
- 10 points-Acceptability numerical scale (ANS)
- Adverse events and severe adverse events

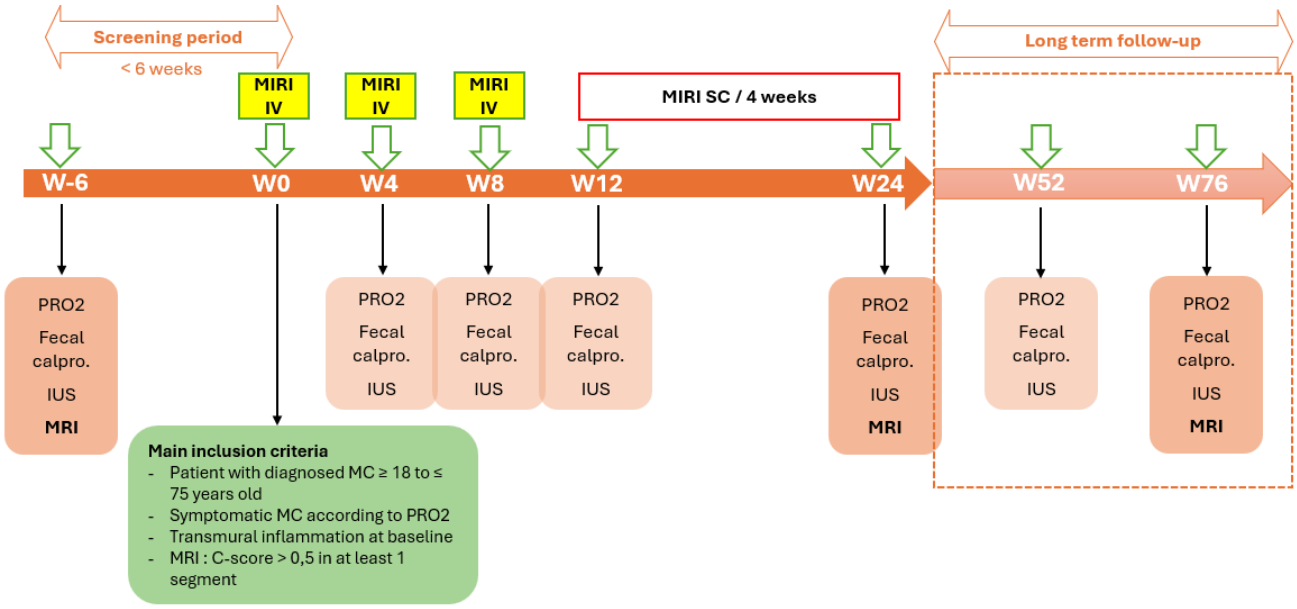
Exploratory endpoints

- Alternative definitions of transmural healing/response
- Microbiota modifications (α and β-diversity, metagenomic…)

5. STUDY DESIGN

EMINENT CD is a multicenter therapeutic open-label prospective study for patients with Crohn's disease.

Patients meeting the inclusion and non-inclusion criteria may be included in the study. After a screening period where they will perform various examinations (MRI, intestinal ultrasound (IUS), fecal calprotectin testing and assessment of the PRO2 score), they will receive mirikizumab intravenously at weeks 0, 4 and 8 (W0, W4 and W8) and will be monitored in accordance with current guidelines. All patients will continue mirikizumab subcutaneously every 4 weeks independently of W12 response as per label. The response to treatment will be assessed at week 24 (W24) according to the PRO2 score (stool ≤ 3 and abdominal pain score ≤ 1) as well as the C-score (reduction of at least 25% in the C score in each segment active initially). Based on VIVID 1 above 40% of patients presented with late response (week 12-24, data on file- UEGW 2025). Patients responding at week 24 will continue subcutaneous mirikizumab every 4 weeks while non-responding patients will exit the study.



As it is an open-label study, the primary endpoint includes objective evaluation of transmural response or healing that will be locally assessed by investigators on site.

The following data will be collected during the study:

- Age, gender, body mass index, smoking habits
- Montreal classification, disease duration, age at diagnosis
- Previous treatment for CD
- Clinical evaluation: PRO2 score, UNRS, URGENT index and patients-reported outcomes (abdominal pain score and number of bowel movements) from the daily symptoms calendar
- Biological data: blood cells count, CRP, albumin, fecal calprotectin level
- Imaging data (MRI and intestinal ultrasound): MRI and IUS parameters
- Acceptability numerical scale
- IBD questionnaires
- Concomitant treatments
- Adverse events

6. STUDY POPULATION

6.1. Number of participants

75 patients to be included in GETAID investigational sites.

6.2. Eligibility criteria

6.2.1. Inclusion criteria

- Patients with CD
- ≥ 18 to ≤ 75 years-old
- Symptomatic CD according to PRO-2 (stool > 3 or abdominal pain score > 1)
- Transmural inflammation on baseline MRI (C-score > 0.5 in at least one segment)

6.2.2. Exclusion criteria

- Prior exposure to anti-p19 biological therapy
- Exposure to more than 1 class of advanced therapies at a dose approved for the treatment of Crohn's disease (janus kinase [JAK] inhibitors, infliximab, adalimumab, certolizumab pegol, vedolizumab, ustekinumab, or approved biosimilars for these agents
- Contra-indication to mirikizumab
- Definitive ostomy
- Colectomy with IPAA
- Isolated or uncontrolled perianal lesions
- Severe obstructive symptoms
- Intra-abdominal abscess
- Contra-indication to MRI
- No health insurance
- Pregnant or lactating women. Women of childbearing potential should use an effective method of contraception during treatment and for at least 10 weeks after treatment
- Patients already included in biomedical research other than an observational study (*e.g.,* registry, cohort)
- Concomitant *Clostridioides difficile* infection

- HIV infection
- Patient under guardianship, curatorship or safeguard of justice

6.3. Concomitant medications

6.3.1. Permitted medications

According to study treatment, study procedure, study arm and study disease the permitted treatments are:

- Thiopurines or methotrexate at stable dose for at least 3 months
- Other medications according to medical situations (non-CD related) that are not influencing the results of the study
- Oral steroids will be allowed (dose ≤ 20 mg) with stable dose within the two weeks before inclusion. Forced tapering will be scheduled to obtain steroids weaning at W4

6.3.2. Prohibited medications

According to study treatment, study procedure, study arm and study disease the prohibited treatments are:

- IV steroids will be not authorized during the study
- Other advanced therapy (JAKi, anti-TNF, ustekinumab, vedolizumab, S1P modulators) including other IBD investigational drugs within 4 weeks before starting mirikizumab and during the study
- Other immunosuppressants (ciclosporin, tacrolimus, mycophenolate mofetil…) within 4 weeks before starting mirikizumab and during the study
- Any other drug that potentially impacts the study results

7. DESCRIPTION OF THE STUDY VISITS

A particular effort will be made to make sure that the patients will complete the symptom calendar and bring stools samples at each visit to reduce the risk of attrition bias. In addition, the primary endpoint will be evaluated at W24 to limit the number of follow-up losses. We will use an electronic case report form (eCRF) with a pragmatic design and incentive strategies to maximize complete registration to minimize the occurrence of missing data.

7.1. Screening period – W-6 to W0

The screening visit will take place after the decision by the investigator to introduce a new biological treatment to the patient. During this visit, the investigator will inform the patient and answer all the questions regarding the purpose, nature of the constraints, foreseeable risks and the expected benefits of the research. The investigator also specifies the patient's rights in the context of a study and checks the eligibility criteria. He will then give a copy of the information note and the consent form to the patient.

After this information session, the patient must have a reflection period. The inclusion can be done on the same day if the patient has had sufficient time to think, all his questions answered appropriately and has signed his informed consent prior to entry into the trial. The investigator must confirm that the patient meets all inclusion criteria and none of the exclusion criteria.

- Information about the protocol
- Checking the inclusion and exclusion criteria
- Checking the contra-indication to mirikizumab
- Blood pregnancy test for women of childbearing age. Women of childbearing potential should use an effective method of contraception during treatment and for at least 10 weeks after treatment
- Consent signature
- MRI (assessment of C-score)
- Intestinal ultrasound
- PRO2 score assessment
- Stool collection (faecal calprotectin and sample collection)
- Blood collection (classic assessment and sample collection)
- Report on concomitant treatments

7.2. Inclusion visit – W0

This visit must be performed by an investigator of the study; he must collect the informed consent form signed by both parties (patient and investigator).

The patient will be hospitalized for the day to start the treatment, during the visit the following assessment must be conducted to fill in the eCRF:

- Checking the inclusion and exclusion criteria
- Checking the contra-indication to mirikizumab
- Collection of demographic data
- Clinical assessment by gastroenterologist including PRO2 score, UNRS, URGENT index for bowel urgency, and delivery of symptoms calendar to the patients (each patient will report daily on this calendar the presence of abdominal pain and the number of stools)
- Quality of life assessed by IBD questionnaires
- IV treatment administration
- Report of concomitant treatments
- Report of adverse events

7.3. V1 – W4 (+/- 7 days)

This visit must be performed by an investigator of the study. The patient will be hospitalized for the day to receive the treatment, during the visit the following assessment must be conducted to fill in the eCRF:

- Clinical assessment including PRO2 score, UNRS, URGENT index for bowel urgency,
- Blood collection (including albumin, CRP and two tubes for identification of blood predictors of treatment efficacy)
- Stool collection (faecal calprotectin and identification of faecal predictors of treatment efficacy)
- Intestinal ultrasound
- Acceptability of drug regimen (numerical scale from 0 to 10)
- IV treatment administration
- Report of concomitant treatments
- Report of adverse events

7.4. V2 – W8 (+/- 7 days)

This visit must be performed by an investigator of the study. The patient will be hospitalized for the day to receive the treatment, during the visit the following assessment must be conducted to fill in the eCRF:

- Clinical assessment including PRO2 score, UNRS, URGENT index for bowel urgency,
- Blood collection (including albumin, CRP and two tubes for identification of blood predictors of treatment efficacy)
- Stool collection (faecal calprotectin and identification of faecal predictors of treatment efficacy)
- Intestinal ultrasound
- Acceptability of drug regimen (numerical scale from 0 to 10)
- IV treatment administration
- Report of concomitant treatments
- Report of adverse events

7.5. V3 – W12 (+/- 7 days)

This visit must be performed by an investigator of the study. The patient will be hospitalized for the day to receive the treatment, during the visit the following assessment must be conducted to fill in the eCRF:

- Clinical assessment including PRO2 score, UNRS, URGENT index for bowel urgency,
- Symptoms calendar recovery
- Blood collection (including albumin, CRP and two tubes for identification of blood predictors of treatment efficacy)
- Stool collection (faecal calprotectin and identification of faecal predictors of treatment efficacy)
- Acceptability of drug regimen (numerical scale from 0 to 10)
- Quality of life assessed by the IBD questionnaire
- Intestinal ultrasound

- SC treatment administration. During this visit, the patient will also be trained for his subcutaneous self-injection. The site will prepare and give the patient their prescription for the next SC injections at visits in W16, W20 and W24.
- Report of concomitant treatments
- Report of adverse events

7.6. V4 – W16 (+/- 7 days) and V5 – W20 (+/- 7 days)

This visit must be performed by an investigator of the study.This visit can be conducted on site or by phone. During the visit the following assessment must be conducted to fill in the eCRF:

- SC treatment administration
- Report of concomitant treatments
- Report of adverse events

7.7. V6 – W24 (+/- 7 days)

This visit must be performed by an investigator of the study. The patient will come on site, during the visit the following assessment must be conducted to fill in the eCRF:

- Clinical assessment including PRO2 score, UNRS, URGENT index for bowel urgency
- Symptoms calendar recovery
- Blood collection (including albumin, CRP and two tubes for identification of blood predictors of treatment efficacy)
- Stool collection (faecal calprotectin and identification of faecal predictors of treatment efficacy)
- Acceptability of drug regimen (numerical scale from 0 to 10)
- Quality of life assessed by the IBD questionnaire
- MRI (assessment of C-score)
- Intestinal ultrasound
- SC treatment administration. The site will prepare and give the patient their prescription for the next SC injection at visit in W52.
- Report of concomitant treatments

- Report of adverse events

7.8. V7 – W52 (+/- 7 days)

This visit must be performed by an investigator of the study. The patient will come on site, during the visit the following assessment must be conducted to fill in the eCRF:

- Clinical assessment including PRO2 score, UNRS, URGENT index for bowel urgency
- Symptoms calendar recovery
- Blood collection (including albumin, CRP and two tubes for identification of blood predictors of treatment efficacy)
- Stool collection (faecal calprotectin and identification of faecal predictors of treatment efficacy)
- Acceptability of drug regimen (numerical scale from 0 to 10)
- Quality of life assessed by the IBD questionnaire
- Intestinal ultrasound
- SC treatment administration. The site will prepare and give the patient their prescription for the next SC injection at visit in W76.
- Report of concomitant treatments
- Report of adverse events

7.9. V8 – W76 (+/- 7 days) – End of study

This visit must be performed by an investigator of the study. The patient will come on site, during the visit the following assessment must be conducted to fill in the eCRF:

- Clinical assessment including PRO2 score, UNRS, URGENT index for bowel urgency
- Symptoms calendar recovery
- Blood collection (including albumin, CRP and two tubes for identification of blood predictors of treatment efficacy)
- Stool collection (faecal calprotectin and identification of faecal predictors of treatment efficacy)
- Acceptability of drug regimen (numerical scale from 0 to 10)

- Quality of life assessed by the IBD questionnaire
- MRI (assessment of C-score)
- Intestinal ultrasound
- SC treatment administration
- Report of concomitant treatments
- Report of adverse events

The patients responding to the treatment will have access to study treatment for 3 years after the end of their participation to the study, see section 8.2.

Women of childbearing potential should use an effective method of contraception during treatment and for at least 10 weeks after treatment

7.10. End of treatment visit

This visit will be conducted in case of premature withdrawal from the study, as a routine care consultation by an investigator of the study. Women of childbearing potential should use an effective method of contraception during treatment and for at least 10 weeks after treatment. During the visit the following assessment will be conducted to fill in the eCRF:

- Clinical assessment including PRO2 score, UNRS, urgent score for bowel urgency
- Symptoms calendar recovery
- Blood collection (including albumin, CRP and two tubes for identification of blood predictors of treatment efficacy)
- Stool collection (faecal calprotectin and identification of faecal predictors of treatment efficacy)
- Acceptability of drug regimen (numerical scale from 0 to 10)
- Quality of life assessed by the IBD questionnaire
- Intestinal ultrasound
- Report of concomitant treatments
- Report of adverse events

TABLE OF STUDY PROCEDURES PER VISIT

	Screening	V0	V1	V2	V3	V4	V5	V6	V7	V8	EOT
	W-6 à W0	W0	W4	W8	W12	W16	W20	W24	W52	W76	
Information*	X										
Medical history	X										
Inclusion criteria*	X	X									
Non-inclusion criteria*	X	X									
Signing of consent*	X										
Treatment administration (IV)*		X	X	X							
Treatment administration (SC)*					X	X	X	X	X	X	
Distribution of symptoms and compliance calendar *		X									
Review of symptoms calendar *			X	X	X			X	X	X	X
Clinical exam		X	X	X	X			X	X	X	X
Weight and height	X	X	X	X	X			X	X	X	X
PRO2 score, UNRS, URGENT index for bowel urgency *	X	X	X	X	X			X	X	X	X
Standard blood test	X		X	X	X			X	X	X	X
Standard stool analysis (fecal calprotectin)	X		X	X	X			X	X	X	X
Collection of biological samples for research (blood and stool) *	X		X	X	X			X	X	X	X
MRI	X							X		X	
C-score	X							X		X	
Abdominal ultrasound	X		X	X	X			X	X	X	X
IBDQ*		X			X			X			X
IBD-disability index		X			X			X			X
Numerical scale of acceptability *			X	X	X			X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X
Concomitant treatments	X	X	X	X	X	X	X	X	X	X	X

**: Research procedures*

8. END OF STUDY

The end of study is defined as the last participant's last visit.

The Investigators and/or the trial steering committee have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the Ethics Committee and Regulatory Authority within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved.

A summary report of the study will be provided to the Ethics committee and Regulatory Authority and will be publicly available within 1 year of the end of the study in accordance with the European Clinical Trial Regulation 536/2014.

8.1. Removal of Subjects from Therapy or Assessment

In accordance with the Declaration of Helsinki and ICH Clinical Guidelines, subjects will be free to withdraw from the study at any time if they wish so, for any reason specified or unspecified.

8.1.1. Patient replacement

No patient replacement procedure is applied in this study

8.1.2. Follow up for withdrawn patients and type of date to be collected

Adverse events up to one month after study withdrawal should be reported to study sponsor.

Study subject participation can be discontinued due to:

- Withdrawal of subject consent, or loss to follow-up, or inability to remain under medical observation including post study examination,
- Non-compliance or major deviation from the protocol when in the opinion of the Investigator, continuation of the study would not be in the interest of the subject,
- SAE occurrence,
- Any other situation when in the opinion of the Investigator, continuation of the study would not be in the interest of the subject,

- Study termination by GETAID.

The reason for withdrawal will have to be recorded in the CRF for all withdrawn subjects.

The CRF must be completed up to the time of drop-out. All drop-outs after the first intake of investigational product should be given a post-study assessment as appropriate. The premature termination form in the CRF must be completed for all drop-outs.

All data, including any drug concentrations from any withdrawn subject, must be included in the final report. These data will only be evaluated if both the Sponsor and the Investigator agree that it is valid to do so.

Subjects withdrawn because of adverse experiences will undergo a physical examination and laboratory tests planned at the follow-up visit. A follow-up of AEs will also be undertaken for withdrawn subjects.

When possible the demographics information and selection criteria not met should be collected from patients if screenfailure.

8.2. CONTINUATION OF DRUG FOLLOWING THE END OF STUDY

At the end of the study, patients and investigators will have the option to continue the mirikizumab therapy for a duration of 3 years after the end of study, in accordance with the contract signed between the GETAID and Eli Lilly.

In addition to the study intervention discontinuation requirements in Section 8.1.2, the following also apply to the CA Period of 3 years:

- A safety concern assessed by investigator as being related to study intervention, that should result in drug discontinuation.
- Loss of response as assessed by the investigator.
- Investigator or sponsor’s assessment based on current evidence that an alternative treatment is an acceptable option.
- Investigator’s assessment that another clinical trial is appropriate for the participant.
- Investigator or sponsor’s periodic reassessment of continued access need based on current environmental and local treatment landscape.

- Mirikizumab is locally commercially available and reimbursable (this includes patient access programs when and where available).
- Once a participant stops the Continued Access Period, they would not be eligible to resume, and continued access will be stopped if commercialization of mirikizumab is not pursued in any markets worldwide for the indication in this protocol.

9. INVESTIGATIONAL MEDICINAL PRODUCT: MIRIKIZUMAB

9.1. IMP description

Mirikizumab is a biological therapy belonging to the class of anti-IL23, targeting specifically the p19 subunit of IL23.

Mirikizumab will be used as scheduled in the drug label: induction with IV infusions (900 mg) at week 0, week 4 and week 8. For clinical responders and non-responders: SC injections (300 mg) at W12 and every 4 weeks

Lilly company will supply the experimental drug (mirikizumab) for the purpose of the study.

Treatment adherence will be checked and recorded in the e-CRF.

For any additional information see *Summary of Product Characteristics.*

9.2. Packaging and labelling

Mirikizumab is given by Eli Lilly in its commercial packaging.

The relabelling in accordance with GCP and pharmacy manual will be performed by investigative sites Pharmacists.

Myonex will be responsible for storing and delivering the drug to the pharmacists' sites.

9.3. Drug supply process

At W0, W4 and W8, each subject will be administered mirikizumab infusion according to the SmPC. A specific clinical trial order signed by a clinical study investigator will be sent to the hospital pharmacy where the study drug will be prepared and dispensed. For all other study visits, the

investigator will write a prescription for mirikizumab syringes for subcutaneous administration, which will be dispensed by hospital pharmacies in the clinical investigation departments.

The drug supply process is described in the Pharmacy manual.

9.4. Treatment compliance and drug accountability

The Sponsor will supply the clinical Investigators with the study drugs and other clinical drug supplies as agreed, upon for the timely completion of the clinical study described above. The study drug will be delivered by Myonex to the study sites.

The study drugs will be dispensed only under the restricted conditions defined in the present protocol.

Upon receipt of the study drugs, the Investigator or the pharmacist will send to the sponsor the corresponding acknowledgement of receipt form. This form must be duly filled (including the date of receipt) and signed by the pharmacist or the Investigator. A drug movement form of all medication dispensed during the study will be maintained.

All investigational materials (medication and packaging) unused in the study will be destructed on site before or at the termination of the study, and pharmacist will send to GETAID an accountability form documenting:

- all administered units,
- all unused treatments,
- all destructed units at the end of the study, and the date of destruction.

10. LABORATORY TESTS

The tests required during the protocol are all considered standard of care and will be performed at the local labs of sites.

Sample collection:

- Blood: Samples serum (1 tube of 5 ml of blood collected at each visit will be centrifuged and the serum will be divided into 2 aliquots of 2 ml) will be frozen at -80°C and stored in each

center for the duration of the study for identification of blood predictors of treatment efficacy.

- Stool: Samples of stool (2 cryovials of 2 ml) collected at each visit will be frozen at -80°C and stored in each center for the duration of the study for analysis of the intestinal microbiota and for identification of predictors of treatment efficacy.

The procedure for sample preparation and storage are describe in a specific manual dedicated to laboratory requirements.

10.1. Central Lab

All laboratory tests will be done at the local hospital labs according to standard care. A list of normal values will be centrally collected. Furthermore, a serum sample, blood sample and stool sample for future assessment will be collected and stored locally. At the end of the study the remaining of the serum sample, blood sample and stool sample will be transferred and stocked for biological samples collection at Laboratory of:

Dr Stéphane Paul
Centre de Ressources Biologiques – CRB42 – Laboratoire d'Immunologie
CHU Saint Etienne - Boulevard Albert Raymond
42055 Saint Etienne, CEDEX 2

Biological samples will be kept at -80°C for 15 years. Patient Inform Consent is required and must be documented, by asking the patient to sign a specific Informed Consent Form for biological samples collection. If a patient disagrees to have his samples kept for the biological collection, the physician will inform the project team so that no sample is kept after the mandatory protocol analysis. This would not affect patient follow up in anyway.

11. STATISTICS

All statistical analyses will be performed with Stata software (version 15, StataCorp, College Station, USA) according to the guidelines of the International Conference on Harmonization-Good Clinical Practice guidelines.

Categorical or discrete data will be described by frequencies and percentages; continuous data will be described by means and standard-deviation or medians and interquartile range, according to statistical distribution (normality assessed by the Shapiro-Wilk test).

The baseline description of the patients included in the analysis will be carried out (according to recommendations). Protocol violations and protocol violations per patient, as well as reasons for study dropout will also be given. The number of patients enrolled, and the accrual curve will be presented. If suitable, the tests will be two-sided, with a type I error set at $\alpha = 0.05$.

11.1. Sample size calculation computation

As aforementioned, no data is currently available on the expected rate of our primary endpoint (transmural response) in patients with CD treated with mirikizumab. However, in the DEVISE project, transmural response (TR25) was achieved in 47.8% in a cohort of 64 patients treated with anti-TNF agents (including 67.4% of bio-naïve patients)[16]. Owing to the promising results of mirikizumab in both bio-naïve and anti-TNF-exposed patients[17], we expect that the rate of TR25 in our study will be at least 40-50%.

With 67 patients analyzed, the 95% confidence interval will be [28.5-53.0] if the primary endpoint was achieved in 40% of the patients.

To consider potential loss of follow-up (< 10 %), we suggest enrolling 75 patients to ensure that approximately 67 patients complete Week 24.

11.2. Statistical Analysis

Primary endpoint

For primary endpoint (transmural response, TR25), descriptive data will be expressed as % observed and applying NRI for discontinuations. Sensitivity analyses would be added to handle missing data. The result will be given considering all the enrolled patients but also after excluding the patients who did not.

Secondary endpoints

To describe the efficacy of the combination of clinical remission and transmural response, descriptive data will be expressed as % and related 95% confidence interval.

To search for predictors of transmural healing/response in patients treated with mirikizumab, univariate and multivariate analyses will be conducted considering center as a random effect. To assess clinical and biochemical efficacy of mirikizumab therapy, descriptive data will be expressed as % and related 95% confidence interval.

To evaluate the impact of mirikizumab therapy on disability and quality of life and to evaluate the acceptability of mirikizumab therapy, linear mixed model will be performed with center and patient as random effects. The normality of residuals will be analyzed using Shapiro-Wilk test. The results will be expressed using effect-sizes and 95% confidence intervals.

To assess the safety of mirikizumab, descriptive data will be expressed as % and related 95% confidence interval.

To assess modifications of intestinal microbiota, specific analyses based on discriminant factorial analyses (such as discriminant principal component analysis) will be conducted.

To study the correlations between symptoms, PRO-2, bowel urgency (UNRS, URGENT score), faecal biomarkers, transmural activity (C-score, MaRIA) in patients treated with mirikizumab following statistical tests will be performed: Student t-test or Mann-Whitney to compare continuous variables between independent groups, chi-squared or Fisher's exact tests for comparisons between categorical variables, and correlation coefficients (Person or Spearman according to the statistical distribution) for relationships between continuous variables. The analyses may be completed by multivariable analyses to consider center effect and other possible confounder variables.

Additional analysis details will be prespecified in the statistical analysis plan.

Method taking into account missing, unused or invalid data

The primary method will be observed case analysis. Sensitivity analysis for some of the binary endpoints will be performed where patients who discontinued therapy will be considered non-responders with additional details to be pre-specified in the SAP. If needed, additional analysis will then be performed to study the statistical nature of the missing data (missing at random or not) and if appropriate to carry out the other imputation approaches.

11.3. Data Collection

Senior data managers from GETAID will build the electronic CRF and will be responsible for the security and the quality of the data.

To meet regulatory requirements (Guidance for Computerized systems Used in Clinical Trials, International Conference on Harmonization, GCP 2001/20/CE), eCRF design, data monitoring and database extractions will be performed with Ennov Clinical software relative package (V8.2). Ennov Clinical is a secure, with integrated audit-trail, web-based software platform designed to support data capture for research studies.

A Data Validation Plan containing suitable coherence test to be performed will be done to clean up the data by identifying the discrepancies. Data blind reviews will define population analysis. A pharmacovigilance base reconciliation will be realized before based locked. No modification in the database is possible after the lock. But in case of a critical issue or for other important operational reasons, privileged users can modify the data even after the database is locked (Self-Evident-Corrections). This, however, requires proper documentation and an audit trail must be maintained with sufficient justification for updating the locked database. Data extraction is done from the final database after locking. Audit trail and database will be transmitted to the study sponsor for archiving purposes.

11.3.1. Data Monitoring

As described in the Monitoring Plan, the complete eCRFs sets will be received and reviewed by the Monitor to check protocol adherence and to detect any data inconsistency or discrepancy. Once corrections made and signed by the investigator and monitor data will be and all the requested modifications will be traced on Data Clarification Forms. Subject diary data will be reviewed by the study site to check protocol adherence and to detect any data inconsistency or discrepancy.

Once monitored, CRFs are not modified anymore, and all the requested modifications are traced on Data Clarification Forms.

11.3.2. Database set-up

The GETAID data management system and standard libraries are used to set up the database and design the screens.

11.3.3. Data Handling Manual

A Data Handling Manual is edited. This document contains the annotated CRF, the data validation plan (list of rules to be applied to validate the data) and the database structure.

This document is provided to Sponsor for approval before starting the double data entry process if any.

11.3.3.1 Data Validation

Automatic checks and listings are designed and performed according to the data validation plan. In case of missing values, out of range values, data inconsistencies or values that fail logical checks, Data Clarification Forms (queries) will be edited and forwarded to the Investigator for clarification. Inconsistencies found to be correct are documented on Data Clarification Form. Modifications performed on electronic study data are also fully tracked.

11.3.3.2 Data Coding

AEs will be coded using MedDRA terminology. The medical coding will be performed by a Data Manager and reviewed by the Investigator before being submitted to the Sponsor for approval.

11.3.3.3 Database Lock

Once validated, the database will be locked so that no more change will be possible on the frozen data.

12. SAFETY ASSESSMENTS

The Investigator is responsible for the detection and documentation of events meeting the criteria and definitions detailed below.

These tasks may also be delegated to a qualified member(s) of the research team. Assessment of events may be delegated to other suitably qualified physicians in the research team who are trained in recording and reporting adverse events (AEs).

Investigational Medicinal Product (IMP) is defined as any active substance or placebo being studied or used as a reference in the trial. This section also applies to medicinal products that are not the active substance or placebo, but are used as a concomitant medication to the IMP or as a

rescue/escape medicine for preventative, diagnostic or therapeutic reasons. These are referred to as non Investigational Medicinal Products (NIMPs).

Full details of contraindications and side effects that have been reported following administration of the IMP can be found in the relevant Summary of Product Characteristics (SmPC).

Participants will be instructed to contact their Investigator at any time after consenting to join the trial if any symptoms develop. All adverse events (AE) that occur after joining the trial must be reported in detail in the Case Report Form (CRF) or AE form. In the case of an AE, the Investigator should initiate the appropriate treatment according to their medical judgment. Participants with AEs present at the last visit must be followed up until resolution of the event.

12.1. Definitions

12.1.1. Adverse Events

Definition: An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a drug, whether the event is considered causally related to the use of the drug.

Worsening of a pre-existing condition or illness is considered an adverse event. An elective surgery/procedure scheduled to occur during a study, as part of the regular study disease treatment, will not be considered as a serious adverse event. If the surgery/procedure is being performed for another pre-existing condition and the surgery/ procedure has been pre planned prior to study entry this should not be considered as a serious adverse event. However, if a preexisting condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered as an adverse event and be evaluated as such. Laboratory abnormalities judged as clinically significant should be regarded as adverse event.

The investigator will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The investigator will assess and record any adverse event in

detail including the date of onset, description, severity, time course, duration and outcome, relationship of the adverse event to study drug, if known, and any action(s) taken.

12.1.2. Serious Adverse Events and significant events

If an adverse event meets any of the following criteria, it is regarded as serious adverse event (SAE) and should be reported within 24 hours of the site being made aware of the serious adverse event to the GETAID and the national Sponsor.

- **Death of Subject** An event that results in the death of a subject.
- **Life-Threatening** An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
- **Hospitalization** An event that results in an admission to the hospital for any overnight hospitalization. This does not include an emergency room visit or admission to an outpatient facility.
- **Prolongation of Hospitalization** An event that occurs while the study subject is hospitalized and prolongs the subject's hospital stay.
- **Congenital Anomaly** An anomaly detected at or after birth, or any anomaly that results in fetal loss.
- **Persistent or Significant Disability/Incapacity** An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
- **Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome** An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of

hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Significant Events may also be considered for expedited reporting.

- **Spontaneous or Elective Abortion** Miscarriage or **Elective abortion** performed on study subject.
- **Pregnancy:** Female subjects who become **pregnant** while participating in this study will be the subject of a notification to the coordinators within two weeks after notification of the pregnancy with the help of the « Pregnancy Initial Statement ». The pregnancy will result in the patient's withdrawal from the study, but a follow-up will continue until the pregnancy is carried to full term.

  The pregnancy follow-up will be recorded on a « Pregnancy Follow-Up » form, which will be sent to the investigator within 6 to 8 weeks following the presumed date of term. Pregnancy is not considered as an adverse event, but any complication such as spontaneous miscarriage or therapeutic interruption of the pregnancy will have to be considered as an adverse event.
- **Overdose:** any administration of a dose over the protocol dosage guidance**.**
- **Misuse:** any administration not following the protocol or drug SmPC.

In case the investigator knows about a serious adverse event after the patient withdrawal from the study, he must inform the sponsor as far as he considers the serious adverse event as related to the study treatment.

For all serious adverse events, the Serious Adverse Event Report Form must be filled and sent to GETAID and to the national Sponsor within 24 hours.

SERIOUS ADVERSE EVENTS MUST BE REPORTED TO:

GETAID Central Office

50 rue Richer, 75009 PARIS France

Tel: + 33 (0) 9 72 57 61 60 Fax: +33 1 84 10 85 45

sae@getaid.org

Qualified Person Pharmacovigilance: Marina NGUON

mnguon@getaid.org

By agreeing with this study procedures, the investigator commits himself to take these responsibilities.

12.2. Identifying AEs and SAEs

All AEs and SAEs will be recorded from the time a participant signs the consent form to take part in the study until one month after LPLV.

Participants will be asked about AEs/SAEs (description, severity, seriousness, causality, outcome) at every visit during the study

AEs and SAEs may also be identified via information from support departments e.g. laboratories.

Biological abnormalities (biochemistry, haematology, urinalysis) or abnormal results of exams (ECG, X-Ray…) considered as clinically significant by the investigator, must, if corresponding to the definition of an adverse event (serious or not), be recorded.

Biological abnormalities or abnormal exams regarded as clinically significant by the investigator are considered adverse event if they are detected after administration of the study drug or are present upon inclusion and worsen during study.

On the contrary, biological abnormalities or abnormal results of exams regarded as clinically significant by the investigator are not considered as adverse or serious adverse even if they are related to the disease under therapy, except if they are more severe than expected according to the patient's condition or are present before inclusion (or discovered at inclusion) and did not worsen during the study.

12.3. Definitions of Adverse Event Severity

The investigator will use the following definitions to rate the severity of each adverse event:

- **Mild** The adverse event is transient and easily tolerated by the subject.

- **Moderate** The adverse event causes the subject discomfort and interrupts the subject's usual activities.
- **Severe** The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

12.4. Relationship to Study Drug

The investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug:

- **Probably Related** An adverse event has a strong temporal relationship to study drug or recurs on re-challenge and other cause of event is unlikely or significantly less likely.
- **Possibly Related** An adverse event has a strong temporal relationship to the study drug and another cause of event is equally or less likely compared to the potential relationship to study drug.
- **Unlikely:** An adverse event for which an alternative explanation is more likely, e.g., concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Note: the term 'severe', used to describe the intensity, should not be confused with 'serious' which is a regulatory definition based on participant/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe.

12.5. ASSESSMENT OF AEs AND SAEs

The Investigator is responsible for assessing each AE.

This may be delegated to other suitably qualified physicians in the research team who are trained in recording and reporting AEs.

The Principal Investigator (PI) may not downgrade an event that has been assessed by an Investigator as an SAE but can upgrade an AE to an SAE, SAR if appropriate.

13. SAFETY COMMITTEE OR DATA SAFETY MONITORING BOARD *(NOT APPLICABLE)*

No monitoring committee is planned for the study in view of the expected adverse effects of Mirikizumab. But if any safety signal were to appear, a DSMB would be set up within a maximum of six months following the alert.

14. ORGANIZATIONAL, LEGAL AND GENERAL CONSIDERATIONS

14.1. Ethical Conduct of the Study

The trial will be carried out in accordance with the Declaration of Helsinki (Edinburgh, 2000) completed by Notes of Clarification to articles 29 (Washington, 2002) and 30 (Tokyo, 2004) respectively and revised in 2008 (Sixth version Seoul). The trial will also be conducted in compliance with the protocol, the ICH Guidelines for Good Clinical Practice (ICH E6), the European Clinical Trial Regulation 536/2014, and the applicable local country laws/regulations.

Written favourable opinion will be obtained from an Independent Ethic Committee (IEC) and the Competent Authority (CA) prior to the study being implemented.

The study will be conducted in accordance with International Guidelines on Good Clinical Practices (GCP) and Standard Operating Procedures (SOP) for clinical trial and documentation in force at GETAID.

The study will be monitored by a monitor designed by the GETAID who will regularly check compliance with the protocol, will compare selected key data in the CRF with its source data, and will verify Drug Accountability and Informed Consent.

14.2. Trial steering committee

This committee will monitor trial progress and conduct, and advice on scientific credibility and ethics issues. It will decide whether the trial needs to be stopped on grounds of safety and efficacy. This committee is composed of two European Crohn and Colitis Organisation representatives and one ethics advisor independent of the trial.

14.3. Submission to Ethics Committee and Health Authorities

This protocol complies with French regulations. Approval by the national and local Ethics Committee and Competent Authority will be required before study start. According to the local regulatory requirements:

- It is the Investigators' responsibility or the Sponsor's responsibility to obtain and maintain written approval of the final Study protocol, including the Patient Information and Informed Consent, from the appropriate Ethics Committee.
- It is the Investigators' responsibility or the Sponsor's responsibility to notify the Independent Ethics Committee (IEC) about any amendments to these documents. In case the protocol amendment changes the scope of the study or increases the risks of the study patients, the investigator or sponsor should wait for approval of this amendment by the Independent Ethics Committee before implementing the protocol amendment. The written approval and the approved versions of the documents and a list of the Ethics Committee members, their titles and occupations should be sent to the responsible study personnel at GETAID. The written approval should identify the study and document the date of review. The Investigators and the sponsor should file all correspondences with the Ethics Committee in the Site Investigator's File and Trial Master File, respectively.
- It is the investigator's responsibility or the Sponsor's responsibility to issue a final report to the Ethics Committee within 12 months after completion, termination or discontinuation of the study.

14.4. Compliance with Good Clinical Practices (GCP)

This clinical investigation will be conducted in accordance with Good Clinical Practices (GCP) as defined by standard ISO 14155:2020 and European Clinical Trial Regulation (EU) 536/2014. The study protocol, data collection procedures, and analyses will be designed to ensure the protection of the rights, safety, and well-being of the subjects participating in the study. All data will be recorded and presented in a manner that ensures their reliability and integrity, in compliance with current regulatory and ethical requirements.

14.5. Emergency procedures

The GETAID accepts the right of the Investigator to deviate from the protocol in an emergency when necessary to safeguard the life or the wellbeing of a study patient. The Investigator must inform the study personnel responsible at GETAID of any emergency deviations and justification for the deviation as quickly as possible after the episode, in any event no later than 24 hours after the emergency. According to the local regulatory requirements, the investigator or the sponsor must inform the Ethics Committees of any emergency deviations and justification for the deviation in the local regulatory timelines.

14.6. Study protocol amendment and study extension

Without a common agreement between all the investigators, national sponsors or the global sponsor GETAID, no alteration or modification of this protocol will be considered valid. In case of such an agreement the planned modifications will be subjected to an amendment linked with the protocol. Any protocol amendment must be notified by the coordinator to the Ethics Committees and Regulatory Authorities.

14.7. Study documents

Prior to initiation, the investigator will supply sponsor representatives with a copy of his personal curriculum vitæ, together with those of his co-investigators. He will commit himself to respect the protocol, local regulations, Helsinki Declaration terms, ICH and Good Clinical Practices.

The sponsor representatives will be supplied with a dated and signed copy of the latest study drug information (e.g SmPC, IB, …).

14.8. Patient information and patient informed consent form

Voluntary written Informed Consent Form (ICF) must be obtained from each subject prior to performing any study related procedures in compliance with the recommendations of the Declaration of Helsinki and ICH guidelines. Subject should not be screened or treated until the subject has signed an approved ICF written in a language that is understandable to the subject.

Each subject should be given both verbal and written information describing the nature and duration of the clinical study. The ICF should be signed and personally dated in 2 originals by the subject and the person who conducted the informed consent discussion. The Investigator, or the attending physician, will explain the nature, purpose and risks of the study. The subject will be informed that he has the right to withdraw at any time from the study, without giving reasons. In this condition, the subject will also be informed that he will not receive any indemnity according to applicable regulations. The informed consent process should take place under conditions where the subject has adequate time to consider the risks and benefits associated with his participation in the study.

The Investigator is responsible for assuring the appropriate content of the ICF and that informed consent is obtained from each subject in accordance with all applicable regulations and guidelines. The ICF will be reviewed and approved by the Sponsor and then submitted to the IEC.

Each subject should receive one original of the signed and dated written ICF and any other information provided for the subject.

The second original of the signed and dated ICF should be retained in the Investigator's file. The Investigator should maintain a log of all subjects who sign the ICF.

Patient Inform Consent is required and must be documented, by asking the patient to sign a specific Informed Consent Form for biological samples collection. If a patient disagrees with having his samples kept for the biological collection, the physician will inform the project team so that no sample is kept after the mandatory protocol analysis. This would not affect patient follow up in any way.

14.9. Data transcription

All information requested by the protocol must be supplied and explanation must be given for every missing entry. These data will be entered in the electronic case report form as soon as they are obtained. Source data will be neatly and legibly written with a black ball-point pen (to make duplication and computerization easier) in the source documents. Electronic hospital files will also be accepted if made available for monitoring. Each fully completed case report form will be dated and signed by the investigator, certifying thereby his agreement with reported data. As the study

goes along, the case report form will be reviewed by the clinical research assistant, who will review each correct entry and perform source data verification and validation.

14.10. Monitoring procedures

The investigator and co-investigators agree to welcome at regular intervals the GETAID monitors. After every visit, monitors will write a visit report and send a letter to the centre to address issues requiring follow up.

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, ethics committee review, and regulatory inspection(s). In the event of an audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

14.11. Responsibilities

GETAID is the main study sponsor. In accordance with the French law, GETAID signed an insurance policy with the RELYENCE group covering civil liability for potential damages that could happen to any subject involved in this research in France under agreement No 127.047.

National Sponsor shall secure and maintain at their own expense in full force and effect through the performance of the Study (and following termination of the Study to cover any claims arising from the Study) insurance coverage in amounts appropriate to the conduct of the Study and in conformance with applicable legal and regulatory requirements as well as comprehensive and professional liability insurance of reasonable policy limits for their own country.

All the information concerning the patients will be anonymized and covered by medical confidentiality. Data collected for the study will be computerized following the General Data Protection Regulation EU directive (May 2018).

Submission of Serious Adverse Events is the responsibility of the investigators who will report SAEs within 24 hours to the GETAID.

14.12. CNIL

This study is part of the "Reference Methodology" (MR-001) under the provisions of the Act of 3 May 2018 on the protection of individuals regarding the processing of personal data and amending Act of 6 January 1978 relating to computers, files and freedoms. GETAID, the study sponsor, has signed a commitment to comply with the "Reference Methodology" dated 20 April 2023.

15. AUTHORSHIP RULES

The GETAID publication charter will apply to the publication of any related study results.

16. STORAGE

The sponsor and the investigator retain the contents of the clinical trial master file for a period of twenty-five years after the end of the clinical trial. However, participants' medical records are kept in accordance with national law.

The contents of the clinical trial master file shall be kept in such a way that it can be easily made available to the competent authorities and can be accessed by them, upon request.

No destruction can be carried out without the agreement of the Promoter. At the end of the 25 years, the promoter will be consulted for destruction. All data, documents and reports are subject to audit or inspection.

17. FINAL STATEMENT

GETAID owns all data. No use and no transmission to a third party will be made possible without its prior consent.

18. STUDY TIME SCHEDULE

The study start is planned in April 2026

Inclusion period is 12 months, April 2026 – April 2027

Follow-up period is 1,5 years for primary endpoint and 2,5 years for long-term data

The total study duration will be 30 months.

19. REFERENCES

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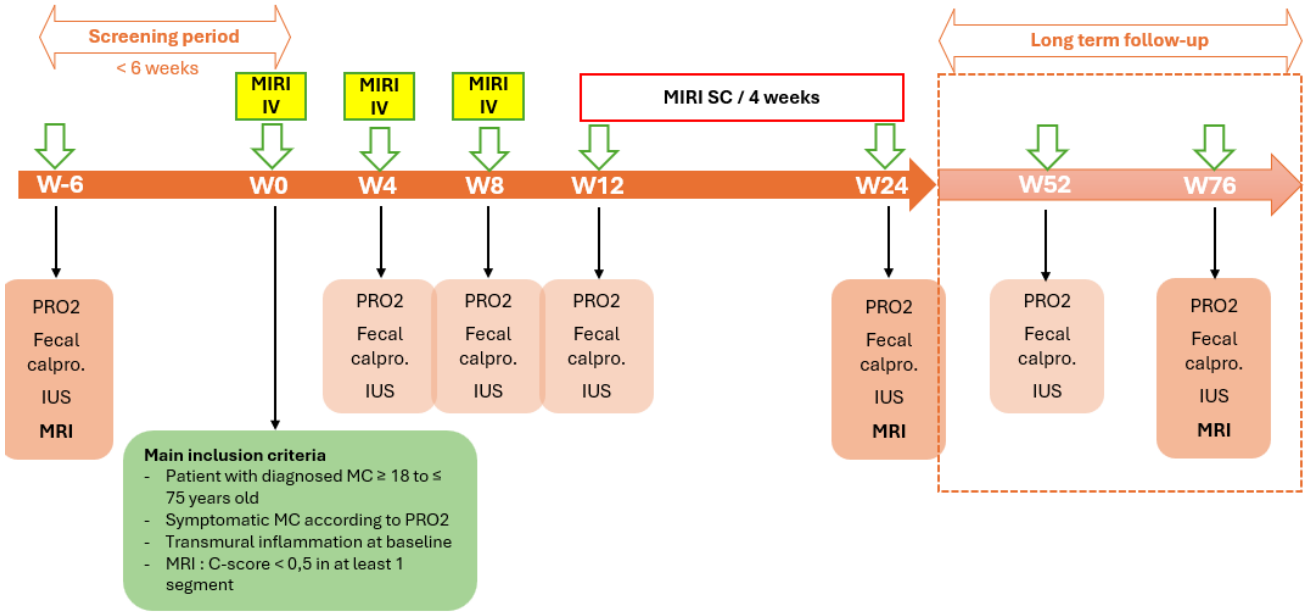
20. ANNEXES

Annex 1 : General outline of the study



Annex 2 : Study monitoring table

	Screening	V0	V1	V2	V3	V4	V5	V6	V7	V8	EOT
	W-6 à W0	W0	W4	W8	W12	W16	W20	W24	W52	W76	
Information*	X										
Medical history	X										
Inclusion criteria*	X	X									
Non-inclusion criteria*	X	X									
Signing of consent*	X										
Treatment administration (SC)*					X	X	X	X	X	X	
Distribution of symptoms and compliance calendar *		X									
Review of symptoms calendar *			X	X	X			X	X	X	X
Clinical exam		X	X	X	X			X	X	X	X
Weight and height	X	X	X	X	X			X	X	X	X
PRO2 score, UNRS, URGENT index for bowel urgency *	X	X	X	X	X			X	X	X	X
Standard blood test	X		X	X	X			X	X	X	X
Standard stool analysis (fecal calprotectin)	X		X	X	X			X	X	X	X
Collection of biological samples for research (blood and stool) *	X		X	X	X			X	X	X	X
MRI	X							X		X	
C-score	X							X		X	
Abdominal ultrasound	X		X	X	X			X	X	X	X
IBDQ*		X			X			X	X	X	X
IBD-disability index		X			X			X	X	X	X
Numerical scale of acceptability *			X	X	X			X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X
Concomitant treatments	X	X	X	X	X	X	X	X	X	X	X

**research procedures*

Annex 3 : Symptom calendar

N° identification du patient dans l'étude : _____

Centre : _____

Nombre de selles habituel (lorsque vous êtes en rémission ou avant la maladie) : _____

Dans les cases de dates appropriées du calendrier, veuillez fournir les 2 scores ci-dessous **chaque jour à partir du 1er jour de traitement** :

Fréquences des selles (S)
Veuillez indiquer le nombre de selles au cours des dernières 24 heures
Douleurs/ Crampes abdominales (A)
0 = Absent
1 = Légères – se font sentir mais tolérables
2 = Modérées – gênantes dans vos activités normales
3 = Sévères - intolérables

Par exemple :

Lundi	Mardi	Mercredi	Jeudi	Vendredi	Samedi	Dimanche
1 **S = 2** **A = 3**	2 **S = 2** **A = 1**	3 **S = 3** **A = 1**	4 **S = 2** **A = 1**	5 **S = 5** **A = 1**	6 **S = 2** **A = 1**	7 **S = 2** **A = 1**

Annex 4: PRO2

Variable	Description	Score
Selles liquides ou très molles	Moyenne du nombre de selles quotidiennes (liquides ou très molles) pendant 7 jours	I___I I___I
Douleur abdominale	Moyenne sur 7 jours de l'évaluation quotidienne des douleurs abdominales selon les critères suivants 0 = aucun, 1 = léger, 2 =modéré, 3 = grave	I___I

Annex 5: Questionnaire Besoins impérieux (Urgency NRS)

Quelle était la sévérité de votre besoin impérieux (besoin soudain ou immédiat) d'aller à la selle au cours des dernières 24 heures ? Veuillez cocher la case correspondant à la sévérité de ce besoin

0	1	2	3	4	5	6	7	8	9	10
Aucun besoin impérieux										Le pire besoin impérieux possible

Annex 6: IBD Disability Index

Les questions ci-dessous passent en revue différentes fonctions de votre corps et différentes activités de votre vie quotidienne. Lorsque vous répondrez à ces questions, vous devrez penser à la semaine passée en tenant compte aussi bien des bons jours que des mauvais jours. Répondez à ces questions en tenant compte de l'aide dont vous disposez. Merci

REPONSES : 0 = Très bon ; 1=Bon ; 2=Moyen ; 3=Mauvais ; 4=Très mauvais	0	1	2	3	4
État de santé général ; Santé physique et santé mentale					
1. Dans l'ensemble, comment trouvez-vous votre état de santé aujourd'hui ?					
REPONSES : **Aucun problème = 0 ; Problèmes légers = 1 ; Problèmes modérés = 2 ; Problèmes importants = 3 ; Problèmes extrêmement importants = 4**	0	1	2	3	4
Sommeil et énergie					
2. Globalement, au cours de la semaine passée, avez-vous rencontré des problèmes de sommeil (par ex. problèmes pour s'endormir, réveils nocturnes fréquents ou réveil trop matinal ? Et, si oui, de quelle ampleur ?					
3. Globalement, au cours de la semaine passée, avez-vous eu des problèmes parce que vous ne vous sentiez pas frais et dispos (fraiche et dispose) pendant la journée (par ex. sensation de fatigue, manque d'énergie) et, si oui, de quelle ampleur ?					
Humeur					
4. Globalement, au cours de la semaine passée, avez-vous rencontré des problèmes parce que vous vous sentiez triste ou déprimé(e) et, si oui, de quelle ampleur ?					
5. Globalement, au cours de la semaine passée, le fait de vous sentir inquiet ou anxieux (inquiète ou anxieuse) vous a-t-il posé des problèmes et, si oui, de quelle ampleur ?					
Image du corps					
6. Globalement, au cours de la semaine passée, votre apparence physique ou l'aspect de certaines parties de votre corps vous ont-ils posé des problèmes et, si oui, de quelle ampleur ?					
Douleurs Abdominales					
7. Globalement, au cours de la semaine passée, avez-vous ressenti des douleurs à l'estomac ou au ventre et, si oui, de quelle ampleur ?					
REPONSES : **Aucune difficulté = 0 ; Difficultés légères = 1 ; Difficultés modérées = 2 ; Difficultés importantes = 3 ; Difficultés extrêmement importantes/ impossibilité = 4**	0	1	2	3	4
Régulation de la défécation (fait d'aller à la selle)					
8. Globalement, au cours de la semaine passée, avez-vous rencontré des difficultés pour coordonner et gérer votre défécation (fait d'aller à la selle), notamment pour choisir un endroit approprié, vous y rendre et vous nettoyer ensuite et, si oui, de quelle ampleur ?					
9. Globalement, au cours de la semaine passée, avez-vous rencontré des difficultés pour prendre soin de votre santé au sens large (faire attention à votre santé, votre alimentation, votre activité physique, et votre confort) si oui, de quelle ampleur ?					
Activités sociales					
10. Globalement, au cours de la semaine passée, avez-vous rencontré des difficultés dans vos relations personnelles et, si oui, de quelle ampleur ?					
11. Globalement, au cours de la semaine passée, avez-vous rencontré des difficultés pour participer à la vie sociale et, si oui, de quelle ampleur ?					
Travail et éducation (veuillez répondre à la question 12a OU 12b en fonction de votre situation)					
12. a. Globalement, la semaine passée, avez-vous eu des difficultés pour travailler et /ou réaliser certaines activités à votre domicile (Tâches ménagères, bricolage, jardinage…) et, si oui, de quelle ampleur ?					
b. Globalement, au cours de la semaine passée, avez-vous rencontrez des difficultés à l'école ou dans vos études et, si oui, de quelle ampleur ?					
13. Nombre de selles liquides ou très molles par jour en moyenne lors des 7 derniers jours :	0	1	2	3	4
REPONSES : **Pas de selle liquide ou très molle durant les 7 derniers jours = 0** **1 selle liquide ou très molle par jour en moyenne lors des 7 derniers jours = 1** **2 selles liquides ou très molles par jour en moyenne lors des 7 derniers jours = 2** **3 selles liquides ou très molles par jour en moyenne lors des 7 derniers jours = 3** **≥ à 4 selles liquides ou très molles par jour en moyenne lors des 7 derniers jours = 4**					
14. Souffrez-vous d'arthrites ou d'arthralgies ?	0	NA	NA	NA	4
REPONSES : (NA : non applicable) **Non = 0** **Oui ou Probablement = 4**					

Annex 7 : IBDS Survey

QUESTIONNAIRE F-IBDQ

Le but de ce questionnaire est de nous permettre de savoir comment vous vous êtes senti(e) au cours des 2 dernières semaines. On vous demande de répondre à des questions sur les symptômes que vous avez eus du fait de votre maladie, sur la manière dont vous vous êtes senti(e) en général, ainsi que sur votre moral.

1. Quelle a été la fréquence de vos selles au cours des deux dernières semaines ? Indiquez la fréquence de vos selles au cours des deux dernières semaines en choisissant l'une des réponses suivantes :
1 SELLES AUSSI FREQUENTES OU PLUS FREQUENTES QUE JAMAIS
2 EXTREMEMENT FREQUENTES
3 TRES FREQUENTES
4 UNE AUGMENTATION MOYENNE DE LA FREQUENCE DES SELLES
5 UNE LEGERE AUGMENTATION DE LA FREQUENCE DES SELLES
6 UNE TRES LEGERE AUGMENTATION DE LA FREQUENCE DES SELLES
7 NORMALES, PAS D'AUGMENTATION DE LA FREQUENCE DES SELLES

2. Au cours des deux dernières semaines, la sensation de fatigue, d'épuisement ou la sensation d'être fourbu(e) vous a-t-elle posé problème ? Veuillez indiquer si cette sensation de fatigue ou d'épuisement a été un problème pour vous au cours des deux dernières semaines en choisissant l'une des réponses suivantes :
1 TOUT LE TEMPS
2 PRESQUE TOUT LE TEMPS
3 ASSEZ SOUVENT
4 PARFOIS
5 RAREMENT
6 TRES RAREMENT
7 JAMAIS

3. Au cours des deux dernières semaines, vous êtes-vous senti(e) frustré(e), agité(e) ou avez vous manqué de patience ?
Veuillez choisir l'une des réponses suivantes :
1 TOUT LE TEMPS
2 PRESQUE TOUT LE TEMPS
3 ASSEZ SOUVENT
4 PARFOIS
5 RAREMENT
6 TRES RAREMENT
7 JAMAIS

4. Au cours des deux dernières semaines, vos problèmes intestinaux vous ont-ils empêché(e) d'aller sur votre lieu d'études ou de travailler ? Veuillez choisir l'une des réponses suivantes :
1 TOUT LE TEMPS
2 PRESQUE TOUT LE TEMPS
3 ASSEZ SOUVENT
4 PARFOIS

5 RAREMENT
6 TRES RAREMENT
7 JAMAIS

5. Au cours des deux dernières semaines, avez-vous eu des selles liquides ? Veuillez choisir l'une des réponses suivantes :
1 TOUT LE TEMPS
2 PRESQUE TOUT LE TEMPS
3 ASSEZ SOUVENT
4 PARFOIS
5 RAREMENT
6 TRES RAREMENT
7 JAMAIS

6. Au cours des deux dernières semaines, avez-vous eu de l'énergie ? Veuillez choisir l'une des réponses suivantes :
PAS D'ENERGIE DU TOUT
PRESQUE PAS D'ENERGIE
TRES PEU D'ENERGIE
UN PEU D'ENERGIE
UNE QUANTITE MOYENNE D'ENERGIE
BEAUCOUP D'ENERGIE
PLEIN(E) D'ENERGIE

7. Au cours des deux dernières semaines, avez-vous été inquiet(e) à l'idée de devoir vous faire opérer un jour à cause de vos problèmes intestinaux ? Veuillez choisir l'une des réponses suivantes :
TOUT LE TEMPS
PRESQUE TOUT LE TEMPS
ASSEZ SOUVENT
PARFOIS
RAREMENT
TRES RAREMENT
JAMAIS

8. Au cours des deux dernières semaines, avez-vous dû retarder ou annuler une sortie avec des amis, de la famille, etc. en raison de vos problèmes intestinaux ? Veuillez choisir l'une des réponses suivantes :
TOUT LE TEMPS
PRESQUE TOUT LE TEMPS
ASSEZ SOUVENT
PARFOIS
RAREMENT
TRES RAREMENT
JAMAIS

9. Au cours des deux dernières semaines, avez-vous eu des spasmes intestinaux ? Veuillez choisir l'une des réponses suivantes :
TOUT LE TEMPS

PRESQUE TOUT LE TEMPS
ASSEZ SOUVENT
PARFOIS
RAREMENT
TRES RAREMENT
JAMAIS

10. Au cours des deux dernières semaines, vous est-il arrivé(e) de ne pas vous sentir bien d'une manière générale ?
TOUT LE TEMPS
PRESQUE TOUT LE TEMPS
ASSEZ SOUVENT
PARFOIS
RAREMENT
TRES RAREMENT
JAMAIS

11. Au cours des deux dernières semaines, avez-vous été gêné(e) par la crainte de ne pas trouver de toilettes ?
TOUT LE TEMPS
PRESQUE TOUT LE TEMPS
ASSEZ SOUVENT
PARFOIS
RAREMENT
TRES RAREMENT
JAMAIS

12. Au cours des deux dernières semaines, avez-vous eu des difficultés à pratiquer les activités sportives ou de loisirs que vous auriez aimé faire, à cause de vos problèmes intestinaux ? Veuillez choisir l'une des réponses suivantes :
D'ENORMES DIFFICULTES ; ACTIVITES DEVENUES IMPOSSIBLES
BEAUCOUP DE DIFFICULTES
PAS MAL DE DIFFICULTES
QUELQUES DIFFICULTES
PEU DE DIFFICULTES
PRESQUE AUCUNE DIFFICULTE
PAS DE DIFFICULTE ; MES PROBLEMES INTESTINAUX N'ONT PAS LIMITE MES ACTIVITES SPORTIVES OU DE LOISIRS

13. Au cours des deux dernières semaines, avez-vous eu mal au ventre ? Veuillez choisir l'une des réponses suivantes :
TOUT LE TEMPS
PRESQUE TOUT LE TEMPS
ASSEZ SOUVENT
PARFOIS
RAREMENT
TRES RAREMENT
JAMAIS

14. Au cours des deux dernières semaines, avez-vous eu des problèmes pour bien dormir ou vous êtes-vous réveillé(e) la nuit ?
TOUT LE TEMPS
PRESQUE TOUT LE TEMPS
ASSEZ SOUVENT
PARFOIS
RAREMENT
TRES RAREMENT
JAMAIS

15. Au cours des deux dernières semaines, vous êtes-vous senti(e) déprimé(e) ou découragé(e) ?
TOUT LE TEMPS
PRESQUE TOUT LE TEMPS
ASSEZ SOUVENT
PARFOIS
RAREMENT
TRES RAREMENT
JAMAIS

16. Au cours des deux dernières semaines, avez-vous dû éviter de sortir dans des endroits où il n'y avait pas de toilettes à proximité ? Veuillez choisir l'une des réponses suivantes :
TOUT LE TEMPS
PRESQUE TOUT LE TEMPS
ASSEZ SOUVENT
PARFOIS
RAREMENT
TRES RAREMENT
JAMAIS

17. Au cours des deux dernières semaines, le fait d'évacuer beaucoup de gaz intestinaux a-t-il été un problème pour vous ?
UN PROBLEME ENORME
UN GROS PROBLEME
UN PROBLEME IMPORTANT
UN PROBLEME MOYENNEMENT IMPORTANT
UN LEGER PROBLEME
PRESQUE PAS UN PROBLEME
PAS UN PROBLEME

18. Globalement, au cours des deux dernières semaines, le fait de maintenir ou d'atteindre le poids que vous souhaitez avoir a-t-il été un problème pour vous ? Veuillez choisir l'une des réponses suivantes :
UN PROBLEME ENORME
UN GROS PROBLEME
UN PROBLEME IMPORTANT
UN PROBLEME MOYENNEMENT IMPORTANT
UN LEGER PROBLEME
PRESQUE PAS UN PROBLEME
PAS UN PROBLEME

19. Beaucoup de patient(e)s ayant des problèmes intestinaux ressentent souvent de l'inquiétude et de l'angoisse à propos de leur maladie. Cette inquiétude peut être la crainte d'avoir un jour un cancer, de ne jamais se sentir mieux ou de faire une rechute. Globalement, au cours des deux dernières semaines, vous êtes-vous senti(e) inquiet(ète) ou anxieux(se) ?
TOUT LE TEMPS
PRESQUE TOUT LE TEMPS
ASSEZ SOUVENT
PARFOIS
RAREMENT
TRES RAREMENT
JAMAIS

20. Au cours des deux dernières semaines, avez-vous eu des ballonnements intestinaux ? Veuillez choisir l'une des réponses suivantes :
TOUT LE TEMPS
PRESQUE TOUT LE TEMPS
ASSEZ SOUVENT
PARFOIS
RAREMENT
TRES RAREMENT
JAMAIS

21. Au cours des deux dernières semaines, vous êtes-vous senti(e) détendu(e) et décontracté(e) ?
TOUT LE TEMPS
PRESQUE TOUT LE TEMPS
ASSEZ SOUVENT
PARFOIS
RAREMENT
TRES RAREMENT
JAMAIS

22. Au cours des deux dernières semaines, avez-vous remarqué qu'il y avait du sang dans vos selles ? Veuillez choisir l'une des réponses suivantes :
TOUT LE TEMPS
PRESQUE TOUT LE TEMPS
ASSEZ SOUVENT
PARFOIS
RAREMENT
TRES RAREMENT
JAMAIS

23. Au cours des deux dernières semaines, vous êtes-vous senti(e) embarrassé(e) à cause de vos problèmes intestinaux ?
TOUT LE TEMPS
PRESQUE TOUT LE TEMPS
ASSEZ SOUVENT
PARFOIS
RAREMENT
TRES RAREMENT
JAMAIS

24. Au cours des deux dernières semaines, avez-vous été gêné(e) par la sensation d'avoir à aller aux toilettes alors que vos intestins étaient vides ? Veuillez choisir l'une des réponses suivantes :
TOUT LE TEMPS
PRESQUE TOUT LE TEMPS
ASSEZ SOUVENT
PARFOIS
RAREMENT
TRES RAREMENT
JAMAIS

25. Au cours des 2 dernières semaines, vous êtes-vous senti(e) perturbé(e) ou sur le point de pleurer ? Veuillez choisir l'une des réponses suivantes :
TOUT LE TEMPS
PRESQUE TOUT LE TEMPS
ASSEZ SOUVENT
PARFOIS
RAREMENT
TRES RAREMENT
JAMAIS

26. Au cours des 2 dernières semaines, avez-vous été gêné(e) parce que vous aviez tâché vos sous-vêtements ?
TOUT LE TEMPS
PRESQUE TOUT LE TEMPS
ASSEZ SOUVENT
PARFOIS
RAREMENT
TRES RAREMENT
JAMAIS

27. Au cours des 2 dernières semaines, avez-vous éprouvé du ressentiment à cause de vos problèmes intestinaux ? Veuillez choisir l'une des réponses suivantes :
TOUT LE TEMPS
PRESQUE TOUT LE TEMPS
ASSEZ SOUVENT
PARFOIS
RAREMENT
TRES RAREMENT
JAMAIS

28. Au cours des 2 dernières semaines, vos problèmes intestinaux ont-ils limité votre activité sexuelle ? Veuillez choisir l'une des réponses suivantes :
PAS D'ACTIVITE SEXUELLE EN RAISON DE MES PROBLEMES INTESTINAUX
LIMITATION IMPORTANTE EN RAISON DE MES PROBLEMES INTESTINAUX
LIMITATION MOYENNE EN RAISON DE MES PROBLEMES INTESTINAUX
LIMITATION LEGERE EN RAISON DE MES PROBLEMES INTESTINAUX
LIMITATION TRES LEGERE EN RAISON DE MES PROBLEMES INTESTINAUX
PRESQUE PAS DE LIMITATION EN RAISON DE MES PROBLEMES INTESTINAUX
AUCUNE LIMITATION EN RAISON DE MES PROBLEMES INTESTINAUX

29. Au cours des 2 dernières semaines, avez-vous eu des nausées ou avez-vous eu envie de vomir ?
TOUT LE TEMPS
PRESQUE TOUT LE TEMPS
ASSEZ SOUVENT
PARFOIS
RAREMENT
TRES RAREMENT
JAMAIS

30. Au cours des 2 dernières semaines, vous êtes-vous senti(e) irritable ? Veuillez choisir l'une des réponses suivantes :
TOUT LE TEMPS
PRESQUE TOUT LE TEMPS
ASSEZ SOUVENT
PARFOIS
RAREMENT
TRES RAREMENT
JAMAIS

31. Au cours des 2 dernières semaines, avez-vous ressenti un manque de compréhension de la part des autres ? Veuillez choisir l'une des réponses suivantes :
TOUT LE TEMPS
PRESQUE TOUT LE TEMPS
ASSEZ SOUVENT
PARFOIS
RAREMENT
TRES RAREMENT
JAMAIS

32. Au cours des 2 dernières semaines, avez-vous été satisfait(e), heureux(se) ou content(e) de votre vie personnelle ? Veuillez choisir l'une des réponses suivantes :
TRES INSATISFAIT(E), MALHEUREUX(SE) LA PLUPART DU TEMPS
GENERALEMENT INSATISFAIT(E), MALHEUREUX(SE)
UN PEU INSATISFAIT(E), MALHEUREUX(SE)
GENERALEMENT SATISFAIT(E), CONTENT(E)
SATISFAIT(E) LA PLUPART DU TEMPS, HEUREUX(SE)
TRES SATISFAIT(E) LA PLUPART DU TEMPS, HEUREUX(SE)
EXTREMEMENT SATISFAIT(E), JE N'AURAIS PAS PU ETRE PLUS HEUREUX(SE) OU CONTENT(E)