Clinical Study Protocol

GETAID-2014-03

SPARE

A proSpective randomized controlled trial comParing infliximAb-antimetabolites combination therapy to anti-metabolites monotheRapy and infliximab monothErapy in Crohn's disease patients in sustained steroid-free remission on combination therapy.

Sponsor	Groupe d´Etude Thérapeutique dans les Affections Inflammatoires Digestives (GETAID)
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LIST OF ABBREVIATIONS

AE	Adverse Event
ATI	Antibody towards infliximab
CDAI	Crohn Disease Activity Index
CDEIS	Crohn Disease Endoscopic Index of Severity
CRF	Case Report Form
EQ5-D	EuroQol measure of health outcome
GCP	Good Clinical Practice
GETAID	Group d'Etude Thérapeutique dans les Affections Inflammatoires Digestives
IBD	Inflammatory Bowel Disease
ICH	International Conference on Harmonisation
IFX	Infliximab
ITT	Intention To Treat
PP	Per Protocol
SAE	Serious Adverse Event
SES-CD	Simple Endoscopic Score for Crohn's Disease
SUSAR	Suspected Unexpexted Serious Adverse Reaction
6TGN	6-thioguanine nucleotide
WPAI	Work Productivity and Activity Impairment

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1. SYNOPSIS

Tittle
A pro**S**pective randomized controlled trial com**P**aring infliximA**b**-antimetabolites combination therapy to anti-metabolites monothe**R**apy and infliximab monoth**E**rapy in Crohn's disease patients in sustained steroid-free remission on combination therapy.

Phase
IV

Design
Prospective, open-label, randomized three-arms study

Main Inclusion criteria
Luminal Crohn's disease patients with steroid free remission for at least 6 months and a combination therapy with infliximab and anti-metabolites for at least 8 months

Primary objective
To demonstrate that Infliximab scheduled maintenance with or without antimetabolites is superior to antimetabolites alone to maintain sustained steroid-free remission over 2 years, while the latter is non inferior with regards to the mean time spent in remission over the same duration

Main co-primary end points
Clinical relapse rate at 2 years
Mean remission duration within 2 years

Study treatment
Infliximab, Mercaptopurine, azathioprine, methotrexate.

Number of subjects
300 randomized patients (100 per arm)

Study duration: 3 +2 years
Enrolment: 3 years
Follow-up: 2 years

MAIN SPONSOR Groupe d'Etude Thérapeutique des Affections Inflammatoires Digestives (G.E.T.A.I.D.)
President: Edouard LOUIS

Signature _____Date_____

National SPONSOR.....

Signature_____Date_____

Site Investigator

I will conduct the trial in compliance with GCP, with the applicable regulatory requirement(s) and with the protocol agreed to by the sponsor and given approval/favorable opinion by the ERB/IEC; I agree to comply with procedure for data recording/reporting, especially to report all SAE to GETAID and to my National Sponsor within 24H of awareness; to permit 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 within the time designated.
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 ERB/IEC 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
_____Signature
_____Date_____

2. INTRODUCTION

The SONIC trial has demonstrated that infliximab+azathioprine combo therapy was superior to infliximab monotherapy and azathioprine monotherapy to achieve steroid free remission and mucosal healing in anti-metabolites-naïve steroid-dependent or steroid-refractory patients (1). Despite this superiority, maintaining such combo therapy long term may generate cost and safety issues. A survey in several European and North-American centres suggests that a minority of patients are currently treated long term with combo-therapy.

The STORI trial suggests that a steroid free remission may be maintained, after infliximab discontinuation, in half of the patients having reached sustained steroid-free remission with infliximab+antimetabolites combo-therapy (2). It also suggests that infliximab retreatment is safe and effective in relapsing patients.

The STEP-UP TOP-DOWN trial also suggests that on demand infliximab under the cover of an anti-metabolites maintenance is feasible (3).

The IMID trial suggests that azathioprine discontinuation after at least 6 months of combination therapy may have limited or no impact on disease activity (4).

A prospective randomized multi-arm study is necessary to assess the benefits of the continuation of a combination therapy and the feasibility of infliximab or antimetabolites discontinuation in patients in sustained steroid free remission after prolonged treatment with a combination of infliximab and anti-metabolites.

3. STUDY OBJECTIVES

3.1. Primary objective

To assess the effect of two withdrawal strategies over two years in patients with stable remission for more than 6 months on combination therapy with infliximab and antimetabolites, and demonstrate that continued combination of infliximab and antimetabolites or continued monotherapy with infliximab are both superior to antimetabolites alone for maintaining sustained steroid-free clinical remission, while antimetabolites alone are not inferior with regards to the mean time spent in remission

3.2. Secondary objectives

- To identify baseline predictive factors of relapse in the three study groups.
- To assess the ability of blood CRP and fecal calprotectin to predict short term relapse in the three groups.
- To assess time spent in clinical remission in the three groups.
- To assess endoscopic remission at baseline and end of study in the three groups
- To assess the rate of treatment failure in the three study groups.
- To assess the time to treatment failure in the three study groups.
- To assess progression of bowel damage in the three groups.
- To assess the evolution of the disability score in the three groups
- To assess the safety and efficacy of infliximab retreatment in the antimetabolites group.
- To assess safety in the three study groups.
- To assess the health related quality of life in the three study groups.
- To assess direct and indirect costs in the three study groups.
- To assess evolution of blood CRP and fecal calprotectin in the three study groups.
- To assess evolution of infliximab trough levels and ATI in the two infliximab scheduled maintenance groups.
- To assess correlations between a series of biomarkers (proteomics, glycomics, DNA methylation, miRNA, metagenomics) and various clinical and biological outcomes.

- To assess the impact of 6TGN levels on the various clinical and biological outcomes in the purine treated patients

4. STUDY POPULATION

4.1. Selection of study population

Patients to be included are those who have been in steroid free remission for at least 6 months and with scheduled infliximab/antimetabolites combination therapy for at least 8 months , with a scheduled infliximab treatment administrated every 8 weeks for the last 4 months.

4.2. Source of recruitment

Patients are recruited from participating GETAID IBD-centers in France and Belgium, SOIBD centers in Sweden, United Kingdom IBD-centers and German IBD-centers. The study is also conducted in Australia IBD -centers and in the Netherlands.

4.3. Inclusion criteria

To be eligible all of the following criteria must be met:

- Diagnosis of Crohn's disease.
- Male or female, age $\geq$ 18 years.
- Currently treated with a combination therapy with infliximab and anti-metabolites for luminal Crohn's disease.
- Combined therapy with scheduled infliximab and anti-metabolites for at least 8 months.
- Scheduled administration of infliximab 5 mg/Kg every 8 weeks over the last 4 months.
- Antimetabolites administered at a stable dosage for the last 3 months: at least 1 mg/Kg or 2 mg/Kg for mercaptopurine and azathioprine, respectively, or the highest tolerated dosage if intolerance to standard dose (lower dose than standard dose is also allowed if 6 TGN > 235 pmol) ; at least 15 mg/week subcutaneously for methotrexate
- Patients in steroid free clinical remission for at least 6 months according to retrospective assessment of the patients' files.

- CDAI < 150 at baseline.
- A contraceptive during the whole study for childbearing potential female patients.
- Patients able to understand the information provided to them and to give written informed consent for the study

4.4. Exclusion criteria

- Patients who have presented a severe acute or delayed reaction to infliximab.
- Perianal fistulae as the main indication for infliximab treatment
- Active perianal/abdominal fistulae at time of inclusion, defined by active drainage
- Patients with ostomy or ileoanal pouch
- Pregnancy or planned pregnancy during the study
- Inability to follow study procedures as judged by the investigator
- Non-compliant subjects.
- Participation in another therapeutic study
- Steroid use ≤6 months prior to screening
- Currently receiving steroids, immunosuppressive agents (other than purine, methotrexate), biologic treatment (other than infliximab) or thalidomide

4.5. Concomitant medications

4.5.1. Permitted medications

All medications for Crohn´s disease apart from infliximab and anti-metabolites according to study design, should remain at stable dosage during the study.

4.5.2. Prohibited medications

- Steroids are not permitted for the last 6 months before entering the study and are not permitted for Crohn's disease during the study period. Infliximab and anti-metabolites will be used according to protocol.
- corticosteroids including budesonide
- cyclosporine, immunosuppressive agents (other than mercaptopurine, azathioprine or methotrexate)

- Biologic treatment other than infliximab
- thalidomide.

5. STUDY DESIGN

5.1. Study design

An open label, multicenter, trial with 3 parallel randomized arms will be performed, comparing three strategies of maintenance therapy in patients in sustained clinical remission without steroids for at least 6 months and having been treated by a combination of anti-metabolites and infliximab for at least 8 months (figure 1).

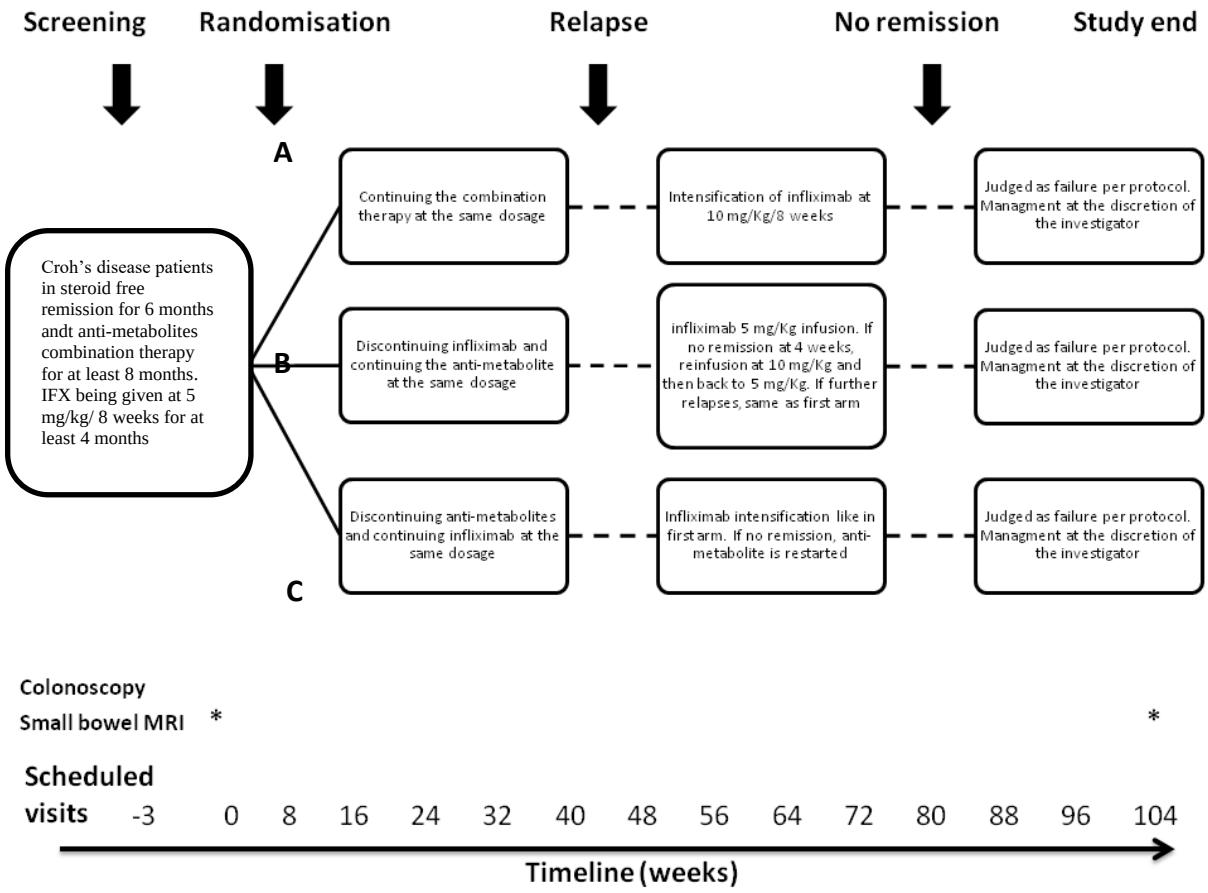

Figure 1: Three parallel arm-trial design

5.2. Description of treatment arms

First treatment arm: continuing scheduled infliximab treatment and anti-metabolite at the same dosage. In case of relapse, infliximab is intensified to 10 mg/Kg every 8 weeks. In case a remission is not achieved 4 weeks after the first 10 mg/Kg infliximab infusion, or if the patient experiences further relapse under an infliximab 10 mg/Kg/8 weeks regimen, the patient is considered as a failure and will be treated according to investigator's choice.

Second arm: discontinuing infliximab and continuing the anti-metabolite at the same dosage. In case of relapse, the patient can be retreated with one infliximab 5 mg/Kg infusion. If remission is not achieved 4 weeks later, a second infusion at 10 mg/Kg must be performed (date of assessment +/- **3** days). If remission is not achieved 4 weeks later, the patient is considered as a failure and will be treated according to investigator's choice. If the patient is in remission 4 weeks after first or second re-infusion, infliximab will be continued at 5 mg/Kg every 8 weeks on a scheduled basis. If a new loss of response occurs, the same protocol as in the first arm is applied.

Third arm: discontinuing anti-metabolites. If a relapse occurs, treatment is intensified as in first arm. If remission is not recaptured 4 weeks after an infliximab 10 mg/Kg infusion or if the patient experienced further relapse under infliximab 10 mg/Kg/ 8 weeks, antimetabolites is restarted at the same dosage as before inclusion in the trial. If remission is not recaptured 16 weeks later (or earlier in case of disease worsening defined by a further increase of the CDAI of at least 70 points -as compared to the last relapse visit- or CDAI >300), the patient is considered as a failure and treated according to investigator's choice.

6. TRIAL END POINTS

6.1. Primary end points

There will be two co-primary efficacy end points

Relapse rate at 2 years, relapse being defined by either one of the following events:

- A CDAI≥250 at any visit or between 150 and 250 with an increase of at least 70 points, over two consecutive visits one week apart. This must be associated with a CRP > 5 mg/l or a fecal calprotectin > 250 microg/g
- A new opening fistula, perianal or entero-cutaneous
- An intra-abdominal abscess (size of at least 3 cm) or perianal abscess (size of at least 2 cm) (also considered as treatment failure, see below)
- An episode of intestinal obstruction due to Crohn's lesions confirmed by medical imaging and requiring hospitalisation (also considered as treatment failure, see below)

Mean restricted time spent in remission

This time will be computed in all patients, from baseline (CDAI <150 and with absence of fistula drainage) until relapse, as defined above, within the 2 first years. First and subsequent remissions (under the predefined treatment strategy according to randomization) will be summed up within the first two years.

6.2. Secondary end points

- Time to relapse in each arm.
- Factors associated with time to relapse.
- Time to relapse according to CRP and calprotectin value measured every 2 months over the follow up.
- Sustained clinical remission defined by CDAI<150 without steroids over two years.
- Treatment failure rate. Treatment failure is defined by not achieving remission after treatment adaptation following a relapse according to protocol (CDAI<150 or, in case of relapse defined by the occurrence of a new fistula, the absence of fistula closure, defined clinically by the persistence of an opened fistulous track and/or drainage upon gentle pressure). Treatment failure will also be defined by a major treatment side-effect leading to treatment cessation. The occurrence of an intra-abdominal or perianal abscess and the occurrence of an intestinal obstruction due to Crohn's lesions and requiring a surgical resection or an endoscopic dilatation

are also directly considered as treatment failure and will not be managed by treatment adaptation according to protocol.

- Time to treatment failure.
- Incidence and severity of acute or delayed infliximab infusion reaction. Severity of the acute infusion reaction wil be assessed according to Ring et Messmer classification (6).
- Tissue damage progression will be assessed by the Lémann Index absolute and relative change between baseline and end of the study (2 years).
- Other secondary judgement criteria: CDEIS/SES-CD, MaRIA score, CDMRIS, disability index, adverse events and SAE, events related to re-infusions, trough levels of infliximab, ATI, hsCRP, fecal calprotectin, direct medical costs, work productivity and activity index, short health scale, EQ-5D.STATISTICS/RATIONALE FOR NUMBER OF PATIENTS
- Endoscopic remission at end of study

6.3. Sample size computation

The trial is conducted with two main objectives, that is, demonstrating

- the superiority of either the infliximab-based arms over the anti-metabolites monotherapy in terms of relapse rate at 2 years,
- the non-inferiority of the antimetabolites monotherapy arm over both infliximab arms with regard to the mean time spent in remission over 2 years.

First, we hypothesized, based on previous trial results (2,4-5), that 2-year relapse rate is about 10% in the infliximab-antimetabolite arm (A) vs. 50% in the antimetabolite alone arm (B), and 20% in the infliximab alone arm (C). Based on these hypotheses, and given a nominal type I error rate of 0.05, a statistical power of 0.90, and correcting for multiple testing using Bonferroni method**, it was computed that 67 patients had to be recruited in each arm.**

Second, we estimated the mean time spent in remission within the first two years by simulating data under the following assumptions. We considered the following assumptions in the standard arm (A):

- First relapse occurs within 2 years in 10% of patients; time to relapse is exponentially distributed (that is, relapse occurs similarly whatever the time spent since randomization), using the 2-year relapse rate as stated above.
- 50% of relapses achieved secondary remission

- A second relapse could occur in 50% of the secondary remitters over the rest of the follow-up (maximum of 2 years)

  Based on simulated data, the mean time spent in remission restricted to the 2 first years was estimated in arm A at 1.9 years, with standard deviation about 0.10.

According to the results of a patients survey the majority of the patients (>50%) accept a difference in restricted mean time spent in remission of 0.095 years over two years (that is, 5% of the mean observed in arm A) (Siegel C et al. Crohn's disease patients' perspectives towards de-escalating immunosuppressive therapy: a comparative French and American survey. ECCO 2018, DOP032 (7)). Hence this has been chosen as a maximum threshold to demonstrate non inferiority in mean difference. For this, a sample size of **30 patients in each arm** is necessary, taking into account the Bonferroni correction of the type I error, based on one-sided 95% confidence intervals.

Thus, taking into account 10% of lost to follow up or drop out (not reaching protocol judgement criteria) a total of **225** patients will be randomized in the trial with a maximum of 300 enrollments.

6.4. Randomization

Randomization will be performed centrally, using the study web site on Cleanweb®.It will be performed once all eligibility criteria have been checked.

Randomization will be stratified according to disease duration before the start of the first anti-TNF (≤, >2 years), failure of the antimetabolite treatment prior to the start of infliximab (yes/no), persistence of ulcers at endoscopy at baseline (yes/no). Accordingly, six separate randomization lists will be pre-established, based on permutation blocks, the size of which will not be communicated to anyone involved in the patient recruitment.

The block size is fixed, and given the required number of patients, appears reasonable regarding the number of strata. It cannot be given to insure the allocation concealment. Indeed, to ensure such concealment, all the investigators will remain unaware of the size of the permutation blocks used in the generation of lists.

6.5. Statistical Analysis

Primary analyses will be performed on an intent-to-treat basis. Thus, primary analysis will use the full analysis set, that is, the set of patients whose data are included in the main primary analysis, is composed of all randomized patients except those who withdraw consent, who are analyzed in the arm thy were allocated to. Secondary exploratory analyses will consider the protocol population, that is, those who completed the treatment according to the scheduled protocol.

Two main comparisons will be performed, namely A vs. B and B vs. C.

The baseline (i.e., at randomization) characteristics of the randomized groups will be compared roughly, based on estimations, with 95% confidence intervals and without any statistical tests of significance. Randomization is the best means for creating balanced groups.

Statistical methods according to the end point

Time to relapse in each arm. Two-year relapse rates will be estimated by the Kaplan Meier method using 24 months after randomization as the cutoff date of analysis (insuring administrative non-informative censoring) then, compared between randomized arms between log-rank test. Estimation of the treatment effect will be based on the estimation of hazard ratio (HR), with 95% confidence interval, adjusted on prognostic factors selected by the literature or the data analysis.

Analysis of non-inferiority will be based on the 95% confidence interval of the difference in mean restricted time spent in remission within the first two years. Low limit of the CI will be plotted against the limit of non-inferiority, that is, 0.095 years.

Factors associated with time to relapse will be assessed by Cox semiparametric models.

Sustained clinical remission will be measured by a ratio of patients with CDAI<150 without steroids over two years divided by the sample size. Comparison over randomized groups will use the Fisher exact test.

Treatment failure rate will be estimated by a ratio of patients with failure (see definition in the end points para), then compared using the exact Fisher test.

Time to treatment failure will be estimated by the Kaplan Meier method, then compared by the log-rank test; in case of informative censoring, a competing risk setting will be considered with comparison of cumulative incidence curves by the Gray test.

Incidence and severity of acute or delayed infliximab infusion reaction will use the cumulative hazard function as a measure of incidence due to the repeated nature of the events. Comparison will use Andersen-Gill model.

Tissue damage progression will be assessed by the Lémann Index absolute and relative change between baseline and end of the study will be compared by nonparametric Wilcoxon rank sum test.

Other secondary quantitative judgement criteria (CDEIS/SES-CD, MaRIA score, CDMRIS, disability index, trough levels of infliximab, ATI, hsCRP, fecal calprotectin, direct medical costs, work productivity and activity index, short health scale, EQ-5D) will be compared by the nonparametric Wilcoxon rank sum test.

Adverse events and SAE, and events related to re-infusions will be compared using cumulative hazard functions and Andersen-Gill models.

Handling of missing data: Multiple imputation, which is a popular approach for handling the pervasive problem of missing data in biostatistics, will be used. It is usually performed under a missing at random (MAR) assumption. Multiple imputation by chained equation (MICE) is to our knowledge the most flexible approach to handle complex patterns of missing data (including categorical data, quantitative data, and survival data).

All tests will be two-sided, with p-values of 0.05 or less denoting statistical significance. All analyses will be performed using the SAS (SAS Inc., Cary, NC) and R (http://www.R-project.org/) software packages.

The statistical analyses will be performed at the INSERM team ECSTRA (from the unit U1153, CRESS), Université Paris 7 under the supervision of Sylvie Chevret.

6.6. Data Collection

All data will be collected in an electronic case report form. The Statistical Centre will perform data collection, data quality control and statistical analysis.

7. DESCRIPTION OF THE STUDY VISITS

Table 1: Study visits

TABLE 1	Screening visit: within 8 weeks	Random visit	Scheduled visit	Every 6 month Scheduled visit	End of study visit	Clinical relapse visit	Re treatment visit	Response assessment visit	Second response assessment visit
Informed consent	X								
Inclusion/ exclusion	X								
Small bowel MRI/Maria score/CDMRIS	X				X				
Colonoscopy/ CDEIS/SES-CD	X				X				
Pelvic MRI*	X				X				
CDAI		X	X	X	X	X	X	X	X
Clin exam		X	X	X	X	X	X	X	X
Perianal lesion assessment*		X			X				
Blood test**	X		X	X	X	X	X	X	X
Blood and stool collection***		X	X	X	X		X		
Hematocrit	X		X	X	X	X	X	X	X
F-Calprotectin						X			
6-TGN (purine treated patients)		X			X		X		
Adverse events		X	X	X	X	X	X	X	X
Medications	X	X	X	X	X	X	X	X	X
Disability IBD score		X			X				
Lémann Index		X			X				
WPAI		X	X	X	X		X	X	X
Short Health scale		X	X	X	X		X	X	X
EQ-5D		X	X	X	X		X	X	X
Stool culture + C Diff toxin						X			

* In case of previous history of perianal lesions

**Routine blood test for the follow up of the patient must be performed at a maximum time interval of 4 months.

***Blood and stool samples will also be collected for biomarkers research: 9 ml in serum separator tube, 6 ml in EDTA tube and 5 grams of stools at each scheduled visit and retreatment visit. A supplementary 9 ml stool tube with stabilization buffer at baseline. 9 ml in EDTA tube at baseline, end of study visit and at the visit closest to months 6, 12, and 18; a 2.5 ml PAXgene RNA tube at baseline, end of study and at the visit closest to month 6, 12 and 18; a second 9 ml in serum separator tube at baseline, end of study visit and at the visit closest to month 6, 12 and 18.

7.1. Screening visit (8 weeks)

Signature and date of informed consent, evaluation of inclusion and exclusion criteria, demographic data (age, sex, smoking habits), medical history, localization and behaviour (Montreal classification), previous resections, fistulas, stenoses and treatment, physical examination, diary given to patient for CDAI calculation, routine blood tests (Hemoglobin, RBC, WBC, platelets, local CRP, Bilirubin, ASAT, ALAT, ALP, GT, Sodium, Potassium, Calcium, Creatinine,

Albumin, urine dipstick including pregnancy test), Hematocrit, colonoscopy with CDEIS/SES-CD calculation, 2 biopsies from most severely affected area and 2 biopsies from unaffected area. Small bowel MRI with Maria and CDMRIS scores. Pelvic MRI if previous history of perianal disease. Lémann index

The patient is also provided with pots for stool sample.

7.2. Randomization visit (day of last infliximab injection)

CDAI calculation, adverse events, spared serum sample (for central CRP measurement, antibodies to infliximab, trough infliximab levels and further biomarker dosage including proteomics), stool sample (for central dosage of fecal calprotectin and microbiome analysis), EDTA and PAXgene tube for DNA and RNA extractions and central measurement of biomarkers, infliximab infusion, WPAI (Work Productivity Activity Index), Short health scale, disability index, EQ-5D. Simple question on the visit to GP or other doctors since last visit and link to Crohn's disease.

7.3. Scheduled visits (every 8 weeks +/-1 week)

CDAI calculation, adverse events, Hematocrit, routine blood tests (only every 16 weeks), stored stool and blood samples (see table comment above), clinical examination. WPAI, Short health scale, EQ-5D will be performed. Simple question on the visit to GP or other doctors since last visit and link to Crohn's disease. In case of relapse, the patient will undergo a series of visits (unscheduled, retreatment, response assessment) which will delay the normal plan of the study visits.

7.4. Clinical relapse visit (unscheduled)

In case of suspicion of relapse, an unscheduled visit will be organised. Recording of the symptoms for the last 7 days is requested to fill in the CDAI diary for the CDAI score. Routine Blood tests and haematocrit. Clinical examination. Adverse events. Request for stool culture and clostridium difficile toxin. Simple question on the visit to GP or other doctors since last visit and link to Crohn's disease.

A relapse is defined as a CDAI > 250 or a CDAI between 150-250 with an increase of 70 compared to baseline reported on two consecutive visits one week apart and a negative stool culture and negative test for clostridium difficile toxin. This relapse must also be confirmed by a CRP >5 mg/l

and/or a fecal calprotectin >250 microg/g (measured locally). A new opening fistula, perianal or enterocutaneous is also defined as a relapse.

7.5. Retreatment visit (max 7 days after clinical relapse)

In case of confirmed clinical relapse, the infliximab and/or anti-metabolites treatment will be adapted specifically in each study arm according to protocol. This visit should be planned within one week of confirmed relapse. At retreatment visit, clinical examination and adverse events will be recorded, stool and blood samples stored (see table comment above), WPAI, Short health scale, and EQ-5D will be performed. Simple question on the visit to GP or other doctors since last visit and link to Crohn's disease. Treatment will be applied according to protocol.

7.6. Response assessment visit (4 weeks after retreatment visits)

A first response assessment visit is performed 4 weeks (+/- 3 days) after retreatment. The following procedures are planned: CDAI, routine blood tests, haematocrit, clinical examination, adverse events, a simple question on the visit to GP or other doctors since last visit and link to Crohn's disease. WPAI, Short health scale and EQ-5D will be performed. If the patient is in remission (CDAI<150) the patients resume his/her scheduled treatment visits every 8 weeks. If the patient is not in remission, the treatment is adapted according to protocol and a subsequent response assessment visit is planned 4 weeks later. The same procedures are performed as in the previous response assessment visit. If the patient is in remission (CDAI<150), he/she resumes his/her scheduled treatment visits every 8 weeks. If the patient is not in remission, he/she is considered as a treatment failure for the rest of the trial and an end of study visit is performed.

7.7. End of study visit (2 years after randomization)

Last study visit will be 2 years after randomization. The timing of this visit can be slightly adapted according to scheduled visits every eight weeks and potential relapse and retreatment visits. The last visit will be performed at the date the closest (before or after) to calendar date of 2 years after randomization. In case of treatment failure or other conditions for premature termination, end of study visit is performed earlier. Procedures performed at this visit include CDAI calculation, clinical examination, adverse events, blood tests, stored serum sample for further biomarkers studies, WPAI, Short health scale, EQ-5D, ileocolonoscopy with CDEIS/SES-CD calculation, small bowel MRI with MaRIA and CDMRIS scores, Pelvic MRI (if previous history of

peri-anal disease), Lémann index calculation, disability index. Simple question on the visit to GP or other doctors since last visit and link to Crohn's disease.

7.8. Criteria for premature termination

- In case of treatment failure according to protocol
- If patient wants to stop
- If investigator decides that the patient is no longer suitable for the study
- If patient flares with contraindication for retreatment start
- In case of an adverse event not compatible with further participation in the study

8. ENDOSCOPY

Ileocolonoscopies will be performed (according to the Endoscopic procedure provided) in all patients at screening, and end of study visit. CDEIS, SES-CD and presence of ulcers yes/no will be scored immediately after the procedure by the endoscopist. Items requested for Lémann index calculation will also be collected. Ileocolonoscopies must be recorded for central reading.

9. MRI INVESTIGATIONAL METHODS

MRI enterography and Pelvic MRI (in case of history of perianal lesions) will be performed according to predefined procedure at screening and end of study visit. MRI must be recorded for central reading.

MR ENTEROGRAPHY INVESTIGATIONAL METHODS:

The method presented here below is the recommended method. However, abdominal MRI with enteroclysis (rather than enterography) can be performed at the discretion of the investigator. The MRI can be done in the morning before the colonoscopy, if feasible. These methods can also be adapted for MR machines other than Siemens using corresponding measures (ex: Philipps etc...)

Patient Preparation:

- Nil per mouth on the day of the examination.

- Oral ingestion of ≈ 1500 ml of PEG 4000 (or 3350), 45 minutes before the examination with in addition oral ingestion of 500 ml water or PEG 15 minutes prior to examination. PEG can be

replaced by barium sulfate suspension (VoLumen®, E-Z-EM Inc.), psyllium seed husks (Metamucil®), or mannitol at the discretion of the radiologist.

- IV administration of 0.5 mg of glucagon at the beginning of the examination and IV administration of 0.5 mg glucagon just prior to IV injection of gadolinium.

Acquisition:

- Procubitus position with a phased array body coil.
- Coronal and axial true fast imaging with steady-state precession (true FISP) sequence, with breath hold, without fat suppressed and with a slice thickness of 5 mm and a skip of 0 mm.
- Coronal true FISP sequence, with breath hold, with fat suppression and with a slice thickness of 5 mm and a skip of 0 mm.
- Coronal and axial T2 weighted images with half-Fourier single-shot turbo spin echo (HASTE) sequence with a slice thickness of 5 mm and a skip of 0 mm.
- Coronal 3-Dimensional (3D) T1-weighted gradient echo sequence with breath hold with a slice thickness of 2-3 mm.
- Coronal and axial gadolinium enhanced 3D gradient echo sequence with breath hold, 60 seconds after injection of gadolinium (0.1 mmol/kg) with a slice thickness of 2-3 mm.
- Axial 2-dimensional T1-weighted gradient echo sequence after injection of the gadolinium with a slice thickness of 5 mm and a skip of 0 mm.

Archiving system:

Data on Picture Archiving and Communication System (PACS) and compact disk.

MaRIA and CDMRIS scores will be calculated. Items requested for Lémann Index calculation will also be collected.

10. LABORATORY TESTS

The tests required during the protocol are all considered standard of care and will be performed at the local labs of the centers. Routine blood sampling for hematology and chemistry follow up will be performed every 4 months. Only hematocrit (for CDAI calculation) will be performed at each visit.

11. SPARED BLOOD SAMPLE FOR BIOMARKER RESEARCH

On top of routine laboratory tests, stool and blood samples will be taken according to table 1/paragraph 8, for central measurement of CRP and fecal calprotectin and for biomarker research

(including proteomics and genomics). These tubes will be transferred and the Biobanking will be centralized at the “Biothèque de l’Université de Liège”, CHU of Liège, Belgium. Secondarily, part of these will be transferred to University of Edinburgh, UK and to the Sheba Medical Centre, Tel-Aviv, Israel for specific measurements (DNA methylation, miRNA, glycomics, proteomics, infliximab trough and anti-infliximab antibodies).

Serum samples need to be centrifuged and be frozen at -20°C before shipment. The remaining of the serum samples will be kept for biological samples collection.

Biological samples will be will be kept at -80°C for 10 years.

A laboratory manual will be available to define the shipment procedures of the biologicals samples (in according to the procedures of the central lab).

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 disagree 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.

12. ANCILLARY PROJECT: SPARE LONG TERM FOLLOW UP

The aim of this ancillary study is to collect medical data up to 5 years after the end of the SPARE research in order to evaluate the long-term effect of patient's treatments on the progression of their Crohn's disease.

All participating centres will be invited to complete a short form evaluating the main patient outcomes, regardless of subsequent treatment.

The data collected will include: dates of hospitalization, surgical procedures such as intestinal resections, ano-perineal surgical treatments received, possible work absences, results of examinations performed to monitor Crohn's disease during routine follow-up (blood tests and stool markers, cross-sectional imaging and endoscopies).

The information collected and the resulting statistical analyses will make it possible to observe the long-term results of the treatments received on the risks of hospitalization, surgery, intestinal damage, disability and the risk of adverse events.

The objective of this ancillary study is to describe the long term evolution with the three treatment strategies tested in the main phase of the controlled trial and to identify markers and characteristics associated with the long-term outcome in the setting of treatment de-escalation.

13. SAFETY ASSESSMENTS

13.1. 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 unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a drug, whether or not 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 will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and the surgery/ procedure has been pre planned prior to study entry. However, if the pre existing 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 an adverse event. 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.

13.2. Serious Adverse 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 length of time. 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.
- **Spontaneous Abortion** Miscarriage experienced by study subject.
- **Elective Abortion** Elective abortion performed on study subject.

13.3. SUSAR reporting

A suspected unexpected serious adverse reaction (SUSAR) on the study drug(s), which is **lethal or life-threatening**, must be reported to the Medical Products Agency (MPA) and the Regional Ethics Committee (REPN) within 7 days from the time-point when the responsible investigator is aware of the event. A complement of the report is sent to the authorities within a maximum of 15 days.

A suspected unexpected serious adverse reaction (SUSAR) on the study drug(s), which is **not lethal or life-threatening**, must be reported to the Medical Products Agency (MPA) and the Regional Ethics Committee (REPN) within 15 days from the time-point when the responsible

investigator is aware of the event. A complement of the report is sent to the authorities as soon as possible.

SUSARs will be reported to the MPA on the CIOMS-form.

13.4. 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.

13.5. 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 an other 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.

The patients will be specifically assessed for infection and malignancies and the incidence rates of these events will be presented as descriptive summary statistics and the number and percentage of patients who experience adverse events will be tabulated.

13.6. Notification

All life-threatening adverse events and all deaths must be notified within 24 hours to the study coordinator at GETAID and to the national Sponsor with standard forms. A serious adverse event

regarded by the investigator as related to the patient participating in the study, even if it occurred before or after study treatment administration, must be reported. Serious Adverse Event up to 60 days after the last study treatment will be reported.

All Serious Adverse Events will be followed until resolution or until it is confirmed by the PI and/or the Study Responsible Physician that it is no longer necessary to do so.

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 National Sponsor within 24 hours.

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

SERIOUS ADVERSE EVENTS MUST BE REPORTED TO

GETAID Central Office

Service de Gastroentérologie

Hôpital Lariboisière 2 rue Ambroise paré 75010 Paris, FRANCE

01 49 95 25 48, Fax: +33 1 84 10 85 45

sae@getaid.org

13.7. 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.

13.8. Biological and other abnormalities

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.

13.9. Cytopenia

In case of cytopenia during Azathioprine, 6-MP or methotrexate treatment:

1. If neutrophils <1,500 and >1,000/mm3, or platelets <150,000 and >100,000/L, Azathioprine, 6-MP or methotrexate regimen will be reduced by 50% of initial dose if patient received the full recommended dose, and blood count will be checked again 7 days later. Doses will be rounded off to the nearest 25 mg value for Azathioprine and 6-MP. For patients already receiving a reduced dose, Azathioprine, 6-MP or Methotrexate treatment will have to be discontinued and blood count checked within 7 days.

2. If neutrophils < 1,000 /mm3, or platelets < 100,000/mm3, Azathioprine 6-MP or Methotrexate treatment will have to be discontinued and blood count checked within 7 days.

3. At the discretion of the investigator, Azathioprine, 6-MP or Methotrexate could be restarted at doses <50% of the initial dose, then adjusted according to blood count values.

13.10. Safety committee

A Safety Committee composed of four international IBD experts and one biostatistician not involved in the study will be constituted to consider life-threatening adverse events and fatalities occurring during the study.

This committee is composed of Iris Dotan from Tel Aviv, Alessandro Armuzzi from Rome and Fernando Gomollon from Zaragoza, and Jean Marie Reimund from France as expert IBD physician and Laurence Seidel from Belgium as biostatistician.

According to recommendations of this committee, the Principal Investigators can decide to interrupt the study as appropriate.

14. ORGANIZATIONAL, LEGAL AND GENERAL CONSIDERATIONS

14.1. 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.

14.2. Submission to ethical committee and Health Authorities

This protocol complies with the French law dated 4th March, 2002. Approval by the national and local Ethics Committee will be required before the study can be started.

14.3. 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 Ethical Committees of Liege, Lund, Paris, Berlin and Edinburgh if the planned modifications are linked with study ethical or medico-scientific aspects (assessment criteria, addition of a new center…).

Administrative minor modifications do not require a new notification to the Ethical Committee. Sponsor will inform supervision authority.

14.4. 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 Law obligations, the Helsinki Declaration terms, to conduct this study respectfully of the protocol and the "Good Clinical Practice" guidelines.

The sponsor representatives will be supplied with a dated and signed copy of the latest infliximab Summary of Product Characteristics (SmPC)

14.5. Patient information and patient informed consent form

Patients are allowed to participate in this study only if they have signed a written consent form. First, they will have received information on study aims, duration, procedures, benefits, predictable risks, disadvantages that could result from the treatments, data confidentiality and insurance cover.

This set of information is summarized in a written consent form given to each patient. The patient and the investigator will sign two copies of the written consent form. A copy of this document will be handed to the patient; the investigator will keep a second copy in his records and make it available for monitoring.

14.6. 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. They will be neatly and legibly written with a black ball-point pen (in order to make duplication and computerization easier) in the source documents. Electronic hospital files will also be accepted if made available for monitoring. Each finished case report form will be dated and signed by the investigator, certifying hereby 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 assess data validation.

14.7. Monitoring procedures

The investigator and co-investigators agree to welcome at regular intervals the GETAID monitors. After every visit, the 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, REC 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.

14.8. Responsibilities

GETAID is the main study sponsor. In accordance with the Huriet Law, GETAID signed an insurance policy with the SHAM 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 and this will be notified to the "Commission Nationale Information et Liberté" (CNIL).

Submission of Serious Adverse Events is the responsibility of the investigators who will report SAE's within 24 hours to both the GETAID and the National Sponsor.

14.9. Storage

The data concerning the study will be stored for 15 years after the end of the study by the investigator.

A copy of these data will also be stored for 15 years after the end of the study by the GETAID offices and the National Sponsor.

14.10. Final Statement

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

14.11. Study time schedule

The study start is planned in 2015. Inclusion period has been extended to 36 months. The total study duration will be 60 months.

14.12. Potential implications of study results

If the study confirms the superiority of continued scheduled treatment with infliximab over infliximab withdrawal to maintain steroid-free remission, this will establish the advantage of continuing this treatment for a prolonged period of time in patients who can tolerate it well. Nevertheless, these results may be qualified by the analysis of the second co-primary end point. If globally, the retreatment with infliximab in case of relapse is confirmed to be effective and safe and if globally the time spent in remission is not dramatically decreased in patients having interrupted infliximab treatment, infliximab withdrawal with a secondary retreatment in relapsers could be contemplated as a possible option when decrease of cost is to be considered. The evolution of tissue damage (Lémann score) as well as disability, assessed in secondary end points will also be important to confirm the validity of this option.

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16. ANNEXES

16.1. Disability IBD Index

- **IBD Disability Index (FRENCH VERSION)**

DATE : _ _ / _ _ / 2 0 _ _

LES QUESTIONS CI DESSOUS PASSENT EN REVUE DIFFERENTES FONCTIONS DE VOTRE CORPS ET DIFFERENTES ACTIVITES DE VOTRE VIE QUOTIDIENNE. LORSQUE VOUS REPONDREZ A CES QUESTIONS, VOUS DEVREZ PENSER A LA SEMAINE PASSEE EN TENANT COMPTE AUSSI BIEN DES BONS JOURS QUE DES MAUVAIS JOURS.
REPONDEZ A 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					
	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**					
	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**					
	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)					
	12a. 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 ?					
	12b. Globalement, au cours de la semaine passée, avez-vous rencontré 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:					
	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 ?					
	REPONSES : *(NA: Non Applicable*) **Non = 0** **Oui ou Probablement = 4**					

Total score = S*100/nx4 **n=nombre de questions répondues** **S= somme des scores des n questions** **S est possible si (14-n)/14<20%**	**Total score :……. …..** **(0= pas d'handicap, 100 = niveau le plus élevé d'handicap)**

- **DISABILITY INDEX (ENGLISH VERSION)**

Version 2, 30/Dec./2014

Pt ID:_____

DATE : _ _ / _ _ / 2 0 _ _

	PLEASE READ ALOUD THIS INSTRUCTIONS TO THE PATIENT **The first question is about the overall health of the patient, including both physical and mental health.**					
	ANSWERS :0 = Very good ; 1=Good ; 2=Moderate ; 3=Bad ; 4=Very Bad					
	Overall Health					
	1. In general, how would you rate your healthtoday?					

PLEASE READ ALOUD THESE INSTRUCTIONS TO THE PATIENT
Now I would like to review different functions of your body and activities of daily life. When answering these questions, I would like you to think about the last week, taking both good and bad days into account. When I ask about difficulty/problem, I would like you to consider how much difficulty/problem you have had on an average, in the past week, while doing the activity in the way that you usually do it. By difficulty I mean that you require increased effort, that you have discomfort or pain, or that the activity is slower or that there are other changes in the way you do the activity. Please answer this question taking into account any assistance you have available.
(Read and show scale to respondent).

	ANSWERS :0 = None ; 1=Mild ; 2=Moderate ; 3=Severe ; 4=Very Extreme					
	Sleep and Energy					
2.	Overall in the last week, how much of a problem did you have with sleeping, such as failing asleep, waking up frequently during the night or waking up too early in the morning?					
3.	Overall in the last week, how much of a problem did you have due to not feeling rested and refreshed during the day (e.g. feeling tired, not having energy)?					
	Affect					
4.	Overall in the last week, how much of a problem did you have with feeling sad, low or depressed?					
5.	Overall in the last week, how much of a problem did you have with worry or anxiety?					
	Body Image					
6.	Overall in the last week, how much of a problem did you have with the way your body or body parts looked?					
	Pain					
7.	Overall in the last week, how much of stomach or abdomen aches or pains did you have?					

	ANSWERS :0 = None ; 1=Mild ; 2=Moderate ; 3=Severe ; 4=Extreme or cannot do					
	Regulating defecation					
8.	Overall in the last week, how much difficulty did you have coordinating and managing defecation including choosing and getting to an appropriate place of defecation and cleaning oneself after defecation?					
9.	Overall in the last week, how much difficulty did you have looking after your health, including maintaining a balanced diet?					
	Interpersonal Activities					
10.	Overall in the last week, how much difficulty did you have with personal relationship?					
11.	Overall in the last week, how much difficulty did you have with participation in the community					
	Work and Education (please answer to question 12a OR 12b)					

12a. Overall <u>in the last week, how much difficulty did you have with work or household activities ?</u>					
12b. Overall <u>in the last week, how much difficulty did you have with school or studying activities ?</u>					

ANSWERS : 0=0 ; 1=1-7; 2=8-18; 3=19-29; 4= >29					
13. Number of liquid or very soft stools in the last week :					

ANSWERS : 0=No ; 4= Yes or uncertain					
14. Is arthritis or arthralgia present?					

Total score = S*100/nx4 **n=number of questions which have been answered** **S= sum of the n questions score** **S is possible if (14-n)/14<20%**	**Total score _____ ranging from 0 (no disability) to 100 (highest disability level)**

N/A: not applicable

16.2. CDAI (Crohn DISEASE ACTIVITY INDEX)

CDAI

1. SUM OF LIQUID OR VERY SOFT STOOLS DURING THE LAST 7 DAYS ⌊_⌋⌊_⌋⌊_⌋X 2 =⌊_⌋⌊_⌋⌊_⌋

2. SUM OF ABDOMINAL PAIN DURING THE LAST SEVEN DAYS ⌊_⌋⌊_⌋X 5 =⌊_⌋⌊_⌋⌊_⌋

(0=none, 1=mild, 2=moderate, 3=severe)

3. SUM OF WELL BEING DURING THE LAST SEVEN DAYS: ⌊_⌋⌊_⌋X 7 =⌊_⌋⌊_⌋⌊_⌋

(0=well, 1=slightly below par, 2=poor, 3=very poor, 4=terrible)

4. One point for each ⌊_⌋**X 20 =**⌊_⌋⌊_⌋⌊_⌋

ARTHRITIS OR ARTHRALGIA

IRITIS OR UVEITIS

ERYTHEMA NODOSUM, PYODERMA GANGRENOSUM OR APTHTHOUS STOMATITIS

ANAL FISSURE, FISTULA OR PERIRECTAL ABSCESS

OTHER BOWEL-RELATED FISTULA

FEVER >38°C

5. USE OF ANTIDIAHREAL TREATMENT: ⌊_⌋X 30 =⌊_⌋⌊_⌋⌊_⌋

(0 = no; 1 = yes)

6. ABDOMINAL MASS: ⌊_⌋X 10 =⌊_⌋⌊_⌋⌊_⌋

(0=none; 2=questionable; 1=present)

7. HEMATOCRIT:

HEMATOCRIT =⌊_⌋⌊_⌋**%**

Normal average: For = 47 For Female = 42

Male: 47 – Hct =⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋X 6 =⌊_⌋⌊_⌋

Female: 42 – Hct =⌊_⌋⌊_⌋

8. WEIGHT:

Optimal weight*⌊_⌋⌊_⌋⌊_⌋– Current weight ⌊_⌋⌊_⌋⌊_⌋x 100 = ⌊_⌋⌊_⌋X 1 =⌊_⌋⌊_⌋

Optimal weight*⌊_⌋⌊_⌋⌊_⌋

TOTAL **CDAI =**⌊_⌋⌊_⌋⌊_⌋

***** *Optimal weight is defined as the weigth before the disease when the disease ocurred in adulthood and the maximum weight in remission when the disease ocurred in the childhood*

16.3. CDEIS/SES-CD

All endoscopies will be registered on CD-ROMS or videotapes (less desirable)
The recording should be as follows:
- terminal ileum, 1-2 minutes
- ascending colon, 1-2 minutes
- transverse colon 1-2 minutes
- descending + sigmoid colon, 1-2 minutes
- rectum 1 minute

After the recording of the segment biopsies can be taken but this should NOT be recorded. The patient number, including site number, and if possible the name of the segment need to be indicated on the recording. An effort needs to be made to include all relevant lesions on the recordings. SES-CD and CDEIS need to be completed by the endoscopist immediately following the procedure. Ideally, the endoscopist is blinded to the management of the patient.

CDEIS SCORE ; SES CD score

DATE : dd/mm/yyyy		Ileum	Right colon	Transverse colon	Sigmoid and left colon	Rectum
Explored	**1: Yes 0: No**					
Ulceration	**1: Yes 0: No**					
Size of the largest ulceration	(cm)					
Deep ulceration	1: Yes 0: No					
Superficial ulceration	1: Yes 0: No					
Stenosis						
None	Type 0					
Single (can be passed)	Type 1					
Multiple (can be passed)	Type 2					
Cannot be passed	Type 3					
Ulcerated stenosis	1: Yes 0: No					
Non-ulcerated stenosis	1: Yes 0: No					
Surface affected						
by lesions	**0 to 100 (%)**					
by ulcerations	**0 to 100 (%)**					

16.4. Lémann Index

Segment and organ	Resection	Stricturing lesions				Penetrating lesions				INDEX
	% *	Grade 1	Grade 2	Grade 3	INDEX	Grade 1	Grade 2	Grade 3	INDEX	
Esophagus										
Stomach										
Duodenum										
Upper tract (sum of segmental indexes / 3)										
Small bowel 1										
Small bowel 2										
Small bowel 3										
Small bowel 4										
Small bowel 5										
Small bowel (sum of segmental indexes / 20)										
Cecum										
Ascending colon										
Transverse colon										
Descending colon										
Sigmoid colon										
Rectum										
Colon/rectum (sum of segmental indexes / 6										
Anus										
Anus (1 segment)										
LEMANN INDEX										

16.5. Maria score

Studies segments are: terminal ileum, right colon, transverse colon, left+sigmoid colon, rectum. For each segment, the following formula is calculated: 1.5*max wall thickness (mm) + 0.02*max RCE (%) + 5*edema (0-1) + 10*ulceration (0-1). The MaRIA score is obtained by summing up the 5 segments subscores.

16.6. WPAI

- **FRENCH VERSION**

Work Productivity and Activity Impairment questionnaire General Health (WPAI-GH)

Date à laquelle vous renseignez ce questionnaire :
L__L__L__L__L__L__L__L__L__L

Les questions suivantes portent sur les conséquences de problèmes de santé sur votre capacité à travailler et à effectuer vos activités habituelles. Par problème de santé, nous entendons tout problème physique ou émotionnel, ou symptôme.

Veuillez, suivant les questions, cochez la case qui convient ou compléter les espaces appropriés comme indiqué.

❑ Occupez-vous un emploi (travail rémunéré) en ce moment ?
❑ Oui ❑ Non

Si vous répondez NON, cochez « NON » et passez directement à la question 6

Les questions qui suivent portent sur les **sept derniers jours**, sans compter aujourd'hui.

❑ Au cours des sept derniers jours, combien d'heures de travail, au total, avez-vous manquées à cause de problèmes de santé ? *Comptez les heures d'absence pour congé de maladie, les retards et départs précoces du travail, etc. dus à des problèmes de santé. Ne comptez pas les moments où vous avez manqué pour participer à cette étude.*

L_ L _L Heures

❑ Au cours des sept derniers jours, combien d'heures de travail avez-vous manquées pour toute autre raison telle qu'un congé, des vacances ou la participation à cette étude ?

L_ L _L Heures

❑ Au cours des sept derniers jours, combien d'heures de travail au total avez-vous effectuées ?

L_ L _L Heures

Si votre réponse est « 0 », passez directement à la question 6

❑ Au cours des sept derniers jours, dans quelle mesure vos problèmes de santé ont-ils diminué votre productivité pendant que vous étiez en train de travailler ? *Tenez compte des jours pendant lesquels vous avez été limité(e) dans la quantité ou le type de travail que vous auriez*

pu accomplir, vous en avez fait moins que vous l'auriez souhaité ou vous ne pouviez pas travailler aussi soigneusement que d'habitude. Si les problèmes de santé n'ont eu qu'une faible incidence sur votre travail, choisissez une note peu élevée. Choisissez une note plus élevée si les problèmes de santé ont beaucoup perturbé votre travail.

Les problèmes de santé n'ont eu aucun effet sur mon travail	L__L__L__L__L__L__L__L__L__L__L__L__L__L__L 0 1 2 3 4 5 6 7 8 9 10	En raison de problèmes de santé, je n'ai pas pu travailler du tout

ENCERCLEZ UN NOMBRE

- Au cours des sept derniers jours, dans quelle mesure vos problèmes de santé ont-ils diminué votre capacité à effectuer vos activités quotidiennes habituelles en dehors de votre lieu de travail ? *Par activités habituelles, nous entendons les activités que vous effectuez régulièrement, telles que les travaux ménagers, les courses, l'exercice, s'occuper des enfants, étudier, etc. Tenez compte des moments où vous avez été limité(e) dans la quantité ou le type d'activités que vous auriez pu accomplir et de ceux où vous en avez fait moins que vous l'auriez souhaité. Si les problèmes de santé n'ont eu qu'une faible incidence sur vos activités, choisissez une note peu élevée. Choisissez une note plus élevée si les problèmes de santé ont beaucoup perturbé vos activités.*

Les problèmes de santé n'ont eu aucun effet sur mes activités quotidiennes	L__L__L__L__L__L__L__L__L__L__L__L__L__L__L 0 1 2 3 4 5 6 7 8 9 10	En raison de problèmes de santé, je n'ai pas du tout pu me consacrer à mes activités quotidiennes

ENCERCLEZ UN NOMBRE

WPAI ENGLISH VERSION
WPAI:CD V2.0 – 18/NOV/2013

Work Productivity and Activity Impairment Questionnaire: CROHN'S DISEASE V2.0 (WPAI-CD)

The following questions ask about the effect of your Crohn's disease on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)?_____NO _____YES
   If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your Crohn's disease? *Include hours you missed on sick days, times you went in late, left early, etc., because of your Crohn's disease. Do not include time you missed in order to participate in this study.*

   _____HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS *(If "0", skip to question 6.)*

5. During the past seven days, how much did your Crohn's disease affect your productivity while you were working?

Think about days in which you were limited in the amount or type of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If Crohn's disease affected your work only a little, choose a low number. Choose a high number if Crohn's disease affected your work a great deal.

Consider only how much Crohn's disease affected productivity while you were working.

Crohn's disease had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	Crohn's disease completely prevented me from working

CIRCLE A NUMBER

6. During the past seven days, how much did your Crohn's disease affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as household activities, shopping, childcare, exercising, studying, etc. Think about times in which you were limited in the amount or type of activities you could do and times in which you accomplished less than you would like. If Crohn's disease affected your activities only a little, choose a low number. Choose a high number if Crohn's disease affected your activities a great deal.

Consider only how much Crohn's disease affected your ability to perform your normal daily activities, excluding your job.

Crohn's disease had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Crohn's disease completely prevented me from doing my daily activities

CIRCLE A NUMBER

Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics. 1993 Nov;4(5):353-65.

16.7. Short Health Scale

- **Short Health Scale (FRENCH VERSION)**

SHS-IBD VAS - France/French - Version of 16 Aug 11 - Mapi Institute.
ID6235 / SHS-IBD-VAS_AU1.0_fre-FR.doc

Nom : _____ Identifiant :_____ Date :_____

ÉVALUATION DE L'ÉTAT DE SANTÉ

Short Health Scale

Maladie chronique inflammatoire de l'intestin

Ce questionnaire comprend quatre questions. Veuillez répondre aux questions en plaçant un trait vertical (I) sur la ligne, à l'endroit qui correspond le mieux à votre situation. Si vous avez l'impression que l'énoncé à l'une ou l'autre extrémité de la ligne vous correspond exactement, veuillez faire un trait sur l'un des cercles. Il n'y a pas de bonnes ni de mauvaises réponses, veuillez simplement indiquer les réponses qui correspondent le mieux à votre situation.

Vos réponses doivent refléter la façon dont vous vous êtes senti au cours des7 derniers jours :

1. **Avez-vous des symptômes associés à votre maladie de l'intestin ?**

Aucun symptôme O----------O Symptômes très graves

2. **Votre maladie de l'intestin a-t-elle un impact négatif sur votre capacité à gérer tout ceque vous devez faire ou voulez faire dans la vie ?**

Pas du tout O----------O Énormément

3. **Êtes-vous inquiet à cause de votre maladie intestinale ?**

Pas du tout O----------O Énormément

4. **Comment décririez-vous votre bien-être général ?**

Excellent O----------O Épouvantable

- **Short Health Scale (ENGLISH VERSION)**
  SHS-IBD VAS - United Kingdom/English - Version of 23 Jun 11 - Mapi Institute.
  ID6235 / SHS-VAS_AU1.0_eng-GB.doc

Name: _____
ID number: _____
Date: _____

HEALTH ASSESSMENT
Short Health Scale
Inflammatory Bowel Disease

This questionnaire consists of four questions. Please answer the questions by placing a vertical mark (I) across the line in the position that best applies to you. If you feel that the statement on either end of the line applies exactly to you, then please indicate this by placing a mark on one of the circles. There are no right or wrong answers, only answers that best apply to you.

Your answers should reflect how you have been feeling during the last 7 days:

1. Do you have any symptoms from your bowel disease?

No symptoms O----------O Very severe symptoms

2. Does your bowel disease affect your ability to manage everything you have to do or want to do in life?

Not at all O----------O Extremely

3. Does your bowel disease worry you?

Not at all O----------O Extremely

4. How is your general well-being?

Excellent O----------O Terrible

16.8. EQ-5D

Questionnaire sur la santé

Version française pour la France

(FRENCH VERSION FOR FRANCE)

Pour chaque rubrique, veuillez cocher UNE case, celle qui décrit le mieux votre santé AUJOURD'HUI.

MOBILITÉ

Je n'ai aucun problème pour me déplacer à pied ❑
J'ai des problèmes légers pour me déplacer à pied ❑
J'ai des problèmes modérés pour me déplacer à pied ❑
J'ai des problèmes sévères pour me déplacer à pied ❑
Je suis incapable de me déplacer à pied ❑

AUTONOMIE DE LA PERSONNE

Je n'ai aucun problème pour me laver ou m'habiller tout(e) seul(e) ❑
J'ai des problèmes légers pour me laver ou m'habiller tout(e) seul(e) ❑
J'ai des problèmes modérés pour me laver ou m'habiller tout(e) seul(e) ❑
J'ai des problèmes sévères pour me laver ou m'habiller tout(e) seul(e) ❑
Je suis incapable de me laver ou de m'habiller tout(e) seul(e) ❑

ACTIVITÉS COURANTES *(exemples: travail, études, travaux domestiques, activités familiales ou loisirs)*

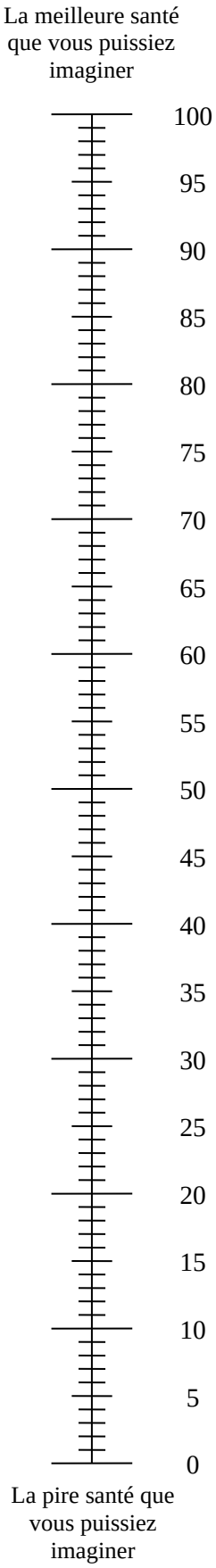
Je n'ai aucun problème pour accomplir mes activités courantes ❑
J'ai des problèmes légers pour accomplir mes activités courantes ❑
J'ai des problèmes modérés pour accomplir mes activités courantes ❑
J'ai des problèmes sévères pour accomplir mes activités courantes ❑
Je suis incapable d'accomplir mes activités courantes ❑

DOULEURS / GÊNE

Je n'ai ni douleur ni gêne ❑
J'ai des douleurs ou une gêne légère(s) ❑
J'ai des douleurs ou une gêne modérée(s) ❑
J'ai des douleurs ou une gêne sévère(s) ❑
J'ai des douleurs ou une gêne extrême(s) ❑

ANXIÉTÉ / DÉPRESSION

Je ne suis ni anxieux(se), ni déprimé(e)	❑
Je suis légèrement anxieux(se) ou déprimé(e)	❑
Je suis modérément anxieux(se) ou déprimé(e)	❑
Je suis sévèrement anxieux(se) ou déprimé(e)	❑
Je suis extrêmement anxieux(se) ou déprimé(e)	❑



VOTRE SANTÉ AUJOURD'HUI = ☐

Nous aimerions savoir dans quelle mesure votre santé est bonne ou mauvaise AUJOURD'HUI.

Cette échelle est numérotée de 0 à 100.

100 correspond à la meilleure santé que vous puissiez imaginer.
0 correspond à la pire santé que vous puissiez imaginer.

Veuillez faire une croix (X) sur l'échelle afin d'indiquer votre état de santé AUJOURD'HUI.

Maintenant, veuillez noter dans la case ci-dessous le chiffre que vous avez coché sur l'échelle.

Health Questionnaire

(ENGLISH VERSION FOR THE UK)

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(E.G. WORK, STUDY, HOUSEWORK, FAMILY OR LEISURE ACTIVITIES)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑

I am severely anxious or depressed ❑

I am extremely anxious or depressed ❑

We would like to know how good or bad your health is TODAY.

This scale is numbered from 0 to 100.

100 means the best health you can imagine.
0 means the worst health you can imagine.

Mark an X on the scale to indicate how your health is TODAY.

Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐