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A 12-month real life efficacy and safety study of IBD patients under stable steroid free clinical and biological remission switched from adalimumab originator Humira® to one of its biosimilars: Amgevita®, Hulio®, Hyrimoz® or Imraldi®: Rhoneswitch Study

Loïc Cabon

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UNIVERSITÉ GRENOBLE ALPES
UFR DE MÉDECINE DE GRENOBLE

Année : 2019

**A 12-MONTH REAL LIFE EFFICACY AND SAFETY STUDY OF IBD PATIENTS
UNDER STABLE STEROID FREE CLINICAL AND BIOLOGICAL REMISSION
SWITCHED FROM ADALIMUMAB ORIGINATOR HUMIRA® TO ONE OF ITS
BIOSIMILARS: AMGEVITA®, HULIO®, HYRIMOZ® OR IMRALDI®.
RHONESWITCH STUDY.**

THÈSE
PRÉSENTÉE POUR L'OBTENTION DU TITRE DE DOCTEUR EN MÉDECINE
DIPLOME D'ÉTAT

Loïc CABON

[Données à caractère personnel]

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LISTE DES ABREVIATIONS (par ordre alphabétique)

ACR American College of Rheumatology

ADA adalimumab

ADL Activities of Daily Living

AE adverse event

ALT alanine aminotransferase

ANC absolute neutrophil count

AP abdominal pain

AST aspartate aminotransferase

AUC area under the concentration

BLQ below the limit of quantitation

BMI body mass index

BMQ Beliefs about Medicines Questionnaire

Bs Biosimilar

CD Crohn's disease

CFR Code of Federal Regulations

CI confidence interval

CMH Cochran-Mantel-Haenszel

CNS central nervous system

CRF case report form(s)

CRO contract (or clinical) research organization

CRP c-reactive protein

CS corticosteroid

CSR clinical study report

CTCAE Common Terminology Criteria for Adverse Events

DA Dalton

DAS disease activity score

DAI disease activity index

DMC data monitoring committee

EC ethics committee

ECCO European Crohn's and Colitis Organisation

CRF case report form(s)

EG Exempli gratia (par exemple)

EMA European Medicines Agency

ET early termination

EU European Union

EudraCT European clinical trials database

FAS Full Analysis Set

FDA (United States) Food and Drug Administration

GCP Good Clinical Practice (Guidelines)

GI gastrointestinal

HBI Harvey Bradshaw Index

HC heavy chain

HCP host-cell protein

HCRU health care resource utilization

HCV Hepatitis C virus

HLGT High-Level Group Term

HLT High-Level Term

HRQoL health related quality of life

IB investigator brochure

IBD inflammatory bowel disease

IBDQ Inflammatory Bowel Disease Questionnaire

ICF informed consent form

ICH International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

IE Id est (c'est-à-dire)

IEC independent ethics committee

IFX infliximab

IL Interleukin IMP investigational medicinal product

IND Investigational new drug

IRB institutional review board

I^{re} Primaire

IUD intrauterine device

IV Intravenous

LC light chain

LLOQ Lower limit of quantitation

LLT Lower-Level Term

LOCF Last Observation Carried Forward

LTE long-term extension

mAb monoclonal antibody

MC Maladie de Crohn

MICI Maladies inflammatoires chroniques de l'intestin

MPR Medication Possession Ratio

NE nocebo effect

NOEL no-observed-effect-levels

NRS 11-point numeric pain rating scale

PASI Psoriasis Area and Severity Index

PBMC peripheral blood mononuclear cell

PE physical examination

PI principal investigator

PK Pharmacokinetic

PMS Partial Mayo Score

PRO2 patient reported outcomes consisting of 2 items: abdominal pain severity and liquid stool frequency

PT Preferred Term

PTx Post-Treatment

PVE Pharmacovigilance

Q1 1st quartile

Q3 3rd quartile

RA rheumatoid arthritis

RCH Rectocolite hémorragique

ROC receiver operating characteristic

RR risk ratio

SADR serious adverse drug reaction

SAE serious adverse event

SatMed-Q Treatment Satisfaction with Medicines Questionnaire

SAP Statistical Analysis Plan

SC Subcutaneous

SD standard deviation

SF stool frequency

SF-36 Short Form Health Survey

SI international system of units

STRIDE Selecting Therapeutic Targets in Inflammatory Bowel Disease

SOC system organ class

SOP standard operating procedure

SUSAR suspected Unexpected Serious Adverse Reaction

TB Tuberculosis

TEAE treatment-emergent adverse event

TDM therapeutic drug monitoring

TNF α tumor necrosis factor-alpha

UC ulcerative colitis

ULN upper limit of the normal range

US United States

Vs versus

WBC white blood cell

2^{dares} Secondaires

Données de vraie vie d'efficacité et de sécurité a 12 mois du switch de l'Humira® vers l'un de ses biosimilaires Amgevita®, Hulio®, Hyrimoz® ou Imraldi® chez des patients MICI en rémission clinique et biologique sans corticoïdes.

Etude Rhoneswitch.

RÉSUMÉ :

Contexte : Les anti-TNF sont efficaces dans le traitement des MICI et sont un progrès incontestable. Le brevet de l'adalimumab étant tombé dans le domaine public en 2018, ses biosimilaires sont arrivés, représentant une possibilité d'économie et de réinvestissement dans la recherche. Des études de non infériorité ont prouvé leur efficacité et sécurité équivalentes à l'Humira® dans le psoriasis notamment. Des données de vraie vie dans les MICI sont aujourd'hui attendues. Atténuer l'effet nocébo (EN) d'un switch est aussi un challenge.

Objectif : Essai multicentrique prospectif observationnel chez des patients MICI en rémission un an après leur switch de l'Humira® vers un de ses biosimilaires. L'objectif I^{er} est d'évaluer l'amplitude de l'EN. Les objectifs 2^{daires} sont le maintien d'efficacité, la sécurité et les facteurs d'adhésion au switch sur 1 an de suivi.

Matériel et méthodes : 200 MICI en rémission depuis ≥ 3 mois sous Humira® switchent vers un biosimilaire après information et avoir signé le consentement. Ils sont suivis tous les 3 mois un an cliniquement et biologiquement et remplissent 3 questionnaires (BMQ, SATMED-Q, IBD Disk) à chaque consultation.

Résultats : Critère principal de jugement : pourcentage de patients qui repassent dans l'année à l'Humira® sans marqueurs objectifs d'inflammation. Critères 2^{daires} : pourcentage de rémission clinique, biologique, réponse clinique, perte de réponse et effets indésirables à un an. Les facteurs favorisant un EN sont explorés par les questionnaires tous les 3 mois.

Conclusion : Nous apporterons les premières données françaises de vraie vie chez des MICI un an après leur « switch » de l'Humira® vers un biosimilaire.

A 12-month real life efficacy and safety study of IBD patients under stable steroid free clinical and biological remission switched from adalimumab originator Humira® to one of its biosimilars: Amgevita®, Hulio®, Hyrimoz® or Imraldi®.

Rhoneswitch Study

SUMMARY :

Background : Anti-TNF are effective drugs in induction and maintenance treatment of moderate to severe inflammatory bowel diseases (IBD) and are an undeniable progress. The patent for adalimumab fell into the public domain in 2018, leading to the arrival of several biosimilars, representing potential health-cost saving and research reinvestment. While studies of non-inferiority have proven similar efficacy and safety to Humira® in psoriasis notably, real-life data in IBD are expected. Reducing the nocebo effect (NE) of a switch is also a challenge.

Objective : One-year observational prospective multicentric real-life study evaluating IBD patients in remission who switch Humira® for one of its biosimilars. Main objective : to assess the magnitude of the NE. Secondary objectives : maintaining efficacy, safety and 1-year adherence factors to switch.

Materials and methods : 200 quiescent IBD patients for 3 months under Humira® are proposed to switch to one of its biosimilars after receiving information and signing the consent. They are clinically and biologically monitored every 3 months for one year and fill-up 3 questionnaires (BMQ, SATMED-Q, IBD Disk) at each appointment.

Results : Primary endpoint : percentage of patients who switch back to Humira® without any objective markers of inflammation during 1 year. Secondary endpoints : percentage of clinical remission, biological, clinical response, loss of response and adverse effects at one year. Risk factors for an NE are assess by the questionnaires every 3 months.

Conclusion : First real-life French data evaluating the one-year impact of Adalimumab originator switch to one of its biosimilars in IBD patients in remission.

Key words: Switch, Anti-TNF agents, Adalimumab, Biosimilars, Inflammatory Bowel Disease, Real-Life study, Prospective study.

Mots-clés: Switch, Anti-TNF alpha, Adalimumab, Biosimilaires, Maladie inflammatoire chronique de l'intestin, Etude de vraie vie, Etude prospective.

Subject field: gastro-enterology, CHU Grenoble Alpes

INTRODUCTION FRANCAISE AU PROTOCOLE

Les Maladies inflammatoires chroniques de l'intestin (MICI), en pratique Maladie de Crohn (MC) et Rectocolite hémorragique (RCH) sont caractérisées par une inflammation chronique du tube digestif atteignant exclusivement le rectum et le colon pour la RCH et tout le tube digestif avec une prédilection pour la région iléo-caecale pour la MC. Ces maladies évoluent de façon chronique, habituellement par poussées entrecoupées de périodes de rémission.

La MC comprend différents phénotypes : le phénotype inflammatoire, le sténosant et le pénétrant. Ces différents phénotypes peuvent s'associer. Les sténoses digestives qui peuvent en résulter nécessitent parfois une prise en charge chirurgicale. Les patients qui répètent les chirurgies avec résection des tissus endommagés sont à risque de développer un syndrome de l'intestin court ou de grêle court, dont la prise en charge nutritionnel peut être complexe.

Le phénotype pénétrant est caractérisé par la formation de fistules, qui peuvent se former entre deux segments de colon, du colon à la peau ou du colon à un autre organe adjacent comme la vessie par exemple. Selon la localisation, la prise en charge de ces fistules peut nécessiter une intervention chirurgicale. La MC pénétrante peut également se manifester par la formation d'abcès intra-abdominaux, qui peuvent engager le pronostic vital en cas de retard de prise en charge par antibiothérapie systémique et drainage selon la taille de l'abcès (1).

La RCH est une maladie chronique qui se caractérise par une diarrhée chronique avec l'émission fréquente de selles sanglantes, un syndrome dysentérique et une dysfonction de la mobilité du colon. La RCH pouvant évoluer jusqu'à la fibrose des tissus et provoquer des dommages définitifs.

De plus, les MICI peuvent entraîner des symptômes plus généraux comme une altération de l'état général, une perte de poids qui peut être significative, des éruptions cutanées comme des érythèmes noueux ou une atteinte articulaire (1).

La gravité est variable d'un malade à l'autre et chez le même malade d'une phase évolutive à l'autre. En France, la prévalence des MICI est estimée à 1/1000 et l'incidence est de l'ordre de 5 pour 100 000 habitants par an (2). Près de 200 000 personnes ont été prises en charge par l'assurance maladie pour MICI en 2013.

Il existe deux pics d'incidence des MICI : les jeunes adultes entre 15 et 35 ans et les adultes plus âgés entre 50 et 70 ans.

L'incidence et la prévalence des MICI en France et dans le monde sont en augmentation : l'incidence globale de la MC dans l'hémisphère nord peut aller de 7 à 20 pour 100 000 personnes par année, avec une prévalence jusqu'à 300 pour 100 000 personnes. L'incidence des MICI est en augmentation également en Asie. Au total, en Europe et aux États-Unis ce sont jusqu'à 1,5 million de personnes qui peuvent être atteintes (3) (4).

En raison de leur survenue tôt dans la vie, de leur chronicité et de leur symptomatologie digestive invalidante, ces maladies induisent une morbidité élevée qui altère la qualité de vie des patients (5) (6). De plus, bien que de façon globale les MICI augmentent peu la mortalité, il existe des risques non négligeables de complications pouvant engager le pronostic vital du patient, telles que la colite aigue grave, l'occlusion, la perforation digestive, les infections, les abcès ou la dénutrition.

L'étiologie des MICI n'est pas certaine et n'est pas entièrement élucidée. Il s'agit probablement d'une interaction complexe entre un terrain génétique prédisposant (gène NOD2 par exemple), des facteurs environnementaux comme le tabagisme actif pour la MC, des antibiothérapies répétées dans la jeune enfance, le stress et une dysrégulation de l'immunité de l'individu en faveur d'un état pro-inflammatoire (7) (8) (9).

Le microbiote intestinal joue également un rôle dans la physiopathologie des MICI. Un déséquilibre du microbiote des patients atteints de MICI appelé « dysbiose » a été observé. Cela se traduit par une diminution globale de la biodiversité avec une diminution de bactéries de la famille des Firmicutes et une augmentation du nombre de Protobactéries notamment. Ces modifications entraînent un déséquilibre de la balance entre les bactéries pro et anti-inflammatoires en faveur des pro-inflammatoires chez les patients atteints de MICI.

Il existe également une théorie dite « hygiéniste » selon laquelle l'incidence en augmentation des MICI sur les dernières décennies est due à l'augmentation des mesures d'hygiène dans les foyers réduisant les contacts entre les nouveau-nés et jeunes enfants avec l'environnement bactériologique naturel pouvant participer à cette dérégulation de l'immunité (10).

Pour déterminer la sévérité de la maladie, des scores existent basés sur les signes cliniques, sur la biologie, l'imagerie et l'endoscopie. Pour la MC, l'indice de Harvey-Bradshaw permet l'évaluation de l'activité de la maladie. Il permet d'établir un score allant de 0 à plus de 12 (43)

en théorie) en se basant sur la scorification de l'état général du patient (allant de bon à très mauvais), la présence de douleurs abdominales, le nombre de selles liquides par jour, la présence d'une masse abdominale à l'examen et la présence ou non de signes extra-digestifs associés, de fissures ou de fistule anales. Cet index permet de définir une maladie active si le score est > 4 , ainsi que qu'une maladie très sévère pour un score > 12 .

L'index d'Harvey-Bradshaw permet également de déterminer si une thérapie est efficace avec un score < 4 qui définit une rémission thérapeutique (11).

Un changement important a eu lieu sur la dernière décennie, l'objectif du traitement dans les MICI n'est plus seulement le contrôle des symptômes cliniques mais celui d'une rémission endoscopique et histologique appelé « mucosal healing » (12) (13). Le but ultime étant de modifier l'histoire naturelle de la maladie en la ralentissant en évitant les chirurgies et les hospitalisations. Ceci peut être atteint en utilisant de manière précoce des thérapies ciblées de manière agressive appelée la stratégie Top-Down puis en simplifiant les traitements si cela est possible selon l'évolution de la maladie (14) (15) (16).

Actuellement, pour les patients présentant une forme modérée à sévère de la maladie, il existe des traitements appelés biothérapies avec notamment les anti-TNF dont l'infliximab, l'adalimumab et le certolizumab pegol (autorisé seulement aux États-Unis), les anti-intégrines $\alpha 4\beta 7$ (védolizumab) et les anti-interleukines 12/23 (ustekinumab).

D'autres traitements sont en cours de développement comme les inhibiteurs des Janus Kinases (upacitinib) (17), des antagonistes de IL-23 p19 (risankisumab) (18) et un anticorps monoclonal dirigé contre l'intégrine $\beta 7$ (etrolizumab).

Les anti-TNF représentent la classe thérapeutique la plus largement utilisée. La fixation de l'anti-TNF au TNF alpha membranaire entraîne un blocage de l'interaction du TNF avec son récepteur et inhibe ainsi toute la voie de signalisation inflammatoire liée au TNF. Il s'agit de la principale voie impliquée dans la physiopathologie des MICI (5) (19). Ces biothérapies ont révolutionné la prise en charge non seulement des MICI mais aussi d'autres pathologies inflammatoires que ce soit en dermatologie avec le psoriasis ou en rhumatologie avec la spondylarthrite ankylosante par exemple.

Les molécules originales des Anti-TNF et en ce qui concerne notre étude celle de l'Adalimumab (Humira®) sont des molécules qui ont prouvé leur efficacité dans le traitement des MICI

notamment en limitant le risque de complications et celui d'hospitalisation (20) mais qui sont onéreuses.

C'est pourquoi, après le délai légal fixé par la loi, les brevets protégeant les molécules originales que ce soit pour le Remicade® ou l'Humira® sont tombés dans le domaine public et les premiers biosimilaires sont apparus.

Un biosimilaire est une molécule extrêmement comparable à la molécule d'origine que ce soit sur le poids, le volume mais aussi sur la pharmacocinétique (21). Certains excipients peuvent varier. Des études de phase III de non infériorité ont été nécessaires pour valider l'efficacité comparable du biosimilaire à la molécule originale. Mais cette non-infériorité doit aussi porter sur la sécurité d'emploi du biosimilaire c'est-à-dire sur les effets indésirables potentiels comme le risque d'infection, le risque d'anaphylaxie et sur son immunogénicité soit le risque de produire des anticorps contre le biosimilaire inactivant ainsi la molécule (22) (23).

Si le biosimilaire parvient à prouver sa non infériorité dans l'une des indications de la molécule originale, alors il obtient son autorisation de mise sur le marché pour toutes les indications validées de la molécule originale par extrapolation (24) (25).

L'un des intérêts principaux d'utilisation des biosimilaires est la réduction du coût de revient de ces molécules et par conséquent pouvoir étendre son utilisation et faciliter leur accès au plus grand nombre de patients. L'argent ainsi économisé peut-être réinvesti dans d'autres recherches (26).

Une déclaration récente d'ECCO a confirmé que le « switch » c'est-à-dire le changement d'une molécule originale vers son biosimilaire était une stratégie thérapeutique acceptable (27). Cette déclaration est étayé par les résultats rassurants de l'essai NOR-SWITCH, une étude de phase IV de non infériorité entre le Remicade® et son biosimilaire CT-P13 chez des patients adultes atteints de MC, de rectocolite hémorragique, de psoriasis ou de maladies rhumatismales inflammatoires (28).

Parallèlement à cela, nous savons que l'observance thérapeutique est un enjeu majeur dans la prise en charge des MICI. De nombreuses études ont étudié l'adhérence à un traitement oral de première ligne des MICI et notamment de la RCH, les 5 amino-salicylés. Ces dernières ont démontré que le pourcentage de non observance pour ce traitement pouvait atteindre 45 % (29). Les patients les moins observants étaient plus souvent en poussée et hospitalisés, augmentant parallèlement les coûts de santé (30) (31).

Pour les traitements Anti-TNF, la non-observance augmente le risque d'être en poussée de sa maladie notamment au niveau périnéale (32).

Cependant, le changement de traitement pour un patient peut se révéler effrayant (33) et c'est au praticien de le mettre en confiance afin qu'il puisse comprendre les bénéfices et les risques et prendre une décision éclairée et sans biais (34).

Le risque d'une mauvaise communication avec le patient avant de switcher une molécule vers un de ses biosimilaires est de voir apparaître un effet nocebo (EN).

L'effet nocebo est défini comme des effets négatifs, ressentis par le patient, d'un traitement pharmacologique ou non sans lien avec l'action physiologique du traitement. Il est l'inverse du plus connu effet placebo.

L'EN est un réel risque à l'ère des biosimilaires car celui-ci va réduire l'adhérence des patients au traitement et limiter par conséquent les bénéfices attendus de ce dernier (35).

Alors que des études ont démontré l'efficacité comparable des biosimilaires de l'Humira® à la molécule originale dans des indications comme le psoriasis ou les maladies rhumatologiques inflammatoires (36) (37), il existe peu de données concernant l'EN chez les patients MICI en particulier dans le cadre d'un switch.

Comprendre les mécanismes psychologiques qui peuvent intervenir dans les attentes d'un patient vis-à-vis de son traitement est un enjeu afin de minimiser l'EN à l'ère des biosimilaires. Des données de vraie vie sont aujourd'hui nécessaires.

CLINICAL STUDY PROTOCOL

STUDY TITLE: A 12-MONTH REAL LIFE EFFICACY AND SAFETY STUDY OF IBD PATIENTS UNDER STABLE STEROID FREE CLINICAL AND BIOLOGICAL REMISSION SWITCHED FROM ADALIMUMAB ORIGINATOR HUMIRA® TO ONE OF ITS BIOSIMILAR: AMGEVITA®, HULIO®, HYRIMOZ® OR IMRALDI®.

RHONESWITCH STUDY

12-month multicenter, observational, prospective cohort study

Sponsor Number:

Version N°31- Date: 26-JUN-2019

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Sponsor	CHU Grenoble Alpes Délégation à la Recherche Clinique et à l'Innovation CS 10217-38043 Grenoble cedex 9

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PROTOCOL UPDATES

VERSION	DATE	REASONS FOR THE UPDATE

PROTOCOL SIGNATURE

A 12-month real life efficacy and safety study of IBD patients under stable steroid free clinical and biological remission switched from adalimumab originator Humira® to one of its biosimilars: Amgevita®, Hulio®, Hyrimoz® or Imraldi®.

RHONESWITCH STUDY

This protocol was read and approved.

The Contracting Parties undertake to promote the research on acting pursuant to the relevant provisions of the Protocol and in conformity with their respective security regulations.

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1. PROTOCOL SYNOPSIS

Title	A 12-month real life efficacy and safety study of IBD patients under stable steroid free clinical and biological remission switched from adalimumab originator Humira® to one of its biosimilars: Amgevita®, Hulio®, Hyrimoz® or Imraldi®.
Short title	RHONESWITCH STUDY
Principal investigator	Mathieu Nicolas MD Hepato-gastroenterology and digestive oncology department, University Hospital, F-38000 Grenoble, France.
Sponsor	CHU GRENOBLE ALPES
Study rational	Biosimilars represent great potential in cost saving and re-investment opportunities in healthcare. Biosimilars of adalimumab appear to be clinically equivalent to the reference product in patients with rheumatoid arthritis and psoriasis. No data are currently available in IBD patients. Real-life data are needed. Minimizing the nocebo effect is another clinical challenge in the current era of biosimilars.
Methodology	48-weeks multicentre, observational, prospective cohort study is performed in 200 inactive IBD outpatients. Patients under stable (more than 3 months) steroid free clinical and biological remission will be proposed to switch from the originator Humira® to one of its biosimilars: Amgevita®, Hulio®, Hyrimoz® or Imraldi® as part of routine care.
Primary Objective	To describe the magnitude of patient's nocebo effect defined as a deterioration of symptoms without objective markers of disease activity, 48 weeks after the switch from ada originator Humira® to one of its biosimilars.
Primary endpoint	The primary endpoint is to assess the percentage of patients who switch back to originator therapy Humira® 48 weeks after switching from ada Humira® to ada Bs: Amgevita®, Hulio®, Hyrimoz® or Imraldi® in IBD patients without any objective markers of inflammation.
Secondary objectives	- To estimate the prevalence of steroid-free clinical remission at 48 weeks after switching.

	<ul style="list-style-type: none"> - To estimate, and investigate factors associated with patient’s adherence to the switch from ada originator to the ada Bs. - To describe the safety of ada Bs (Amgevita®, Hyrimoz®, Hulio®, Imraldi®) over the 48-week period following switching in IBD patients in clinical remission. - To evaluate whether there is a difference in nocebo effect according to the ada Bs, 48 weeks after switching from Humira®. - To explore patient’s beliefs and satisfaction about medication before and 48 weeks after switching from Humira® to an ada Bs, and whether they differ according to the ada Bs.
<p>Secondary endpoints</p>	<ul style="list-style-type: none"> -Percentage of patients on steroid free clinical remission at week 48 after the switch. Steroid-free Clinical Remission (CR) is defined as a Harvey Bradshaw Index (HBI) score ≤ 4 for CD patients and a Partial Mayo Score (PMS) ≤ 2 with each sub-score of 1 or less for UC. When HBI scoring will be infeasible (stoma, pouch), evaluation of clinical remission will be estimated by stoma emptying count and/or by the physician global assessment. Patients having discontinued adalimumab biosimilar therapy whatever the reason during the 48 weeks of follow-up as well as patients referred to disease-related surgery and patients lost to follow-up before week 48 will be considered as failure to adalimumab biosimilar therapy (intention to treat analysis) and will be classified in the group of patients having failed to maintain steroid free clinical remission under adalimumab biosimilar: Amgevita®, Hulio®, Hyrimoz® or Imraldi®, during the whole study period. - Percentage of PRO2 response and remission at week 48. -Percentage of biological remission rates (FC $< 250 \mu\text{g/g}$, CRP $< 5 \text{ mg/L}$) at week 48. -Percentage of clinical relapse free rates at week 48. -Percentage of loss of response rates at week 48. -Percentage of clinical response and remission at week 12.

	<ul style="list-style-type: none"> -Mean change from baseline in HBI or PMS, and mean change from baseline in CRP and fecal calprotectin. -Proportion of patients with positive antibodies (ADA, ANA) comparing therapy with original and biosimilar adalimumab. -Adherence to biosimilar switch during the follow-up: MPR ratios. * Safety Endpoints of interest: <ul style="list-style-type: none"> - Twelve-month cumulative surgery rates. - Hospitalization rate at week 48. - Cumulative infection rate at week 48. - Cumulative injection reactions at week 48. - Discontinuation of biosimilar adalimumab therapy cumulative rates at week 48. - Incidence of specific anti-drug antibodies detected during the study. *Explanatory factors behind a placebo effect during the follow-up: BMQ, SATMED-Q and the IBD Disk at week 12, 24 and 48.
<p>Inclusion criteria</p>	<ul style="list-style-type: none"> - Male or female subjects who are 18-75 years of age, on the day of signing informed consent. - Documented diagnosis of CD or UC established on the basis of standard clinical, endoscopic and histological criteria at least 3 months prior to inclusion. - Inactive CD or UC outpatients are defined per clinical assessment as a Harvey Bradshaw Index (HBI) score ≤ 4 for CD patients and a Partial Mayo Score (PMS) ≤ 2 with each sub-score of 1 or less for UC and/or according to ECCO classification within previous 3 months, demonstrating an adequate clinical remission to adalimumab originator. - May be receiving the following drugs (but must remain on stable dose for 10 weeks): <ul style="list-style-type: none"> * Oral 5-aminosalicylates (5ASA) compounds or rectal formulations of 5ASA provided the dose to be stable at least 4 weeks before switching.

	<p style="text-align: center;">* Azathioprine, 6-Mercaptopurine or methotrexate provided the dose has been stable for 4 weeks prior to inclusion (dose must remain stable for 10 weeks after switching).</p> <ul style="list-style-type: none"> - Each patient is required to provide written informed consent in order to be included in the study.
Exclusion criteria	<ul style="list-style-type: none"> - Diagnosis of indeterminate colitis, ischaemic colitis, fulminant colitis. - Current use of another TNF inhibitor included (but not limited to) infliximab, certolizumab, golimumab. - Current use of vedolizumab or ustekinumab. - Current use of JAK inhibitors or S1P modulators. - Treatment with any investigational agent in the past 30 days or five half-lives prior to the screening visit. - Hospitalized patients. - Active flaring CD or UC patients defined as an HBI > 4 for CD and a PMS>1 for UC and/or concomitant corticosteroid (CS) medication. - Current CD abscess. - Current use of oral corticosteroids. - Active clinically significant infection or HIV, Hepatitis B, Hepatitis C, untreated tuberculosis. - History of cancer or lymphoproliferative disease, other than completely treated cutaneous squamous cell, basal cell carcinoma. - Central nervous system demyelinating disease. - Poorly controlled medical conditions including uncontrolled diabetes mellitus with documented history of recurrent infections, unstable ischaemic heart disease, recent cerebrovascular accidents. - Pregnancy or breast feeding.

study design	<p>A 12-month multicentre, observational, prospective cohort study.</p> <p>Patients under stable (more than 3 months) steroid-free clinical and biological remission will be proposed to switch from the originator Humira® to one of adalimumab biosimilars (Amgevita®, Hyrimoz®, Hulio® or Imraldi®) as part of routine care. All patients are proposed to participate in the study during their regular outpatients' visits. Patients are first asked to read an information letter on biosimilars (pre-inclusion visit). During this appointment the physician will give to the patient a thorough explanation with a locally written patient information brochure on the biosimilar concept and on the switch modalities. After these 2 steps, if the patients agree to this switch from adalimumab originator to one of adalimumab biosimilars: Amgevita®, Hulio®, Hyrimoz® or Imraldi®, they will be asked to sign informed consent. Patients fill in 2 self-administered questionnaires to complete alone and collected 30 min later: BMQ (screening and week 48), SATMED-Q (weeks 12, 24 and 48) and the IBD Disk (each visit). The switch will be performed in a controlled setting: as a standard of care, blood and faecal samples (for monitoring faecal calprotectin, serum CRP and adalimumab specific antibodies) will be collected just prior the switch and then a tight monitoring of the previous biomarkers and TDM during the routine visits will be performed at week 12, 24 and week 48 after the switch with the IBD Disk filled-in at each visit accordingly. The patient's charts will be prospectively reviewed from medical records.</p>
Subjects number	Two hundred
Study centers	<p>A 12-month multicentre, observational, prospective cohort study.</p> <p>Study Centers:</p> <ul style="list-style-type: none"> - Hepato-gastroenterology and digestive oncology department, University Hospital, F-38000 Grenoble, France. - Department of Gastroenterology, Lyon-Sud University Hospital, Hospices Civils de Lyon, Pierre Bénite, and University Claude Bernard Lyon 1, France.
Study duration	<p>Study Duration: 30 months.</p> <p>Inclusion period: 12 months.</p>

	<p>Duration of treatment: 12 months.</p> <p>Follow-up: 6 months.</p> <p>Statistical analysis and manuscript writing: 6 months.</p>
<p>Statistical considerations</p>	<p>This study is a prospective cohort follow-up, which main objective is purely descriptive. Quantitative variables normally distributed will be described by the mean \pm standard deviation. They will be expressed as median with the 25th and 75th percentiles when normality is rejected. Nominal variables will be expressed in number and percentages. The Shapiro-Wilks test will be used to demonstrate the normality of the parameters and, if needed, Levene's will be used test assess the homogeneity of variances. Demographic summaries will include age, sex, race and ethnicity. Baseline characteristics may include height, weight, body mass index (BMI), HBI/PMS scores, PRO2 score, number of years since diagnosis of IBD, concomitant use of oral 5ASA, concomitant use of immunomodulators, fecal calprotectin, serum CRP, Time since ada initiation, previous use of other biologics and other variables of interest. All analyses will be conducted after the database is locked, following the procedures Grenoble Alpes University Hospital, under the supervision of the Cellule Data Stat.</p> <p>Based on data on ifx switch from originator to Bs, we anticipate that the NE occurred in 12.8%. A sample size of 196 allows estimating a two-sided 95% confidence interval for a single proportion, using the large sample normal approximation, extending 0,05 from the observed proportion for an expected proportion of 0,15.</p>
<p>Expected benefits</p>	<p>As the first french multicentre real life prospective cohort study, examining objective disease markers outcome and interpretation of subjective health complaints after switching from an adalimumab originator to one of its biosimilars, Amgevita®, Hulio®,Hyrimoz® or Imraldi®, the Rhoneswitch study will provide inserts for prevention and management of the nocebo effect in those biosimilar treated IBD patients. The contextualized informed consent of the Rhoneswitch study will identify the high-risk patients for the nocebo effect and minimize it. Regarding ifx biosimilar, assuming that the NE occurred in 12.8% of patients in a study that converted patients with different IMIDs from ifx originator to ifx biosimilar, and monitored the NE rate after a switch back to the originator, and that similar rates were observed</p>

	<p>in biosimilar treated patients with IBD and biosimilar treated patients with a rheumatologic condition (12.9% vs 12.5% respectively), when the sample size is 196, a two-sided 95% confidence interval for a single proportion using the large sample normal approximation will extend 0,05 from the observed proportion for an expected proportion of 0,15.</p>
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2. STUDY RATIONALE

2.1. Background

Ulcerative Colitis (UC) and Crohn's disease (CD) are relapsing and remitting forms of inflammatory bowel disease (IBD) that causes gastrointestinal signs and symptoms of diarrhea, abdominal pain, weight loss, and the passage of blood or mucous per rectum. The inflammation of IBD can involve the mucosal surface of the gastrointestinal tract and penetrate through the full thickness of the gastrointestinal wall, including the serosal surface. CD is characterized by phenotype and location of involved bowel. CD phenotypes include inflammatory, structuring and penetrating subtypes. Stricture formation can result in intestinal obstruction requiring surgical management. Over time, patients with repeated surgeries are at risk for developing short bowel syndrome and/or intestinal failure. Penetrating disease is characterized by fistula formation, which can be bowel to bowel, bowel to skin, or bowel to adjacent organ. Depending on location, penetrating disease can also require surgical management. Penetrating disease can also manifest with intra-abdominal abscess, a condition which can be life threatening if not treated early with systemic antibiotics (1). Ulcerative colitis (UC) is a chronic disease with a remitting and relapsing course that can progress from asymptomatic mild inflammation to extensive inflammation of the colon, resulting in frequent bloody stools, colonic motility dysfunction, potentially permanent fibrosis and tissue damage, systemic symptoms, and the need for surgery (38). In addition, IBD may affect other organ systems leading to rashes, joint pain and stiffness, fever, and weight loss (1). The incidence and prevalence of IBD has been increasing, with bimodal peaks affecting young adults (15 to 35 years of age) and older adults aged 50 to 70 with the age of onset often occurring in children < 12 years of age. Although geographic variation does occur, the overall incidence of CD in the northern hemisphere ranges from 7 to 20 per 100,000 person years, with a prevalence of up to 300 per 100,000 people. In the United States (US) and Europe, up to 1.5 million individuals may be affected and the incidence is on the rise in parts of Asia and the Middle East (3).

The cause of IBD is poorly understood, however a complex interplay of genetic predisposition, aberrant immune activation, and early infection during childhood may be involved. The importance of environmental triggers is suggested by increasing rates due to industrialization and improved domestic hygiene and sanitation. This "hygiene hypothesis" has also been implicated in various other autoimmune disorders (10).

To assess disease severity, a number of clinical scoring systems are utilized based upon signs, symptoms, laboratory parameters, imaging modalities and endoscopy. For CD, the Harvey

Bradshaw Index (HBI) is one such scoring tool with scores ranging from 0 to over 12 based upon a composite of symptoms (eg, abdominal pain), signs (the presence of abdominal mass and weight) and physician assessment amongst others. In this scoring system, patients with a score between 4 and 12 are defined as active disease and patients with a score > 12 are defined as severe, these comprise the patients with the greatest unmet medical need. The HBI can also be used to determine how well a therapy is working, with therapeutic remission defined as an HBI of < 4 points (11).

A significant change in CD management and therapeutic strategy has occurred over the last decade. Recent therapeutic goals extend beyond symptomatic control and include long-term mucosal and endoscopic remission (12). The ultimate aim is to change the natural course of the disease by slowing down or halting its progression, thus avoiding surgery or hospitalization. This is achieved by using earlier, aggressive and goal-directed therapy. Risk assessment and prediction by means of complex clinical, biochemical and endoscopic markers has become the key to patient management, therapy optimization and prediction of the outcome and side effects of medical therapy.

Currently available biologic therapies focus on neutralizing cytokine activity or altering T-cell differentiation and homing. Three monoclonal antibodies which inhibit tumor necrosis factor- α (TNF α), are currently marketed for the treatment of CD: infliximab (Remicade®), adalimumab (Humira® [approved in US and European Union]) and certolizumab pegol (Cimzia® [approved in US]). Vedolizumab (Entivyo®), a monoclonal antibody against $\alpha 4\beta 7$ integrin is also approved for moderately to severely active CD. Recently, ustekinumab (Stelara®), a monoclonal antibody directed against the p40 subunit of IL-23 and therefore an antagonist for both IL-12 and IL-23 signaling, has been approved for the treatment of CD.

Leukocytapheresis therapy may be used in Japan. Other investigational treatment approaches still in development include the administration of cytokines to stimulate innate immunity, the use of prebiotics to alter the gut flora and blocking the IL-6 signaling pathway (10). New treatments being tested in clinical trials include janus kinase (JAK) inhibitors (eg, upadacitinib), (17) and new biologic agents such as IL-23 p19 antagonists (eg, risankizumab) (18) and a monoclonal antibody directed against $\beta 7$ integrin (eg, etrolizumab) . While the introduction of biologic therapies has significantly improved response rates in patients with moderately to severely active CD, long-term or durable remission rates are still low at approximately 20%. Many patients receiving biologic therapies develop neutralizing antibodies with resulting loss of efficacy (39). These agents may be associated with specific safety issues including but not limited to anaphylaxis, increased risk of infection including progressive multifocal

leukoencephalopathy and liver injury. Safe and effective treatment options which may be conveniently administered in a chronic setting would provide a significant treatment advance for patients with moderately to severely active CD.

Biological medicines have clearly revolutionized the management of immune-mediated inflammatory diseases (IMIDs), like IBD, rheumatoid arthritis (RA) and ankylosing spondylitis (AS). As the first patent protections for biologicals began to expire, the market has been opened to copy versions of the originators. A biosimilar (Bs) is a product highly similar to an already authorized biological, with no clinically meaningful difference in efficacy, safety and immunogenicity, compared with the originator (21). Bs are expected to reduce health-care spending and increase treatment access (26). A recently published European Crohn's and Colitis Organisation (ECCO) position statement supported the use of Bs in IBD (27). It has been confirmed that switching from an originator biological to a Bs is an acceptable strategy (27). This statement is underpinned by the reassuring results of the NOR-SWITCH trial, a phase IV non-inferiority study initiated to examine the effects of such a switching strategy in different IMIDs (28). The data available on infliximab (ifx) Bs supports its biosimilarity and clinical equivalence compared to the reference originator. Several adalimumab (ada) Bs have been approved and are available in the market for the treatment of CD and UC. It is anticipated that Bs for IBD are here to stay, as they provide cost-effective alternatives to reference biologics, leading to an increase in physician treatment options and patient access to effective biologic treatment.

However, switching from an originator to a biosimilar can be daunting (33), and it is the responsibility of the physician to ensure patients are fully confident in understanding the benefits and risks, so that they can help patients make informed choices without bias (34). Where confidence in Bs is not built through traditional clinical training, knowledge of and access to high-quality data, and subsequently unsuccessfully communicated to patients, the nocebo effect (NE), which is defined as a negative effect of a pharmacological or non-pharmacological medical treatment that is induced by patients' expectations, and that is unrelated to the physiological action of the treatment, is becoming a real risk with possible negative implications (35).

2.2. Biosimilars

2.2.1. Amgevita

2.2.1.1. General Information

ABP 501 (Amgevita®, Solymbic®, Amgen) is a fully human monoclonal antibody of the immunoglobulin G1 (IgG1) subclass. It consists of 2 heavy chains (HC) and 2 light chains (LC) of the κ subclass. ABP 501 contains 32 total cysteine residues involved in both intrachain and interchain disulfide bonds. Each HC is composed of 451 amino acids with 4 intrachain disulfides. Each LC comprises 214 amino acids with 2 intrachain disulfides. Each HC contains an N-linked glycan at the consensus glycosylation site on Asn301. The experimentally determined predominant ABP 501 mass is 148,083 Dalton (da), in agreement with the theoretical value (40).

2.2.1.2. Preclinical Pharmacology and toxicology

The primary and higher-order structure, size and charge variants of ABP 501 have been shown to be similar to ada reference product. The aggregate and particle levels between ABP 501 and the originator are similar and the residual host-cell impurities, including host-cell protein (HCP) and DNA, in ABP501 are below the levels observed in the originator.

Functional biological characterization, including apoptosis inhibition bioassay, effector functions such as ADCC and CDC, soluble TNF- α and Fc neonatal receptor binding assays revealed equivalent biological activity compared to the originator (41).

2.2.1.3. Clinical Trials of Amgevita

Papp et al conducted a 52-week, double-blind study randomized patients with moderate to severe psoriasis to ABP 501 or ada reference product. Depending on the response status at week 16, those with 50% or more improvement in Psoriasis Area and Severity Index (PASI) score from baseline on ABP 501 continued the same treatment, whereas reference product-treated patients were re-randomized to ada or ABP 501. A treatment difference and 2-sided 95% confidence interval (CI) within the equivalence margin of ± 15 was set as criteria for nondifference between the two products. PASI improvement at week 16 was 80.9% for ABP 501 and 83.1% for ada (mean difference 2.18 [95% confidence interval -7.39 to 3.02]). Adverse events (67.2% vs 63.6%) and antidrug antibody incidence (55.2% vs 63.6%) for ABP 501 vs reference product were similar. Safety and immunogenicity were similar among groups after single transition at week 20. At week 16, 308 patients were re-randomized and followed up

through week 50. PASI percentage improvements from baseline were similar across groups at weeks 16, 32 and 50 (range: 85.8–88.2%), with no significant differences detected across groups in percentages of PASI 50, 75, 90 and 100 responders. Changes from baseline in percentage body surface area affected were similar across groups. No new safety signals were detected and AEs were balanced between groups. Binding and neutralizing anti-drug antibodies were similar across treatments (42).

One randomized controlled trial double-blind, active comparator-controlled, 26-week equivalence study, was conducted on 526 patients with moderate to severe active rheumatoid arthritis (RA) randomized (1:1) to ABP 501 or ada (40 mg) every 2 weeks. The primary endpoint was risk ratio (RR) of ACR20 (American College of Rheumatology) between groups at week 24. Equivalence was defined if the 90% CI for RR of ACR20 at week 24 fell between 0.7 and 1.3. Secondary endpoints included Disease Activity Score 28-joint count-C reactive protein (DAS28-CRP). Safety was assessed via adverse events (AEs) and laboratory evaluations. Antidrug antibodies were assessed to determine immunogenicity. Among the 494 patients who completed the study, ACR20 response at week 24 was 74.6% (ABP 501) vs. 72.4% (ada), with a 1.039 (0.954, 1.133) RR of ACR20 (90% CI). Changes from baseline in DAS28-CRP, ACR50 and ACR70 at week 24 were similar. There were no clinically meaningful differences in AEs and laboratory abnormalities. Binding antidrug antibodies were found in 38.3% (ABP 501) and 38.2% (ada) of patients, supporting the equivalence of ABP 501 and the originator. Those findings have been confirmed in an open label extension study through week 72 (37).

2.2.2. Imraldi

2.2.2.1. General Information

PD SB5 (Imraldi®, Samsung Bioepis UK Limited) is a recombinant human Y-shaped monoclonal antibody, a large glycoprotein consisting of two κ LC each with a molecular weight of approximately 24 kDa and two IgG1 HC each with a molecular weight of approximately 49 kDa. The total molecular weight of adalimumab is approximately 148 kDa. Each LC consists of 214 amino acid residues and each HC consists of 451 amino acid residues (40).

2.2.2.2. Clinical Trials of Imraldi

In a randomised phase I, single-blind trial, 189 healthy volunteers were randomized to a single 40 mg dose of SB5, adalimumab- EU or adalimumab-US. Pharmacokinetic (PK) was evaluated

for 71 days afterwards and equivalence was determined using predefined margins of 0.8–1.25. Mean values of area under the concentration (AUC)- time curve from time zero to infinity (AUC_{inf}), maximum serum concentration (C_{max}) and AUC from time zero to the last quantifiable concentration (AUC_{last}) were similar between groups and 90% confidence interval for these parameters remained within the predefined equivalence margins for all pairwise comparisons.

No discontinuations due to treatment emergent adverse events (TEAEs) or deaths were reported. The incidence of subjects with antidrug antibodies (ADA) and the overall incidence of neutralizing antibody (NAb) were comparable across the three groups (43).

A phase III, randomized, double-blind, parallel-group study, patients with moderately to severely active RA despite treatment with methotrexate was conducted on 542 patients, randomized 1:1 to receive SB5 (n = 269) or reference product (n = 273) at a dosage of 40 mg subcutaneously every other week. ACR20 improvement at week 24 was the primary endpoint, whereas additional end points included efficacy, PK, safety and immunogenicity assessments. The full analysis set was done on 476 patients (239 receiving SB5, 237 receiving reference ADA). The ACR20 response rate at week 24 was equivalent between those SB5 and reference product group (72.4% and 72.2%, respectively); the difference in the ACR20 response rate was within the predefined equivalence margin ($\pm 15\%$). The SB5 and reference product treatment groups were comparable across other endpoints, including the ACR 50% and ACR 70% improvement response rates, DAS28 based on the erythrocyte sedimentation rate, PK data, incidence of treatment-emergent adverse events and the antidrug antibody response (44).

Patients completing week 24 under reference product were re-randomized 1:1 to continue with reference product or to switch to SB5 up to week 52; patients receiving SB5 continued with SB5 for 52 weeks. At the end of the study, 542 patients (269 in the SB5 group, 273 in the reference product overall group) were included in the final analysis. ACR20 response rates ranged from 73.4% to 78.8% at week 52. Radiographic progression was minimal and comparable across treatment groups. The safety profile and the incidence of antidrug antibodies were comparable across treatment groups after transition (45) (44).

2.2.3. Hyrimoz

2.2.3.1. General Information

GP2017 (Hyrimoz®, Sandoz GmbH) is an IgG antibody composed of two κ LC each with a molecular weight of approximately 23 kDa and two IgG1 HC each with a molecular weight of

approximately 51 kDa (glycosylated). Adalimumab binds specifically to TNF and neutralizes the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors. One adalimumab molecule contains a total of four inter-chain and twelve intra-chain disulfide bridges. The total molecular weight of adalimumab is 148 kDa (glycosylated). Each LC consists of 214 amino acid residues and each HC consists of 451 amino acid residues. In total GP2017 consists of 1330 amino acids (40).

2.2.3.2. Preclinical pharmacology and toxicology

The primary and higher-order structure, size and charge variants of ABP 501 have been shown to be similar to ada reference product. The aggregate and particle levels between GP2017 and the originator are similar; the residual host-cell impurities, including HCP and DNA, in GP2017 are below the levels observed in the originator.

Functional biological characterization, including apoptosis inhibition bioassay, effector functions such as ADCC and CDC, soluble TNF- α and Fc neonatal receptor binding assays revealed equivalent biological activity compared to the originator (46).

2.2.3.3. Clinical trials of Hyrimoz

Blauvelt et al conducted a 51-week double-blinded, phase III study in 465 patients with psoriasis randomly assigned to GP2017 (n = 231) or reference product (n = 234) 80 mg subcutaneously at week 0, then 40 mg biweekly from week 1. At week 17, patients were re-randomized to be switched (n = 126) or to continue (n = 253) the same treatment. Similar efficacy between GP2017 and reference product was found for achieving $\geq 75\%$ PASI improvement (66.8% and 65.0%, respectively; 95% CI -7.46 to 11.15) at week 16. There were no relevant safety or immunogenicity differences between GP2017 and reference product at week 16 or between the switched and continued groups through week 51. No hypersensitivity to adalimumab was reported upon switching (47).

2.2.4. Hulio

2.2.4.1. General Information

FKB327 (Hulio®, Mylan) is a fully human monoclonal antibody of the immunoglobulin G1 (IgG1) subclass. It consists of 2 HC and 2 LC of the κ subclass. FKB327 contains 32 total cysteine residues involved in both intrachain and interchain disulfide bonds. Each HC is composed of 451 amino acids with 4 intrachain disulfides. Each LC comprises 214 amino acids

with 2 intrachain disulfides. Each HC contains an N-linked glycan at the consensus glycosylation site on Asn301. The experimentally determined predominant FKB327 mass is 148,083 Da, in agreement with the theoretical value (48).

2.2.4.2. Preclinical pharmacology and toxicology

The primary and higher-order structure, size and charge variants of FKB327 have been shown to be similar to the reference product. The aggregate and particle levels between FKB327 and the originator are similar; the residual host-cell impurities, including HCP and DNA, in FKB327 are below the levels observed in the originator.

Functional biological characterization, including apoptosis inhibition bioassay, effector functions such as ADCC and CDC, soluble TNF- α and Fc neonatal receptor binding assays revealed equivalent biological activity compared to the originator (49).

2.2.4.3. Clinical trials of Hulio

Alten et al treated 728 RA patients with either FKB327 (n=366) or reference product (n=362). Demographics and baseline RA characteristics were comparable between the groups, with overall mean age of 55.3 years, mean DAS28-CRP score of 6.1 and mean methotrexate dose of 15.7 mg/wk. ACR20 response rates at week 24 (full analysis set) were comparable between the FKB327 (270/363; 74.4%) and reference product groups (271/358; 75.7%). 95% CIs for treatment difference (FKB327 – reference product: -7.6 to 5.0) fell within the $\pm 13\%$ equivalence margins, meeting the primary study objective. ACR20 response rates over time overlapped during weeks 4–24. Least squares mean DAS28-CRP at week 24 were 3.43 on FKB327 and 3.42 on reference product and were equivalent using prespecified margins; changes in scores over time were also comparable. The proportions of patients reporting treatment-emergent AEs (TEAEs) on FKB327 or reference product were similar (FKB327 55.5% vs reference product 61.6%). AEs were mainly mild or moderate. The most common TEAEs ($\geq 5\%$) were nasopharyngitis (7.1% vs 8.0%) and upper respiratory tract infection (3.6% vs 5.0%). Incidences of serious AEs were similar (4.1% vs 5.2%). One death due to treatment-related disseminated tuberculosis (TB) was reported in the FKB327 group; reports of active TB were slightly higher with reference product (1 vs 3 patients). Mean serum trough concentration-time profiles of the two groups were comparable. The prevalence and level of antidrug antibodies (ADA) were similar, including at final sampling (57.9% vs 55.8%) (36).

2.3. Rationale for This Study

2.3.1. Generality

Two main typologies of IBD patients may approach to biological Bs: naïve and non-naïve to the reference drug. In the first case, the main concerns of patients are typically related to the efficacy and safety of Bs. In case of a switch, patients in stable clinical remission may be worried to lose the difficulty gained clinical benefit (50). Ensuring patients have a good understanding of what Bs are, confidence in their treatment and managing expectations of adverse events will help to reassure patients and avoid NE (51). The NE is defined as a negative effect of a pharmacological or non-pharmacological medical treatment that is induced by patients' expectations and that is unrelated to the physiological action of the treatment (52). It has been recognized as an important clinical challenge in the current era of Bs, since it can lower patients' quality of life and negatively affect treatment adherence rates (33). Evidence that the NE might indeed lead to unnecessary cessation of biologic treatment is mainly indirectly derived from open label observational studies, because double blinded trials are less susceptible to the NE. For example, The NOR-SWITCH study, a 52-week, randomized, double blind, non-inferiority, phase IV study, was conducted in adult patients with axial spondyloarthritis, RA, ankylosing spondylitis, CD, UC or psoriasis. Patients with informed consent were randomized to either continue originator ifx or to transition to Bs ifx (CT-P13) (28). This trial demonstrated that switching from ifx to CT-P13 was non-inferior to continued treatment with ifx. However, discordance in patient and physician outcome reporting was observed, which is a phenomenon previously reported (28).

Although data from controlled blinded trials have shown Bs used for treatment of autoimmune diseases to be equivalent to their reference biologic, data on open label transitioning to Bs are scarce. BIO-SPAN, the abstract of which was presented at EULAR 2017 and BIO-SWITCH are two such observational studies (53).

These two studies (BIO-SWITCH, from IFX to CT-P13 and BIO-SPAN, from reference etanercept [ETN] to biosimilar ETN [SB4]) were conducted in patients with rheumatic disease using different communication strategies to assess how an effective communication strategy may impact on reducing the nocebo effect (54). In patients transitioning from ETN to SB4, communication around transitioning was enhanced with additional information on the lower costs of treatment and data regarding potentially fewer injection-site reactions. During 84 person-years of follow-up, 47 patients discontinued CT-P13 (56/100 person-years; 26% due to inefficacy, 74% due to AEs). In contrast, 36 patients discontinued SB4 during 230 person-years

of follow-up (16/100 person-years; 53% due to inefficacy, 42% due to AEs and 5% due to remission) (55) demonstrating that improved communication resulted in much higher acceptance and persistence rates in those switching from a reference product to a Bs (54). In these examples, where effectiveness and safety were generally maintained, the authors hint to the NE to explain some of the observations where patient expectations may have affected the outcome and not the pharmacological properties of the agents involved. Considering the widespread influence that the NE can have, interest in how to negate this effect to improve clinical outcomes and reduce cost burdens is increasing (56). Although data about the NE and its impact in Bs treated IBD patients remain scarce, research in many other fields, such as depression, neuropathic pain perception and primary headache supports the influence of negative expectations on the occurrence of adverse symptoms and consequently on patients' well-being and adherence (56). However, only supported by indirect evidence (57), the NE can also lead to unnecessary cessation of biologic treatment, thereby altering IBD patients' outcomes in clinical practice and in clinical trials. Regarding ifx Bs, the NE occurred in 12.8% of patients in a study that converted patients with different IMIDs from ifx originator to ifx Bs and monitored the NE rate after a switch back to the originator (58). Similar rates were observed in Bs-treated patients with IBD and Bs treated patients with a rheumatologic condition (12.9% vs 12.5% respectively) (58). In that context, as Bs of ada appear to be clinically equivalent to the reference product in patients with RA and psoriasis, no data regarding the NE are currently available in IBD patients and particularly in the switch setting. Real-life data are needed. Multiple patient-related factors and psychological mechanisms can play a role in patients' expectations and reactions to medical treatment. Minimizing the NE while switching is indeed a clinical challenge in the current era of Bs. Health-care providers should identify patients at risk for the NE. Therefore, managing the NE and identifying factors that contribute to it seem out of outstanding interest while switching.

2.3.2. Rationale for Endpoints and Timing

The switch from ada original to ada Bs will be performed in a controlled setting. As a standard of care, blood, PKs, fecal samples (to monitor fecal calprotectin, serum CRP and adalimumab through levels and specific antibodies) will be collected just prior the switch and then a tight monitoring of those previous biomarkers and TDM during the routine visits will be performed at 3 months, 6 months and at one year after the switch. As the NE appears during the year following the switch from originator to Bs, we will evaluate patients at screening, Week 12, Week 24 and Week 48, those standard of care routine visits intervals follow the 2015 Selecting

Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) recommendations and ECCO ESGAR Guidelines that defined a follow-up approach for inflammatory bowel disease, which shifted the goal of IBD treatment to long-term prevention of disease complications (dysplasia/cancer, hospitalizations, colectomy) and proposed monitoring of objective disease activity measurements (59) (60).

A first approach to the NE is to indirectly evaluate the percentage of patients who switch back to innovator therapy Humira® 48 weeks after switching adalimumab Humira® to Bs (Amgevita®, Hyrimoz®, Hulio® or Imraldi®) without any objective markers of inflammation. Despite the existence of clinical tools designed to enable the standardized assessment of patients' expectations to a medical treatment, straightforward tools specifically identifying biosimilar treated IBD patients at risk for the NE are lacking. To date, there are no questionnaires clearly dedicated to identify NE risk factors. Nevertheless, some of them can help to explain treatment decisions, treatment adherence and reported side-effects (61): the Beliefs about Medicines Questionnaire (BMQ) for example measures attitudes toward medication in general and medication prescribed for personal use, including beliefs about its necessity and concerns about potential harms (62). We think that using three self-administered questionnaires that investigate patients' ideas about their illness, with each of them quickly filled-in at each visit accordingly (screening, Week 12, Week 26 and Week 48) can help us to approach patients NE risk factors. Meanwhile, to facilitate assessment of IBD related disability relevant to both patients and physicians, discussion on specific disability-related issues and tracking changes in disease burden at each visit, that parallel the NE, we will also use the IBD Disk.

As the first french multicentre real life prospective cohort study, examining objective disease markers outcome with interpretation of subjective health complaints after switching from an adalimumab originator to a Bs, the Rhoneswitch study will provide inserts for prevention and management of the NE in those Bs treated IBD patients. More, the contextualized informed consent of the Rhoneswitch study could assess and identify more efficiently those high-risk patients for the NE and minimize it.

2.3.3. Rationale for Dose

As IBD patients are in stable steroid free clinical and biological remission, Humira® doses are those expected under adalimumab maintenance treatment, according to daily practice and guidelines (63).

2.4 Risk/Benefit Assessment for the Study

UC and CD are progressive and potentially life-threatening diseases with few treatment options, many of which result in primary or secondary nonresponse. IBD may lead to increased risk of gastrointestinal malignancies, impairment in quality of life and ultimate need for life-altering surgery. Current treatment options are limited in ability to establish mucosal healing and clinical remission and have significant safety and efficacy limitations. For example, biologics have significant immunogenic risks and steroids are associated with increased morbidity and mortality. Remission rates are generally low when compared to placebo rates across most therapies for IBD. There remains substantial unmet need in IBD, particularly in moderate to severe disease. The lifelong nature of IBD increases the probability that subjects have cycled through various therapies, leaving few approved options.

2.5 Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP) and all applicable regulatory requirements.

3. Objectives and Endpoints

3.1. Objectives

3.1.1. Primary Objectives

The primary objective of Rhoneswitch is to describe the magnitude of patient's nocebo effect defined as a deterioration of symptoms without objective markers of disease activity, 48 weeks after the switch from ada originator Humira®.

3.1.2. Secondary Objectives

The secondary objectives are:

- To estimate the prevalence of steroid-free clinical remission at 48 weeks after switching.
- To estimate and investigate factors associated with patient's adherence to the switch from ada originator to the ada Bs.
- To describe the safety of ada Bs (Amgevita®, Hyrimoz®, Hulio®, Imraldi®) over the 48-week period following switching in IBD patients in clinical remission.

- To evaluate whether there is a difference in placebo effect according to the ada Bs, 48 weeks after switching from Humira®.
- To explore patient's beliefs and satisfaction about medication before and 48 weeks after switching from Humira® to an ada Bs and whether they differ according to the ada Bs.

3.2. Endpoints

3.2.1. The primary Endpoint

The primary endpoint is to assess the percentage of patients who switch back to originator therapy Humira® 48 weeks after switching from ada Humira® to ada Bs: Amgevita®, Hulio®, Hyrimoz® or Imraldi® in IBD patients without any objective markers of inflammation.

3.2.2. The key secondary endpoints

- Percentage of patients on steroid free clinical remission at week 48 after the switch. Steroid-free Clinical Remission (CR) is defined as a Harvey Bradshaw Index (HBI) score ≤ 4 for CD patients and a Partial Mayo Score (PMS) ≤ 2 with each sub-score of 1 or less for UC. When HBI scoring will be infeasible (stoma, pouch), evaluation of clinical remission will be estimated by stoma emptying count and/or by the physician global assessment (64).
- Patients having discontinued ada Bs therapy whatever the reason during the 48 weeks of follow-up as well as patients referred to disease-related surgery and patients lost to follow-up before week 48 will be considered as failure to ada Bs therapy (intention to treat analysis) and will be classified in the group of patients having failed to maintain steroid free clinical remission under ada Bs (Amgevita®, Hyrimoz®, Hulio®, Imraldi®) during the whole study period.
- Percentage of patient Reported Outcomes PRO2 rates at week 48.
- Percentage of biological remission rates (FC $<250 \mu\text{g/g}$, CRP $<5 \text{ mg/L}$) at week 48.
- Percentage of clinical relapse free rates at week 48.
- Percentage of loss of response rates at week 48.
- Percentage of clinical response and remission at Week 48.
- Mean change from baseline in HBI or PMS and mean change from baseline in CRP and fecal calprotectin.

- Proportion of patients with positive antibodies (ADA, ANA) comparing therapy with original and Bs ada.
- Measure adherence to Bs switch based on pharmacy data during the follow-up with Medication Possession Ratio (MPR).

3.2.3. The safety endpoints

The Safety Endpoints of interest of the Rhoneswitch study are:

- Twelve-month cumulative surgery rates.
- Hospitalization rate at week 48.
- Cumulative infection rate at week 48.
- Cumulative SC reactions at week 48.
- Discontinuation of Bs ada therapy cumulative rates at week 48.
- Incidence of specific anti-drug antibodies detected during the study.

3.2.4. The exploratory endpoints

The Exploratory efficacy endpoints are to identify the factors behind a NE during the 1-year follow-up with the results of three questionnaires (Appendix 5):

- The BMQ (62)
- The SATMED-Q (65)
- The IBD Disk (66)

4. Study Design

This is a 12-month multicenter, observational, prospective cohort study that will assess the magnitude of the patient's NE following the the switch from ada originator Humira® to ada Bs

(Amgevita®, Hyrimoz®, Hulio® or Imraldi®). A schematic of this study is provided in Appendix 2

This study includes:

- Screening (Days -30 to -1)
- Follow-up visit 1 (Week 12)
- Follow-up visit 2 (Week 24)
- Follow-up visit 3 (Week 48)

- At screening, Week 12, Week 24 and Week 48, HBI or PMS, PRO2 to assess clinical remission.
- At screening, Week 12, Week 24 and Week 48, Fecal Calprotectin and CRP to monitor inflammation and ada trough levels and ada antibodies for therapeutic drug monitoring (TDM).
- At screening, Week 12, Week 24 and Week 48, PBMC and liver tests to rule out myelotoxicity or liver injury.
- Subjects who secondary lose response and achieve neither clinical remission by HBI or PMS PRO2 nor Biomarkers response at Week 12, Week 24 or Week 48 will be treated by their IBD specialist according to local guidelines. Briefly, intensifying the ada regimen, changing to a different TNF Inhibitor or another class of biological agent and/or surgery will be led decided at the discretion by the managing physician in case of ada secondary non response.
- Post-Treatment (PTx) safety assessments.
- Subjects who complete all procedures per protocol, including biomarkers and therapeutic drug monitoring, of the 48-week study will be offered the option to continue ada Bs.

4.1. Study Treatments

Based on protocol eligibility criteria, subjects will be screened for enrollment in the cohort. Subjects who meet protocol eligibility criteria will be assigned to the Cohort and subsequently received ada Bs treatment.

4.2. Duration of Treatment

Subjects who meet protocol eligibility criteria will receive a maximum of 48 weeks of study drug. Subjects who are non-responders based on the results of the Week 12, week 24 or week

48 assessments will be treated by their IBD specialist according to local guidelines. Briefly, intensifying the ada regimen, changing to a different TNF Inhibitor or another class of biological agent, and/or surgery will be led decided at the discretion by the managing physician in case of ada secondary non response. (See Section 4.4, Disease Worsening Criteria).

4.3. Criteria for Study Drug Interruption or Discontinuation

4.3.1. Study Drug Interruption Considerations

The Medical Monitor should be consulted prior to study drug interruption when medically feasible by the investigator.

Study drug interruption should be considered in the following circumstances:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree.
- Subject is scheduled for elective or emergency surgery (excluding minor skin procedures under local or no anesthesia); timing of study drug pausing should be determined in consultation with the Medical Monitor.
- Any subject who develops a new infection during the study should undergo prompt and complete diagnostic testing appropriate for an immunocompromised individual and the subject should be closely monitored.

NOTE: During the time of study drug interruption for any of the above, the subject may continue to have study visits and to take part in procedures and assessments, if deemed medically appropriate by the investigator.

4.3.2. Study Drug Discontinuation Considerations

The Medical Monitor should be consulted prior to study drug discontinuation when medically feasible.

Study drug must be permanently discontinued in the following instances:

- Any opportunistic infection.
- Any serious infection that requires antimicrobial therapy or hospitalization or any infection that meets SAE reporting criteria.

- Febrile neutropenia (temperature $> 38.3^{\circ}\text{C}$ or a sustained temperature of $> 38^{\circ}\text{C}$ for more than one hour) with absolute neutrophil count of $< 1,000/\text{mm}^3$.
- Symptomatic anemia (eg, signs/symptoms including pallor, shortness of breath, new heart murmur, palpitations, lethargy, fatigue) with hemoglobin $< 7.5 \text{ g/dL}$ or if transfusion is indicated regardless of hemoglobin value.
- Complicated herpes zoster infection (with multi-dermatomal, disseminated, ophthalmic, or CNS involvement).
- Evidence of active HCV during the study, as evidenced by HCV RNA positivity.
- Evidence of active HBV during the study, as evidenced by HBV DNA positivity.
- Unacceptable toxicity, or toxicity that, in the judgment of the investigator, compromises the subject's ability to continue study-specific procedures or is considered to not be in the subject's best interest.
- Subject request to discontinue for any reason.
- Subject noncompliance.
- Discontinuation of the study at the request of Amgen, Sandoz, Mylan or Biogen, a regulatory agency or an institutional review board or independent ethics committee (IRB/IEC).
- Subject use of prohibited concurrent therapy may trigger study drug discontinuation; consultation should be made with the Medical Monitor.
- Laboratory Criteria: After becoming aware of any of the below described abnormal laboratory changes occurring at any one time, an unscheduled visit should occur to retest within 3 to 7 days (except creatinine, which should be retested 7 to 14 days apart):
 - 2 sequential neutrophil counts $< 750 \text{ neutrophils}/\text{mm}^3$ (international system units [SI] : $< 0.75 \times 10^9 \text{ cells/L}$)
 - 2 sequential platelet counts $< 75,000 \text{ platelets}/\text{mm}^3$ (SI : $< 75.0 \times 10^9 \text{ cells/L}$),
 - 2 sequential aspartate aminotransferase (AST) or alanine aminotransferase (ALT) 3 times the upper limit of normal range (ULN) and at least one of the following confirmed values :
 - Total bilirubin $> 2 \times \text{ULN}$
 - International normalized ratio (INR) > 1.5
 - Or accompanied by symptoms consistent with hepatic injury
 - For any subject with an initial AST or ALT elevation $> 3 \times$ the upper limit of normal (ULN), at the time of the second confirmatory draw, an INR,

prothrombin time (PT) and partial thromboplastin time (PTT) must also be drawn.

- 2 sequential AST or ALT > 5x ULN
- Subjects are free to withdraw from the study at any time without providing reason(s) for withdrawal and without prejudice to further treatment. The reason(s) for withdrawal will be documented in the electronic case report form (eCRF).
- Subjects who permanently discontinue study drug for any reason should discuss their continued care plan with their physician.
- Subjects who permanently discontinue study drug for pregnancy should not continue in the study; if there are any questions regarding permanent discontinuation, these should be discussed with the PI and the Sponsor.
- Subjects withdrawing from the study should complete Early Termination (ET), followed by post-Treatment (PTx) assessments 6 months after the last dose of study drug. Reasonable efforts will be made to contact subjects who are lost to follow-up. All contacts and contact attempts must be documented in the subject's file. The Sponsor has the right to terminate the study at any time in case of safety concerns or if special circumstances concerning the study medication or the Bs company itself occur, making further treatment of subjects impossible. In this event, the investigator(s) and relevant authorities will be informed of the reason for study termination.

4.4. Disease Worsening Criteria

Subjects meeting the following disease worsening criteria evaluated after screening must be treated by their IBD specialists accordingly.

- Active disease is defined as an HBI>4 for CD and a PMS>1 for UC and/or concomitant CS medication (64).
- Active biological disease will be defined as fecal calprotectin >250 µg/g and/or serum CRP >5 mg/L (60).
- The disease worsening visits may include unscheduled visits (eg, a study visit followed by an unscheduled visit or 2 sequential unscheduled visits anytime subsequent to the Week 12 visit). If a subject experiences significant worsening of underlying ibd, which requires any of the prohibited medications (refer to Section 5.2), or surgical intervention at any point during the study, study discontinuation should be considered at investigator's discretion, in

consultation with medical monitor if feasible (refer to Section 4.5.2); these subjects do not qualify for LTE study.

4.5. End of Study

End of Study is defined as when the last subject has completed 48 weeks of treatment plus 6 months follow-up.

4.6. Post Study Care

After the subject has completed their study participation, the long-term care of the participants will remain the responsibility of their primary treating physicians.

4.7. Biomarker Testing

4.7.1. Biomarker Samples to Address the Study Objectives:

The following biological specimens will be collected in this study and will be used to evaluate the association of exploratory systemic and/or tissue specific biomarkers with study drug response, including efficacy and/or AEs and to increase knowledge and understanding of the biology of CD

- CRP.
- PK: ada through levels. (Theradiag)
- PK : ada antibodies. (Theradiag)
- Fecal calprotectin. (Bühlman)

Active biological disease will be defined as fecal calprotectin >250 µg/g and/or serum CRP >5 mg/L (60).

5. STUDY POPULATION

200 inactive and stable (more than 3 months) IBD outpatients in steroid free clinical and biological remission under ada originator.

5.1. Inclusion Criteria

- Male or female subjects who are 18-75 years of age, on the day of signing informed consent.
- Documented diagnosis of CD or UC established on the basis of standard clinical, endoscopic and histological criteria at least 3 months prior to inclusion.
- Inactive CD or UC outpatients are defined per clinical assessment as a Harvey Bradshaw Index (HBI) score ≤ 4 for CD patients and a Partial Mayo Score (PMS) ≤ 2 with each sub-score of 1 or less for UC and/or according to ECCO classification (64) within previous 3 months, demonstrating an adequate clinical remission to ada originator.
- May be receiving the following drugs (but must remain on stable dose for 10 weeks):
 - Oral 5-aminosalicylates (ASA) compounds or rectal formulations of 5ASA provided the dose to be stable at least 4 weeks before switching.
 - Azathioprine, 6-MP or methotrexate provided the dose has been stable for 4 weeks prior to inclusion (dose must remain stable for 10 weeks after switching).
- Each patient is required to provide written informed consent in order to be included in the study.

5.2. Exclusion Criteria

- Diagnosis of indeterminate colitis, ischaemic colitis, fulminant colitis.
- Current use of another TNF inhibitor included (but not limited to) infliximab, certolizumab, golimumab.
- Current use of vedolizumab or ustekinumab.
- Current use of JAK inhibitors or S1P modulators.
- Treatment with any investigational agent in the past 30 days or five half-lives prior to the screening visit.
- Hospitalized patients.
- Active flaring CD or UC patients defined as an HBI > 4 for CD and a PMS > 1 for UC and/or concomitant CS medication.
- Current CD abscess.
- Current use of oral corticosteroids.

- Active clinically significant infection or HIV, Hep B, Hep C and untreated tuberculosis.
- History of cancer or lymphoproliferative disease, other than completely treated cutaneous squamous cell, basal cell carcinoma.
- Central nervous system demyelinating disease.
- Poorly controlled medical conditions including uncontrolled diabetes mellitus with documented history of recurrent infections, unstable ischaemic heart disease, recent cerebrovascular accidents.
- Pregnancy or breast feeding.

6. STUDY PROCEDURES

The study procedures to be conducted for each subject enrolled in the study are presented in tabular form in Appendix 2 and described in the text that follows.

6.1. Subject Enrollment and Treatment Assignment

Subjects will be screened within 30 days before to determine eligibility for participation in the study. The following will be performed and documented during the screening period:

All stable steroid free clinical and biological remission IBD patients are proposed by their treating physician to participate in the study during their regular outpatients' visits. Based on protocol eligibility criteria, subjects will be screened for enrollment. Subjects who meet the protocol criteria will be assigned to the ada Bs cohort.

6.2. Visit Assessments

6.2.1. Screening visit

- Patients are first asked to read an information letter on Bs.
During this appointment, to limit the risk of inappropriate negative bias and the NE, the physician will give to the patient a tailored, confident information exchange with a standard of care locally written patient information brochure on the Bs concept and on the switch modalities.
The information technique routinely used is positive framing which involves drawing attention to benefits rather than losses, while not refraining from delivering the necessary information. It has been shown that using gentle, reassuring words, with the focus on beneficial effects, improved subjective patients' experiences following neuraxial anesthetic

injection (35). Likewise, when presenting adverse events, it is advisable to use percentage formats (e.g. ‘5% of patients had an adverse event’) rather than frequency formats (e.g. ‘50 people in 1000 had an adverse event’) to comfort patients (52). For Bs, positive framing includes highlighting the similarities with biological originators regarding efficacy, safety, immunogenicity and accentuating that Bs lower health-care cost, instead of drawing attention to small existing biophysical batch-to-batch differences due to the complex manufacturing process of biological medicines. After discussion with the IBD team, patients develop an understanding of the science and evidence behind Bs.

The NE is directly addressed in the discussion with the patients. The whole health care staff will have been trained to the information technique during launch meeting. All members of the healthcare team will be educated about Bs and deliver the same message so as not to confuse patients Bs choice will be left at the discretion of each patient and the set of criteria for patient choice will be identified.

- Obtain written informed consent.
- Review inclusion/exclusion criteria and other protocol restrictions.
- Obtain medical history and concomitant medications, including CD history and treatment. The patient’s charts will be prospectively reviewed from medical records. Patients’ demographic and clinical characteristics will be collected, including age, gender, Body Mass Index (BMI), smoker status, disease duration, previous IBD related surgeries, CD disease location and behavior and UC extent, according to the Montreal classification. We will also collect prospectively data on surgery, clinical and biochemical disease activity and changes in concomitant medication during one-year of follow-up until the Bs switch.

Baseline disease severity (endoscopic, radiographic or clinical assessments), injections (dates, intervals, doses, premedication) and follow-up assessments (drug trough levels, endoscopic, radiographic or clinical assessments) will be recorded.

In addition, previous and current concomitant medications such as steroids including budesonide, immunomodulators (azathioprine, 6-mercaptopurine, methotrexate, tacrolimus and cyclosporine) and prior exposure to anti-TNF antibodies (infliximab, golimumab, certolizumab) or to other biologics (ustekinumab, vedolizumab) will be recorded.

- Obtain abdominal pain assessment by 11-point NRS.
- Ask Anchor Questions for abdominal pain and stool frequency.
- Complete physical examination (PE) including, vital signs, body weight and height.

- Record any SAEs and all AEs related to protocol mandated procedures occurring after signing of the informed consent form.
- Instruct subjects to maintain concomitant medication at a stable dose.
- Collect the variables to calculate baseline HBI/PMS scores (reference Appendix 4).
- Baseline PRO2 (Appendix 4) –calculated using the patient reported symptoms of stool frequency and abdominal pain captured during the clinical appointment.
- Questionnaires –To evaluate the explanatory factors behind a NE, patients fill in one self-administered questionnaire and the IBD Disk to complete alone and collected 30 min later: BMQ and IBD Disk (62) (66).
- Obtain blood samples (Appendix 2).
- Obtain stool sample (Appendix 2).
- In order to keep tracks of medicine (ada Bs) refills and to calculate the MPR, defined as the proportion of days’ supply obtained over refill interval or fixed interval, study coordinator will call patients’ pharmacies (67).
- Patients are advised to contact an IBD clinical nurse if they had any concerns.

6.2.2. Week 12, week 24 and Week 48

The following tests and procedures must be completed and dosing/dispensing:

- Review inclusion/exclusion criteria and other protocol restrictions.
- Symptom directed PE.
- Obtain body weight and vital signs (resting blood pressure, respiratory rate, pulse and temperature).
- Review AEs and concomitant medications.
- Review Diary for compliance and scores – remind subjects of diary instructions at every visit.
- Obtain abdominal pain assessment by 11-point NRS.
- Have subject complete BMQ (week 48), SATMED questionnaires and the IBD Disk.
- Obtain fasting blood samples (Appendix 2).
- Obtain stool sample for fecal calprotectin.
- Monitor Adherence: adherence to Bs switch will be assess by combining direct and indirect methods: Plasma trough concentrations of ada, measured according to standard medical follow-up and the MPR.

- In order to keep tracks of medicine (ada Bs) refills and to calculate the MPR, defined as the proportion of days' supply obtained over refill interval or fixed interval, study coordinator will call patients' pharmacies.

6.3. Study Assessments

Please refer to the Study Procedure Table in Appendix 2 for all procedures and time points to be conducted.

6.3.1. Priority of Assessments

Subject-reported outcomes are recommended to be completed before any other study procedures.

Invasive study procedures such as blood draws should be done at the end of a study visit, as much as possible. Investigator questionnaires/assessments should be performed prior to reviewing subject-reported outcomes for that visit, as much as possible.

6.3.2. Efficacy

Efficacy assessments will be performed at the time points indicated in the Study Procedures Table (Appendix 2, 4 and 5).

6.3.2.1.HBI/PMS and Patient Reported Outcomes – 2 items (PRO2)

The HBI is a tool used to assess the disease activity of CD. The PMS is a tool used to assess the disease activity of UC (64). Refer to Appendix 4. Active disease is defined as an HBI>4 for CD and a PMS>1 for UC and/or concomitant CS medication. The PRO2 is to patient reported outcomes of liquid or very soft stool and abdominal pain which are components of the HBI (64).

6.3.2.2.Patient Global Impression - Severity (PGI-S) and Patient Global Impression - Change (PGI-C)

The Patient Global Impression of Severity (PGI-S) is a global index that is used to rate the severity of IBD by patients (a single-state scale). The Patient Global Impression of Change (PGI-C) is a scale that aims at evaluating all aspects of patients' health related to IBD and determining if there has been an improvement or not. The patient has to select the one response

from the response options that gives the most accurate description of his/her state of health (overall status).

6.3.2.3. Abdominal Pain Assessed by 11-Point Numeric Rating Scale (NRS)

The 11-Point Numeric Rating Scale (NRS) is an 11-point scale to assess the severity of abdominal pain related to Crohn's disease.

6.3.2.4. BMQ

Beliefs about medications will be measured using a standardized self-administered questionnaire, the BMQ, which comprises two sections: the "BMQ-Specific" and the "BMQ-General". (Refer to Appendix 5). The BMQ consists of 18 items, each comprising a 5-point Likert scale ranging from 1 "strongly agree" to 5 "strongly disagree". 10 items measure specific beliefs about the prescribed treatment, in terms of its perceived necessity (specific-necessity: e.g., "My life would be impossible without my medicines") and concerns about it (specific-concerns e.g., "Having to take medicines worries me"). A further 8 items measure general beliefs about medicine, including perceptions of harm (general-harm, e.g., «Medicines do more harm than good») and overuse (general-overusing., "Doctors use too many medicines"). For each, a total score will be computed by adding together items' reverse scores. Each specific belief (specific-necessity and specific-concerns) scores between 5 and 25 and each general belief (general-harm and general-overuse) between 4 and 20. Higher values denote stronger beliefs. For specific beliefs, a differential score will be computed by subtracting specific-concerns from specific-necessity (necessity-concerns differential). For this additional score, a value above 0 means the perceived necessity of the treatment exceeded the concerns about taking it (62). To evaluate if patients' beliefs on drugs can be changed with lived user experience during the study period, BMQ will be filled in at inclusion and week 48.

6.3.2.5. SATMED-Q

Satisfaction with medications will be measured with a validated self-administered questionnaire, the SATMED-Q. (Refer to Appendix 5). This questionnaire is designed to be used in chronically ill patients undergoing pharmacological treatment and explores 6 dimensions: treatment effectiveness, convenience of use, impact on daily activities, medical care, global satisfaction and undesirable side effects. The SATMED-Q contains 17 items, each

scored on a 5-point Likert scale (65). The SATMED-Q and the BMQ are considered as two effective and easy to implement tools for use in everyday practice for chronic diseases (68) (69). Patients will fill in the SATMED-Q at each visit after the switch (week 12, 24, 48).

6.3.2.6. IBD Disk

Lastly, to track changes in disease burden over time, assess and monitor treatment efficacy in terms of disease burden, patients will be monitored by the IBD Disk Questionnaire and scoring disk. Refer to Appendix 5. The IBD Disk includes 10 items (Table 1). The tool comprises a questionnaire with an explanatory statement for each of the items, which should be scored on a disc-shaped visual analog scale from 0 (absolutely disagree) to 10 (absolutely agree) (66).

6.4. Safety

Safety will be assessed via AEs, concomitant medications, physical examinations (complete and symptom-driven), vital signs, ECGs and clinical laboratory results.

6.4.1. Clinical Laboratory Evaluations

The hematology, serum chemistry, coagulation laboratory and stool analyses will be performed at laboratory centers. Blood samples will be collected by venipuncture in the arm at the time points indicated in the Study Procedures Table (Appendix 2). In addition, stool samples for the clinical laboratory assessments will be collected. An overnight fast (no food or drinks, except water) of at least 8 hours will be required prior to collection of blood samples for liver testing. A stool sample should also be collected at any time during the study for culture for pathogenic bacteria, ova and parasites, and *Clostridium difficile* toxin assay when a subject becomes symptomatic, including worsening or return of disease activity.

Refer to Appendix 8 for table of clinical laboratory tests.

Laboratory values outside the normal range will be flagged and clinical relevance will be assessed by the investigator. More frequent sampling as well as additional tests may be performed as deemed necessary by the investigator.

Note that in the case where clinically significant laboratory test results are a potential reason for discontinuation from the study drug and/or withdrawal from the study, retesting of the affected parameter(s) should be prompt (within 3 to 7 days).

6.4.2. Pregnancy testing (for females of childbearing potential)

If any pregnancy test is positive during the follow-up study the subject should be treated by her IBD specialist according to local guidelines.

6.4.3. Vital Signs

Vital signs will be measured at the time points indicated in the Study Procedures Table (Appendix 2).

Vital signs should be taken after the subject has been resting in the seated or supine position for at least 5 minutes and will include pulse rate, respiratory rate, systolic and diastolic blood pressure and temperature.

6.4.4. Physical Examination

A physical examination should be performed at the time points indicated in the Study Procedures Table (Appendix 2). Any changes from screening will be recorded. Weight will be measured at all visits. Height will be measured at screening only. Subjects should be instructed to remove shoes prior to measurement of height.

At screening, a complete physical examination will be performed. A complete physical examination will include source documentation of general appearance and the following body systems: head, neck and thyroid; eyes, ears, nose, throat, mouth and tongue; chest (excluding breasts); respiratory; cardiovascular; lymph nodes; abdomen; skin, hair, nails; musculoskeletal and neurological. Symptom-driven physical examinations will be performed at all other visits based on reported signs and symptoms.

6.5. Biomarker Assessments

Blood and stool samples will be collected on Screening and at Weeks 12, 24 and 48.

Blood samples may be analyzed for assessment of markers of inflammation, immune status. Active biological disease will be defined as fecal calprotectin $>250 \mu\text{g/g}$ and/or serum CRP $>5 \text{ mg/L}$.

6.6. Post-Treatment Assessments

All subjects must complete the PTx assessments 6 months after the last dose of study drug.

The following will be performed and documented:

- Symptom-directed PE.

- Obtain body weight and vital signs (resting blood pressure, respiratory rate, pulse and temperature).
- Review AEs and concomitant medications.
- Obtain blood samples (reference Study Procedures Appendix 2).
- Obtain Stool sample (reference Study Procedures Appendix 2).

6.7. Early Termination Assessments

The following will be performed and documented:

- Symptom-directed PE.
- Obtain body weight and vital signs (resting blood pressure, respiratory rate, pulse and temperature).
- Review AEs and concomitant medications.
- Obtain abdominal pain assessment by 11-point NRS Collect the variables to calculate HBI/PMS/PRO2 score (reference Appendix 4).
- Obtain fasting blood samples (reference Study Procedures Appendix 2).
- Obtain stool sample (reference Study Procedures Appendix 2).
- Pregnancy test (for females of child bearing potential only).

6.8. End of Study

Please refer to Section 4.5.

6.9. Post Study Care

Please refer to Section 4.6.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events, Adverse Reactions, and Serious Adverse Events

7.1.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical study subject administered a medicinal product, which does not necessarily have a causal relationship with

the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Adverse events may also include pre- or post-treatment complications that occur as a result of protocol specified procedures, lack of efficacy, overdose, drug abuse/misuse reports or occupational exposure. Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction and transfusion. The condition that led to the procedure may be an adverse event and must be reported.
- Pre-existing diseases, conditions or laboratory abnormalities present or detected before the screening visit that do not worsen.
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions).
- Overdose without clinical sequelae.
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history CRF.

7.1.2. Serious Adverse Events

A serious adverse event (SAE) is defined as an event that, at any dose, results in the following:

- Death.
- Life-threatening (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).
- In-patient hospitalization or prolongation of existing hospitalization.
- Persistent or significant disability/incapacity.
- A congenital anomaly/birth defect.
- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and

scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency of drug abuse. For the avoidance of doubt, infections resulting from contaminated medicinal product will be considered a medically important event and subject to expedited reporting requirements.

7.2. Assessment of Adverse Events and Serious Adverse Events

The principal investigator (PI) or qualified sub investigator (SI) is responsible for assessing AEs and SAEs for causality and severity and for final review and confirmation of accuracy of event information and assessments.

7.2.1. Assessment of Causality for Study Drugs and Procedures

The PI or qualified SI is responsible for assessing the relationship to IMP therapy using clinical judgment and the following considerations:

- No: Evidence exists that the adverse event has an etiology other than the IMP. For SAEs, an alternative causality must be provided (eg, pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).
- Yes: There is reasonable possibility that the event may have been caused by the investigational medicinal product.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of adverse event reporting.

The relationship to study procedures (eg, invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- No: Evidence exists that the adverse event has an etiology other than the study procedure.
- Yes: The adverse event occurred as a result of protocol procedures (eg, venipuncture).

7.2.2. Assessment of Severity

The severity of AEs will be graded using the modified Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. For each episode, the highest grade attained should be reported.

If a CTCAE criterion does not exist, the investigator should use the grade or adjectives:

Grade 1(mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening) or Grade 5 (fatal) to describe the maximum intensity of the adverse event.

For purposes of consistency with the CTCAE, these intensity grades are defined in Table 7-1 and Appendix 6.

Table 7-1. Grading of Adverse Event Severity

Grade Adjective Description:

-Grade 1: Mild. Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

-Grade 2: Moderate. Local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.

-Grade 3: Severe. Severe or medically significant but not immediately life-threatening. hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.

-Grade 4: Life-threatening. Urgent intervention indicated.

-Grade 5: Death related AE.

* Activities of Daily Living (ADL) Instrumental ADL refer to opening preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bedridden.

7.3. Investigator Requirements and Instructions for Reporting Adverse Events and Serious Adverse Events to Amgen, Sandoz, Mylan or Biogen.

Requirements for collection prior to study drug initiation:

After informed consent, but prior to initiation of study medication, the following types of events should be reported on the CRF: all SAEs and adverse events related to protocol-mandated procedures.

7.3.1. Adverse Events

Following initiation of study medication, all AEs, regardless of cause or relationship, until

30 days after last administration of study IMP must be reported to the CRF database as instructed. All AEs should be followed up until resolution or until the adverse event is stable, if possible.

Amgen, Sandoz, Mylan or Biogen may request that certain AEs be followed beyond the protocol defined follow up period.

7.3.2. Serious Adverse Events

All SAEs, regardless of cause or relationship, that occurs after the subject first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the protocol-required post-treatment follow-up period, must be reported to the CRF database and Amgen, Sandoz, Mylan or Biogen PVE as instructed in 24 hours. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

Any SAEs and deaths that occur after the post-treatment follow-up visit but within 30 days of the last dose of study IMP, regardless of causality, should also be reported. Investigators are not obligated to actively seek SAEs after the protocol defined follow up period. However, if the investigator learns of any SAEs that occur after study participation has concluded and the event is deemed relevant to the use of IMP, he/she should promptly document and report the event to PVE.

- All AEs and SAEs will be recorded in the CRF database within the timelines outlined in the CRF completion guideline.
- At the time of study start, SAEs may be reported using a paper serious adverse event reporting form.
- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by e-mail or fax when requested and applicable.
- Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject identifiers
- Additional information may be requested to ensure the timely completion of accurate safety reports.
- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's CRF and the event description section of the SAE form.

7.4. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities are usually not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) independent of the underlying medical condition that require medical or surgical intervention or lead to investigational medicinal product interruption or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, ECG, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE (or SAE) as described in Sections 6.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (ie, anemia) not the laboratory result (ie, decreased hemoglobin).

Severity should be recorded and graded according to the CTCAE Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Appendix 6). For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

7.5. Toxicity Management

All clinical and clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in Appendix 3 and as outlined below.

Specific toxicity discontinuation criteria in Section 4.3 supersede below general toxicity guidelines and in general, where discrepancy is present, the more conservative criteria apply. The Medical Monitor should be consulted prior to study drug discontinuation when medically feasible.

7.5.1. Grades 1 and 2 Laboratory Abnormality or Clinical Event

Continue study drug at the discretion of the investigator.

7.5.2. Grade 3 Laboratory Abnormality or Clinical Event

- For a Grade 3 clinically significant laboratory abnormality or clinical event, IMP may be continued if the event is considered to be unrelated to IMP.

- For a Grade 3 clinical event or clinically significant laboratory abnormality confirmed by repeat testing, that is considered to be related to IMP, IMP should be withheld until the toxicity returns to \leq Grade 2.
- If a laboratory abnormality recurs to \geq Grade 3 following re-challenge with IMP and is considered related to IMP, then IMP should be permanently discontinued and the subject managed according to local practice. Recurrence of laboratory abnormalities considered unrelated to IMP may not require permanent discontinuation.

7.5.3. Grade 4 Laboratory Abnormality or Clinical Event

- For a Grade 4 clinical event or clinically significant Grade 4 laboratory abnormality confirmed by repeat testing that is considered related to IMP, IMP should be permanently discontinued and the subject managed according to local practice. The subject should be followed as clinically indicated until the laboratory abnormality returns to baseline or is otherwise explained, whichever occurs first. A clinically significant Grade 4 laboratory abnormality that is not confirmed by repeat testing should be managed according to the algorithm for the new toxicity grade. Investigational medicinal product may be continued without dose interruption for a clinically non-significant Grade 4 laboratory abnormality or a clinical event considered unrelated to IMP.

Treatment-emergent toxicities will be noted by the investigator and brought to the attention of the Medical Monitor, who will have a discussion with the investigator and decide the appropriate course of action. Whether or not considered treatment-related, all subjects experiencing AEs must be monitored periodically until symptoms subside, any abnormal laboratory values have resolved or returned to baseline levels or they are considered irreversible or until there is a satisfactory explanation for the changes observed.

Any questions regarding toxicity management should be directed to the Medical Monitor.

7.6. Special Situations Reports

7.6.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, reports of adverse events associated with product complaints, pregnancy reports regardless of an associated AE, an AE in an infant following exposure from breastfeeding and an occupational exposure with an AE.

Medication error is any unintentional error in the prescribing, dispensing or administration of a medicinal product while in the control of the health care provider, subject or consumer.

Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a subject.

Misuse is defined as any intentional and inappropriate use of a medicinal product that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labelling (as it applies to the daily dose of the subject in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).

Occupational exposure with an AE is defined as exposure to medicinal product as result of one's professional or non-professional occupation. Product complaint is defined as complaints arising from potential deviations in the manufacture, packaging or distribution of the medicinal product.

7.6.2. Instructions for Reporting Special Situations

7.6.2.1. Instructions for Reporting Pregnancies

The investigator should report pregnancies in female study subjects that are identified after initiation of study medication and throughout the study, including the post study drug follow-up period, to Amgen, Sandoz, Mylan or Biogen PVE using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

Refer to Section 7.3 and the CRF completion guidelines for full instructions on the mechanism of pregnancy reporting.

The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons. Abortion due to complications or other medical reasons must be reported within 24 hours as an SAE. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 7.3.2. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to PVE.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Amgen, Sandoz, Mylan or Biogen PVE using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Amgen PVE.

7.6.2.2. Reporting Other Special Situations

All other special situation reports must be reported on the special situations report form and forwarded to Amgen, Sandoz, Mylan or Biogen PVE within 24 hours of the investigator becoming aware of the situation.

Refer to Section 7.3 and the CRF completion guidelines for full instructions on the mechanism of special situations reporting.

All clinical sequelae in relation to these special situation reports will be reported as AEs or SAEs at the same time using the AE CRF and/or the SAE report form. Details of the symptoms and signs, clinical management and outcome will be reported, when available.

8. STATISTICAL CONSIDERATIONS

8.1. Collection and protection of data

A case report form (paper or eCRF) (Ennov Inc., Paris, France) will be created for the study and validated by a data manager from Grenoble Alpes University Hospital (Cellule Data Stat). Data entry will be performed by the investigation team, under the responsibility of the principal investigator. Any person allowed to complete the eCRF will be clearly identified in the document describing task distribution.

Electronic data will be kept on a specific, secured research shared drive hosted by Grenoble Alpes University Hospital. No data will be stored on personal computers or USB drives.

8.2. General principles of the statistical analysis

This study is a prospective cohort follow-up, which main objective is purely descriptive. We will follow the strengthening the reporting of observational studies in epidemiology statement. Quantitative variables normally distributed will be described by the mean \pm standard deviation. They will be expressed as median with the 25th and 75th percentiles when normality is rejected. Nominal variables will be expressed in number and percentages. The

Shapiro-Wilks test will be used to demonstrate the normality of the parameters and, if needed, Levene's will be used test assess the homogeneity of variances.

Demographic summaries will include age, sex, race and ethnicity. Baseline characteristics may include height, weight, body mass index (BMI), HBI/PMS scores, PRO2 score, number of years since diagnosis of IBD, concomitant use of oral 5ASA, concomitant use of immunomodulators, fecal calprotectin, serum CRP, time since ada initiation, previous use of other biologics and other variables of interest. All analyses will be conducted after the database is locked, following the procedures Grenoble Alpes University Hospital, under the supervision of the Cellule Data Stat.

8.3. Sample size calculation

Based on data on ifx switch from originator to Bs, we anticipate that the NE occurred in 12.8% (58). A sample size of 196 allows estimating a two-sided 95% confidence interval for a single proportion, using the large sample normal approximation, extending 0,05 from the observed proportion for an expected proportion of 0,15.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

Ethical approval for the present study will be previously obtained from the Ethics Committee on Clinical research, in compliance with the Declaration of Helsinki.

The investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki, International Council for Harmonization (ICH) guidelines or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject. These standards are consistent with the EU Clinical Trials Directive 2001/20/EC and GCP Directive 2005/28/EC.

The investigator will ensure adherence to the basic principles of GCP.

9.1.2. Institutional Review Board/Independent Ethics Committee Review and Approval

The investigator (or sponsor as appropriate according to local regulations) will submit this protocol, ICF and any accompanying material to be provided to the subject (such as advertisements, subject information sheets or descriptions of the study used to obtain informed consent) to an IRB/IEC. The investigator will not begin any study subject activities until approval from the IRB/IEC has been documented and provided as a letter to the investigator. Before implementation, the investigator will submit to and receive documented approval from the IRB/IEC any modifications made to the protocol or any accompanying material to be provided to the subject after initial IRB/IEC approval, with the exception of those necessary to reduce immediate risk to study subjects.

9.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives and potential hazards of the study and before undertaking any study-related procedures. The investigator must use the most current IRB/IEC approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion and also by an impartial witness if required by IRB/IEC or local requirements. The consent form will inform subjects about genomic testing and sample retention.

9.1.4. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials, date of birth, another unique identifier (as allowed by local law) and an identification code will be recorded on any form or biological sample submitted to the Sponsor, IRB/IEC or laboratory. Laboratory specimens must be labeled in such a way as to protect subject identity while allowing the results to be recorded to the proper subject. Refer to specific laboratory instructions or in accordance with local regulations.

NOTE: The investigator must keep a screening log showing codes and names for all subjects screened and for all subjects enrolled in the trial. Subject data will be processed in accordance with all applicable regulations.

9.1.5. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following two categories:

- (1) Investigator's study file.
- (2) Subject clinical source documents.

The investigator's study file will contain the protocol/amendments, CRF and governmental approval with correspondence, informed consent, drug records, staff, curriculum vitae and authorization forms and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each subject:

- Subject identification (name, date of birth, gender).
- Documentation that subject meets eligibility criteria, ie, history, PE and confirmation of diagnosis (to support inclusion and exclusion criteria).
- Documentation of the reason(s) a consented subject is not enrolled Participation in study (including study number).
- Study discussed and date of informed consent.
- Dates of all visits.
- Documentation that protocol specific procedures were performed.
- Results of efficacy parameters, as required by the protocol.
- Start and end date (including dose regimen) of IMP, including dates of dispensing and return.
- Record of all AEs and other safety parameters (start and end date, and including causality and severity).
- Concomitant medication (including start and end date, dose if relevant; dose changes).
- Date of study completion and reason for early discontinuation, if it occurs.

9.1.6. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by PI and Medical Monitor. The investigator must submit all protocol modifications to the IRB/IEC in accordance with local requirements and receive documented IRB/IEC approval before modifications can be implemented.

9.2.2. Study Report and Publications

Investigators in this study may communicate, orally present, publish in scientific journals or other scholarly media only after the following conditions have been met:

- The results of the study in their entirety have been publicly disclosed by or with the consent of Amgen, Sandoz, Mylan or Biogen in an abstract, manuscript or presentation form or the study has been completed at all study sites for at least 2 years.
- The investigator will submit to Amgen, Sandoz, Mylan or Biogen any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation.
- No such communication, presentation or publication will include Amgen, Sandoz, Mylan or Biogen confidential information.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Study Discontinuation

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory authority(ies), IRBs and IECs. In terminating the study, Amgen, Sandoz, Mylan or Biogen and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

10. PROJECTED STUDY MILESTONES

Planned Start (estimated # of months from approval to study start) :	january 2020
Study Duration (estimated # of months of planned data collection) :	30
Final data available (estimated # of months after project or study completion) :	6
Estimated duration of research (study start to final study deliverable) :	30
Estimated duration of first patient enrolled to last patient out :	30
Estimated duration for ada Bs to supply study drug :	-
Inclusion period (estimated # of months) :	12
Duration of treatment (estimated # of months) :	12
Follow-up (estimated # of months) :	6
Statistical analysis and manuscript writing (estimated # of months) :	6

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12. APPENDICES

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Appendix 1. Investigator Signature Page

Investigator statement

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within time designated.

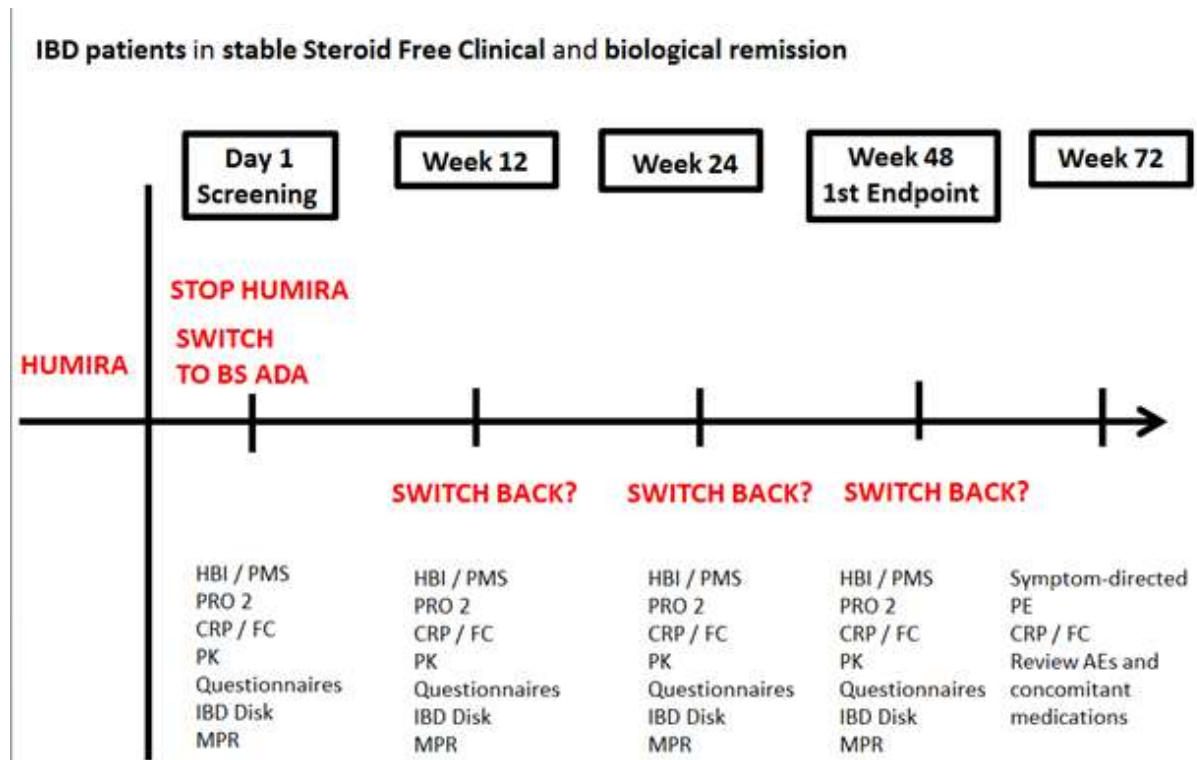
I will provide all study personnel under my supervision copies of the protocol. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal investigator Name (printed):

Signature:

Date :

Appendix 2. Study Procedures Table



HBI : Harvey-Bradshaw Index

PMS : Partial Mayo Score

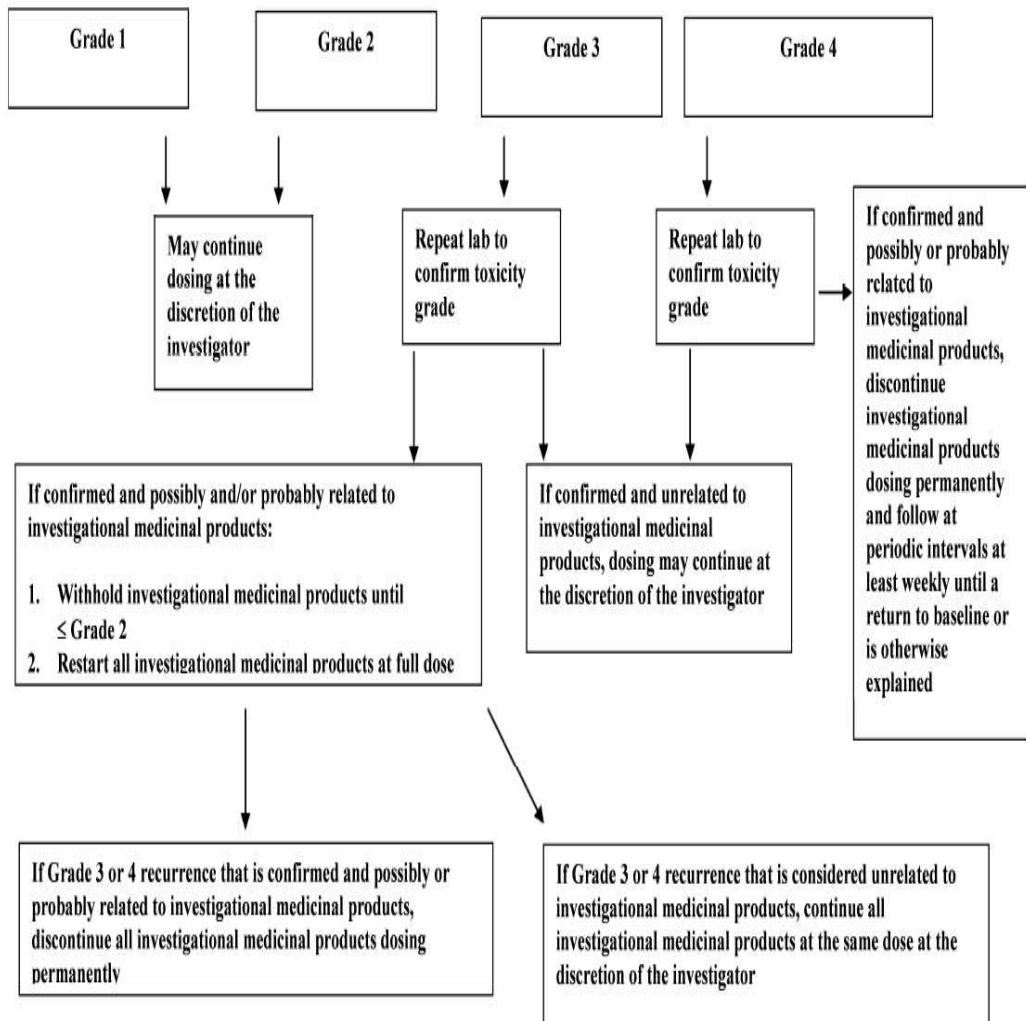
PE : Physical Examination

FC : Fecal Calprotectin

Questionnaire : BMQ (screening and week 48), SATMED-Q (weeks 12, 24, 48) questionnaires

MPR : Medications possession Ratio

Appendix 3. Management of Clinical and Laboratory Adverse Events



Appendix 4. Harvey Bradshaw Index (HBI) Partial Mayo Score (PMS) and Patient Reported Outcomes – 2 items (PRO2)

- Harvey-Bradshaw Index

Harvey-Bradshaw Index

General well-being (yesterday) *

- Very well Slightly below par Poor Very poor Terrible
-

Abdominal pain (yesterday) *

- None Mild Moderate Severe
-

Number of liquid or soft stools per day (yesterday) *

- | | |
|-------------------------|--------------------------|
| <input type="radio"/> 0 | <input type="radio"/> 5 |
| <input type="radio"/> 1 | <input type="radio"/> 6 |
| <input type="radio"/> 2 | <input type="radio"/> 7 |
| <input type="radio"/> 3 | <input type="radio"/> 8 |
| <input type="radio"/> 4 | <input type="radio"/> >8 |
-

Abdominal mass *

- None Dubious Definite Definite and tender
-

Complications

Please check all that apply

- | | |
|---|---|
| <input type="checkbox"/> Arthralgia | <input type="checkbox"/> Pyoderma gangrenosum |
| <input type="checkbox"/> Uveitis | <input type="checkbox"/> Anal fissure |
| <input type="checkbox"/> Erythema nodosum | <input type="checkbox"/> New fistula |
| <input type="checkbox"/> Aphthous ulcers | <input type="checkbox"/> Abscess |

- Partial Mayo Score

1. Stool frequency (per day)	<ul style="list-style-type: none"> ▪ normal number of stools ▪ 1-2 more than normal ▪ 3-4 more than normal ▪ ≥ 5 more than normal 	0 1 2 3
2. Rectal bleeding (indicate the most severe bleeding of the day)	<ul style="list-style-type: none"> ▪ none ▪ streaks of blood with stool in less than half of the cases ▪ obvious blood with stools in most cases ▪ blood alone passes 	0 1 2 3
3. Physician's global assessment	<ul style="list-style-type: none"> ▪ normal ▪ mild disease ▪ moderate disease ▪ severe disease 	0 1 2 3

Calculation formula: sum of the scores the three parameters.

Clinical response is defined as a decrease of at least 2 points of the Mayo Clinical Score (4).

Decoding table (1)

Score	Decoding
< 2	remission
2 - 4	mild activity
5 - 7	moderate activity
> 7	severe activity

- Patient Reported Outcomes- 2 items (PRO2)

The patient reported outcomes of liquid or very soft stool and abdominal pain (PRO2) score will be assessed as follows:

Variable no.	Variable	Variable description
1	Liquid or very soft stool	Mean of the daily (liquid or very soft) stool count for 7 days
2	Abdominal pain	Mean of 7 days of daily ratings as 0 = none, 1 = mild, 2 = moderate, 3 = severe

Appendix 5. BMQ, SATMED-Q questionnaires and the IBD Disk

- Beliefs about medicine- BMQ questionnaire

Beliefs about medicines questionnaire (BMQ) Home, Weinman, Hankins, (1999)
Psychology and Health, 14, 1-24

BMQ –Specific

Your views about medicines prescribed to you.

- I would like to ask you about your personal views about medicines prescribed for your asthma
- These are statements other people have made about their asthma medication.
- Please indicate the extent to which you agree or disagree with them by placing a cross in the appropriate box.
- There are no right or wrong answers. I am interested in your personal views.
- Please only cross one box per question.

1) My health at present depends on my asthma medicines

Strongly agree	agree	uncertain	disagree	strongly disagree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

2) Having to take asthma medication worries me

Strongly agree	agree	uncertain	disagree	strongly disagree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

3) My life would be impossible without my asthma medication

Strongly agree	agree	uncertain	disagree	strongly disagree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

4) Without my asthma medication I would be very ill

Strongly agree	agree	uncertain	disagree	strongly disagree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

5) I sometimes worry about the long term effects of my asthma medication

Strongly agree	agree	uncertain	disagree	strongly disagree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

6) My asthma medication is mystery to me

Strongly agree	agree	uncertain	disagree	strongly disagree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

7) My health in the future will depend on my asthma medication

Strongly agree	agree	uncertain	disagree	strongly disagree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

8) My asthma medication disrupts my life

Strongly agree	agree	uncertain	disagree	strongly disagree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

9) I sometimes worry about becoming too dependent on my asthma medication

Strongly agree	agree	uncertain	disagree	strongly disagree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

10) My asthma medication protects me from becoming worse.

Strongly agree	agree	uncertain	disagree	strongly disagree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

BMQ-General

- I would like to ask you about your personal views about medicines in general.
- These are statements other people have made about medicines in general.
- Please indicate the extent to which you agree or disagree with them by ticking the appropriate box.
- There are no right or wrong answers. I am interested in your personal views.
- Please only tick one box per question.

11) Doctors use too many medicines

Strongly agree	agree	uncertain	disagree	strongly disagree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

12) People who take medicines should stop their treatment for a while every now and again.

Strongly agree	agree	uncertain	disagree	strongly disagree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

13) Most medicines are addictive.

Strongly agree	agree	uncertain	disagree	strongly disagree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

14) Natural remedies are safer than medicines

Strongly agree	agree	uncertain	disagree	strongly disagree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

15) Medicines do more harm than good.

Strongly agree	agree	uncertain	disagree	strongly disagree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

16) All medicines are poisons

Strongly agree

agree

uncertain

disagree

strongly disagree

17) Doctors place too much trust on medicines

Strongly agree

agree

uncertain

disagree

strongly disagree

18) If doctors had more time with patients they would prescribe fewer medicines.

Strongly agree

agree

uncertain

disagree

strongly disagree

QUESTIONNAIRE DU BMQ®

Ce questionnaire consiste en un certain nombre d'appréciations personnelles à propos des médicaments que vous prenez. Veuillez s'il vous plaît indiquer votre avis en cochant la case correspondante (Pas du tout d'accord, plutôt pas d'accord, Ni en désaccord, ni d'accord, plutôt d'accord, tout à fait d'accord). Il n'y a ni de bonnes, ni de mauvaises réponses. Vos réponses seront toujours bonnes si vous dites vraiment ce que vous pensez.

	Pas du tout d'accord	Plutôt pas d'accord	Ni en désaccord ni d'accord	Plutôt d'accord	Tout à fait d'accord
1. Mes médicaments me permettent de ne pas aller plus mal					
2. Tout de suite, ma santé dépend de mes médicaments					
3. Dans l'avenir, ma santé dépend de mes médicaments					
4. Sans mes médicaments, je serai très malade					
5. Ma vie serait impossible sans mes médicaments					
6. Je m'inquiète quelques fois des effets à long terme de mes médicaments					
7. Mes médicaments sont un mystère pour moi					
8. Je m'inquiète quelques fois d'être devenu trop dépendant à mes médicaments					
9. Je m'inquiète d'avoir à prendre des médicaments					
10. Mes médicaments perturbent ma vie					
11. Les docteurs utilisent trop de médicaments					
12. Si les docteurs passaient plus de temps avec les patients, ils prescriraient moins de médicaments					
13. Les docteurs placent trop de confiance dans les médicaments					
14. Les remèdes naturels sont plus sûrs que les médicaments					
15. La plupart des médicaments sont addictifs					
16. Les personnes qui prennent des médicaments devraient arrêter leur traitement de temps en temps					
17. Les médicaments font plus de mal que de bien					
18. Tous les médicaments sont des poisons					

Nous vous remercions de votre collaboration

- SATMED-Q questionnaire

TREATMENT SATISFACTION WITH MEDICINES QUESTIONNAIRE[®]

(SATMED-Q[®] Questionnaire)

We want to ask you about **your satisfaction with the medicine** you are taking. You may be taking medicines to treat more than one medical condition. If so, please answer the questionnaire for **ONLY ONE** of the conditions and the one of the medicine you have taken for the condition.

Medical condition for which you are taking the medicine

For each question, **put a cross through** the number that best reflects your opinion. There are no right or wrong answers. If you are not sure of any of the answers, mark the one you consider most appropriate.

- Have you experienced any side effects caused by the medicine?

No, none

Yes, at least one

- This section is about the undesirable side effects of the medicine

	Not at all	A little bit	Some-what	Quite a bit	Very much
1. The side effects of the medicine interfere with my physical activity (e.g. lifting, walking, jogging, etc.).	⓪	①	②	③	④
2. The side effects of the medicine interfere with my leisure and free time activities (e.g. gardening, reading, dancing, visiting friends, etc.)	⓪	①	②	③	④
3. The side effects of the medicine interfere with my daily activities (e.g. shopping, working, housekeeping, etc.).	⓪	①	②	③	④

- This section is about the efficacy of the medicine, i.e., its effectiveness in treating your condition and reducing its symptoms.

	Not at all	A little bit	Some-what	Quite a bit	Very much
4. The medicine I am taking reduces my symptoms.	⓪	①	②	③	④
5. I am satisfied with the time it takes for the medicine to start to have an effect.	⓪	①	②	③	④
6. I feel better now than I did before starting the treatment.	⓪	①	②	③	④

*Ruiz M, et al. Value Health 2008. doi: 10.1111/j.1524-4733.2008.00323.x.
SATMED-Q © Miguel A. Ruiz, 2008. All Rights Reserved.*

- This section is about the convenience and ease of use of the medicine.

	Not at all	A little bit	Some-what	Quite a bit	Very much
7. I find my medicine convenient to take.	⓪	①	②	③	④
8. I find it easy to use/take the medicine in its present form (taste, size, etc).	⓪	①	②	③	④
9. The timetable for taking the medicine suits me.	⓪	①	②	③	④

- This section is about the impact of the medicine on your everyday life.

	Not at all	A little bit	Some-what	Quite a bit	Very much
10. Thanks to the medicine I am taking I can undertake my leisure and free time activities.	⓪	①	②	③	④
11. Thanks to my medicine I can more easily look after my personal hygiene (e.g. shaving, brushing my hair, bathing, etc.)	⓪	①	②	③	④
12. Thanks to my medicine I can perform my everyday chores better.	⓪	①	②	③	④

- This section is about the medical follow-up/review of your condition

	Not at all	A little bit	Some-what	Quite a bit	Very much
13. My doctor has informed me in detail about my medical condition.	⓪	①	②	③	④
14. My doctor has informed me about the right way to treat my medical condition.	⓪	①	②	③	④

- Finally, some questions on your overall opinion of the medicine and your health

	Not at all	A little bit	Some-what	Quite a bit	Very much
15. I intend to continue using this treatment.	⓪	①	②	③	④
16. I feel happy with my treatment.	⓪	①	②	③	④
17. In general, I feel satisfied with the treatment.	⓪	①	②	③	④

Thank you for your cooperation

*Ruiz M, et al. Value Health 2008. doi: 10.1111/j.1524-4733.2008.00323.x.
SATMED-Q © Miguel A. Ruiz, 2008. All Rights Reserved.*

• SATMED-Q Questionnaire (french version)

QUESTIONNAIRE DU SATMED-Q®

Nous souhaiterions connaître votre degré de satisfaction quant au traitement médicamenteux que vous prenez actuellement.
Ce questionnaire comprend 2 pages. Pour chaque question, cochez le numéro qui reflète le mieux votre opinion, sachant qu'il n'y a pas de bonnes ou mauvaises réponses. Si vous hésitez concernant l'une des réponses, sélectionnez celle qui vous semble la mieux adaptée à votre cas.

▪ Avez-vous ressenti un quelconque effet indésirable lié au traitement médicamenteux ?

Non, aucun Oui, au moins un

Lequel/lesquels :

▪ Les questions suivantes portent sur les effets indésirables liés au traitement médicamenteux :

	Non, pas du tout	Un peu	Modéré-ment	Assez	Oui, beaucoup
1. Les effets indésirables du traitement ont un impact sur mes capacités physiques	0	1	2	3	4
2. Les effets indésirables du traitement ont un impact sur mes activités de loisir et de temps libre	0	1	2	3	4
3. Les effets indésirables du traitement ont un impact sur mes tâches quotidiennes	0	1	2	3	4

▪ Les questions suivantes portent sur l'efficacité du traitement médicamenteux, c'est-à-dire sa capacité à traiter votre maladie et à soulager vos symptômes :

	Non, pas du tout	Un peu	Modéré-ment	Assez	Oui, beaucoup
4. Le traitement que je prends actuellement soulage mes symptômes	0	1	2	3	4
5. Le traitement commence à faire effet après une durée que j'estime satisfaisante	0	1	2	3	4
6. Je me sens mieux maintenant qu'avant de commencer le traitement	0	1	2	3	4

▪ Les questions suivantes portent sur les aspects pratiques du traitement médicamenteux et sur sa facilité d'administration :

	Non, pas du tout	Un peu	Modéré-ment	Assez	Oui, beaucoup
7. Mon traitement est pratique à prendre	0	1	2	3	4
8. Mon traitement est dans l'ensemble facile à prendre/ utiliser sous sa forme actuelle (goût, taille, etc.)	0	1	2	3	4
9. Les horaires de prise sont pratiques	0	1	2	3	4

▪ Les questions suivantes portent sur les effets du traitement médicamenteux sur votre quotidien :

	Non, pas du tout	Un peu	Modéré-ment	Assez	Oui, beaucoup
10. Le traitement que je prends actuellement facilite mes activités de loisir et de temps libre	0	1	2	3	4
11. Mon traitement facilite ma toilette	0	1	2	3	4
12. Mon traitement facilite mes tâches quotidiennes	0	1	2	3	4

▪ Les questions suivantes concernent le suivi médical de votre maladie :

	Non, pas du tout	Un peu	Modéré-ment	Assez	Oui, beaucoup
13. Mon médecin (ou autre professionnel de santé) m'a fourni des informations détaillées sur ma maladie	0	1	2	3	4
14. Mon médecin (ou autre professionnel de santé) m'a expliqué comment traiter correctement ma maladie	0	1	2	3	4

▪ Pour finir, voici quelques questions concernant votre opinion générale sur ce traitement médicamenteux et sur votre état de santé :

	Non, pas du tout	Un peu	Modéré-ment	Assez	Oui, beaucoup
15. J'ai l'intention de poursuivre ce traitement	0	1	2	3	4
16. Je me sens bien avec ce traitement	0	1	2	3	4
17. Je suis globalement satisfait(e) de ce traitement	0	1	2	3	4

Nous vous remercions de votre collaboration

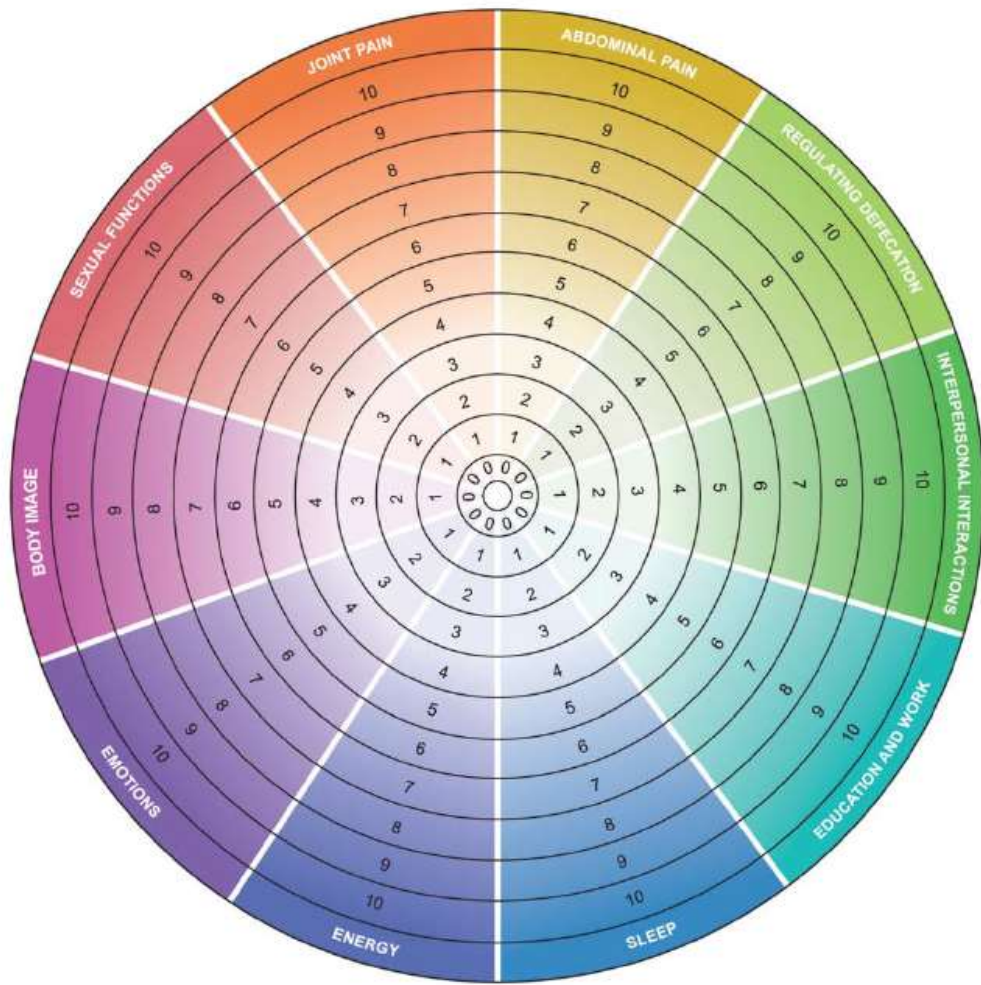
(Authors authorization mandatory)

- IBD Disk (Ghosh 2017)

For each of the ten statements below, score your level of agreement on a scale of 0 to 10.
Circle your scores on the coloured disc.

Absolutely disagree	Neither agree or disagree	Absolutely agree
←	→	
0	1	2
3	4	5
6	7	8
9	10	→
In the last week, because of my Crohn's disease or ulcerative colitis...		
Abdominal pain	...I have had aches or pains in my stomach or abdomen	
Regulating defecation	...I have had difficulty coordinating and managing defecation, including choosing and getting to an appropriate place for defecation and cleaning myself afterwards	
Interpersonal interactions	...I have had difficulty with personal relationships and/or difficulty participating in the community	
Education and work	...I have had difficulty with school or studying activities, and/or difficulty with work or household activities	
Sleep	...I have had difficulty sleeping, such as falling asleep, waking up frequently during the night or waking up too early in the morning	
Energy	...I have not felt rested and refreshed during the day, and have felt tired and without energy	
Emotions	...I have felt sad, low or depressed, and/or worried or anxious	
Body image	...I have not liked the way my body or body parts look	
Sexual functions	...I have had difficulty with the mental and/or physical aspects of sex	
Joint pain	...I have had pains in the joints of my body	

IBD DISK (Ghosh 2017)



Appendix 6. CTCAE Grading Scale for Severity of Adverse Events

Please refer to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, which can be found at:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

The only modification to the CTCAE criteria is the addition of a Grade 1 upper respiratory infection as follows:

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.03 AE Term Definition
Upper respiratory infection	Mild symptoms; symptomatic relief (eg, cough suppressant, decongestant)	Moderate symptoms; oral intervention indicated (eg, antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by an infectious process involving the upper respiratory tract (nose, paranasal sinuses, pharynx, larynx, or trachea).

<i>LETTRE D'INFORMATION ET DE NON OPPOSITION</i>
Titre identifiant la recherche : Numéro IDRCB: Numéro promoteur : 38RC

Madame, Monsieur,

Le Dr Mathieu vous propose de participer à une recherche impliquant la personne humaine non interventionnelle. Cette recherche est organisée par le CHU GRENOBLE Alpes. Vous êtes libre de participer ou non à cette recherche. Votre refus n'a pas à être justifié et ne modifiera en rien votre prise en charge ou votre relation avec le médecin. Vous avez également le droit à tout moment de vous opposer à l'utilisation de vos données de santé sans encourir de préjudice.

Vous disposez également d'un délai de réflexion de 7 jours avant de prendre votre décision.

Cette recherche étant non interventionnelle, votre prise en charge médicale sera celle habituelle pour votre pathologie. Des données supplémentaires pourront être recueillies afin de mieux comprendre votre maladie. Cette recherche n'engendrera aucun frais supplémentaire vous concernant. Vous ne percevrez aucune indemnité.

DESCRIPTIF DE L'ETUDE

Cette recherche a pour but de suivre des personnes ayant une maladie inflammatoire chronique de l'intestin, Maladie de Crohn ou rectocolite hémorragique, après avoir remplacé leur traitement par Humira® (adalimumab) par un médicament biosimilaire de l'Humira®. L'objectif de ce suivi est d'évaluer les perceptions et le vécu des personnes au moment du changement et sur une période de 1 an.

Un médicament biosimilaire est une copie d'un médicament biologique. Un médicament biologique étant un médicament fabriqué à partir d'organismes vivants comme des bactéries, des champignons ou des cellules végétales. Cette copie a les mêmes modalités et exigences de fabrication que le médicament biologique initial. Il peut exister des modifications minimales de la molécule d'adalimumab n'ayant pas d'influence sur l'efficacité et la tolérance du médicament biosimilaire qui sont identiques à l'Humira®. L'efficacité et la tolérance du médicament biosimilaire ont été évaluées par des études cliniques ayant la même rigueur scientifique que celles réalisées pour l'Humira® et auprès d'un grand nombre de patients ayant des maladies autoimmunes dont les MICI, les rhumatismes inflammatoires. Les modalités d'utilisation et de surveillance sont les mêmes que celles de l'Humira®.

Il existe plusieurs biosimilaires de l'Humira®: Amgevita®, Hulio®, Hyrimoz®, Imraldi®.

Vous pourrez choisir si vous le souhaitez le médicament biosimilaire de votre choix après avoir eu une présentation des différents stylos existants. Les critères de choix que vous retiendrez pour sélectionner votre stylo vous seront demandés afin d'identifier si besoin des pistes d'améliorations des différents dispositifs proposés.

Cette étude est réalisée dans deux centres hospitaliers de la région Rhône-Alpes, le CHU Grenoble Alpes et l'hôpital Lyon Sud.

Environ 200 personnes vont participer à cette étude.

En pratique, quand vous aurez donné votre accord pour participer à cette étude, lors de la première visite de l'étude, il vous sera proposé par votre médecin gastroentérologue référent de changer votre traitement par Humira® pour l'un des ses biosimilaires. Les différents stylos vous seront présentés par une infirmière et/ou une pharmacienne clinicienne spécialisées de l'équipe d'Hépatogastroentérologie. Elles pourront à ce moment répondre à l'ensemble de vos questions concernant ce changement. Vous bénéficierez aussi d'une formation à l'utilisation du stylo choisi. Le nom et les coordonnées de votre pharmacie d'officine dans laquelle vous récupérez l'Humira® vous seront demandés afin de les informer du changement de prescription pour qu'ils puissent commander le médicament biosimilaire choisi.

L'étude comporte une consultation médicale lors de la première visite puis à 3 mois, 6 mois et à un an.

Lors de chaque consultation médicale, les examens cliniques habituels en lien avec la prise en charge de votre maladie seront réalisés c'est-à-dire les prises de sang, échantillons de selles, examens radiologiques (échographie, entéroIRM...) et/ ou endoscopiques spécifiques nécessaires.

L'ordonnance du médicament biosimilaire choisi vous sera remise à la fin de la première visite pour toute la durée de l'étude c'est à dire pour 1 an.

Il vous sera également demandé de remplir 3 questionnaires dont 2 sur votre perception et votre ressenti sur les médicaments en général et spécifiquement sur le médicament biosimilaire (BMQ et SATMED-Q) et le troisième sur votre vécu en lien avec votre maladie et votre traitement tout au long de la durée de l'étude (IBD-Disk). Le temps de réponse à ces questionnaires est estimé à une vingtaine de minutes environ. Il vous sera demandé de les remplir seul à la fin de chaque visite et de les rendre avant de partir.

Ce suivi régulier ainsi que vos retours par l'intermédiaire des questionnaires permettent durant toute la durée de l'étude de suivre votre vécu et perception de ce changement ainsi que l'efficacité et la tolérance de votre traitement comme habituellement.

DUREE DE L'ETUDE

Cette étude devrait débuter en janvier 2020 et il est prévu qu'elle s'achève en juillet 2022. Vous serez inclus dans l'étude pour une durée de 1 an. Vous ne pourrez pas vous prêter à une autre étude clinique durant votre participation à cette étude.

BENEFICES, CONTRAINTES ET RISQUES

Cette recherche non interventionnelle ne vous procurera pas de bénéfice direct du fait de votre participation. Mais elle vous permettra de participer à la compréhension par les professionnels de santé des besoins des patients suite à un changement de prescription d'un médicament.

Quel que soit le type et les raisons de ce changement de traitement, ces résultats permettront d'envisager l'accompagnement le plus adapté.

De plus, cette étude n'entraînera pas de risque supplémentaire car elle se fait uniquement dans le cadre du suivi habituel de votre pathologie pour laquelle vous consultez au CHU Grenoble Alpes. Votre participation à cette recherche n'entraînera aucune modification de votre prise en charge médicale.

Il est uniquement rajouté le temps de remplissage des 3 questionnaires à chaque visite soit une durée supplémentaire de présence d'une demi-heure environ.

Aucune indemnité n'est prévue dans le cadre de cette étude.

Aucun frais supplémentaire ne vous sera facturé du fait de votre participation à l'étude.

PROTECTION DES PERSONNES

Cette recherche impliquant la personne humaine a reçu l'avis favorable d'un Comité de Protection des Personnes (en attente) et a été transmis pour information à l'Agence Nationale de Sécurité du Médicament et des produits de santé (ANSM).

CONFIDENTIALITE DES DONNEES

Dans le cadre de cette recherche, un traitement de vos données personnelles va être mis en œuvre pour permettre d'analyser les résultats de la recherche au regard de l'objectif de cette dernière.

Le responsable du traitement des données est le promoteur, dont les coordonnées figurent sur la première page de ce document et dans la partie « Contact » du document.

Ce traitement des données a pour fondement juridique l'article 6 du règlement UE 2016/679 (Règlement Général sur la Protection des Données (RGPD)) à savoir l'exécution d'une mission

d'intérêt public dont est investi le responsable de traitement et les intérêts légitimes poursuivis par ce dernier. De plus, au titre de l'article 9 du RGPD le responsable de traitement peut de manière exceptionnelle traiter des catégories particulières de données, incluant des données de santé notamment à des fins de recherche scientifique.

Les données que nous prévoyons de collecter sont les suivantes:

- Paramètres de suivis habituels (clinique, biologique, selles).
- Données d'entretien sur votre avis concernant les critères de choix du biosimilaire choisi.
- Données sociodémographiques (âge, sexe, lieu de naissance, activité professionnelle, lieu de vie).
- Données issues des 3 questionnaires.

Les données ne permettront pas de remonter à votre identité.

A cette fin, les données médicales vous concernant et les données relatives à vos habitudes de vie seront transmises à la personne responsable du traitement de la recherche ou aux personnes ou sociétés agissant pour son compte, en France ou à l'étranger, dans des conditions assurant un niveau de protection suffisant pour ce transfert. Ces données seront identifiées par un numéro de code et/ou vos initiales.

Ces données pourront également, dans des conditions assurant leur confidentialité, être transmises aux autorités de santé françaises ou étrangères et à d'autres entités du CHU Grenoble Alpes ou à des tiers, sous une forme qui ne permettra pas votre identification directe ou indirecte.

Ces données pourront également être utilisées et transmises pour des fins scientifiques dans le cadre de recherches conduites sur les maladies inflammatoires chroniques de l'intestin. En cas de retrait de consentement et sauf précision de votre part, les données collectées jusqu'à cette date pourront être utilisées.

Ces données pourront également être utilisées et transmises de manières codées et sécurisées à des tiers à des fins de recherche et d'exploitation des résultats de l'étude.

Les données électroniques sont stockées dans un serveur sécurisé hébergé par le CHU de Grenoble Alpes. Aucune donnée se sera stockée dans un ordinateur privé ou sur une clé USB. Le promoteur procédera à la collecte de ces données, notamment lors des consultations de suivi et à leur traitement.

Dans le cas où le traitement des données serait délégué à une autre entité, les précautions nécessaires au maintien de votre anonymat seront prises et un contrat sera établi. Ces données seront stockées sur un serveur sécurisé du CHU Grenoble Alpes et seront archivées dans la limite de la durée légale.

VOS DROITS

Les données seront transférées et collectées conformément à la méthodologie de référence MR003 de la Commission Nationale de l'Informatique et des Libertés (CNIL) pour laquelle le CHU Grenoble Alpes a signé un engagement de conformité.

Conformément aux dispositions de loi relative à l'informatique aux fichiers et aux libertés, vous disposez d'un droit d'accès et de rectification.

Vous disposez également d'un droit d'opposition à la transmission des données couvertes par le secret professionnel susceptibles d'être utilisées dans le cadre de cette recherche et d'être traitées.

Vous disposez d'un droit à la limitation du traitement de vos données.

Vous disposez d'un droit à l'effacement des données et à l'oubli.

Si vous souhaitez exercer votre droit à l'effacement de vos données, le responsable de traitement peut au titre des Articles 17.3.c et 17.3.d. du RGPD ne pas faire droit à cette demande si celle-ci est susceptible de rendre impossible ou de compromettre gravement la réalisation des objectifs de la recherche. Ainsi, vos données recueillies préalablement au retrait de votre consentement pourront ne pas être effacées et pourront continuer à être traitées dans les conditions prévues par la recherche.

Vous disposez d'un droit de réclamation à une autorité de contrôle (CNIL).

Vous pouvez également accéder directement ou par l'intermédiaire d'un médecin de votre choix à l'ensemble de vos données médicales en application des dispositions de l'article L 1111-7 du Code de la Santé Publique. Ces droits s'exercent auprès du médecin qui vous suit dans le cadre de la recherche et qui connaît votre identité.

A l'issue de cette recherche vous pourrez être informé de ses résultats globaux par l'investigateur principal et ses co-investigateurs.

VOS CONTACTS

Pour exercer vos droits, ou pour toute question à ce sujet:

Vous pouvez contacter le délégué à la protection des données du CHU Grenoble Alpes par mail (protection-donnees@chu-grenoble.fr) ou par téléphone au 04.76.76.75.75.

Une demande peut aussi être envoyée par courrier à ce délégué à la protection des données ou à la direction générale du CHU Grenoble Alpes à l'adresse mentionnée ci-dessous.

Si vous estimez, après avoir contacté le DPO du CHUGA, que vos droits sur vos données ne sont pas respectés, vous pouvez adresser une réclamation à la CNIL:

- Déposer une plainte en ligne: <https://www.cnil.fr/fr/plaintes/>
- Adresser un message à la CNIL: <https://www.cnil.fr/fr/webform/nous-contacter>

Si vous avez des questions sur l'étude, vous pouvez contacter votre référent MICI.

Médecin investigateur responsable de l'étude : Dr Nicolas MATHIEU	Promoteur : CHU Grenoble Alpes
Coordonnées : CHU Grenoble Alpes, service Gastro-entérologie CS10217 CHU, 38043 GRENOBLE Cedex 09 Tel : 04 76 76 54 50	Coordonnées : CHU Grenoble Alpes - DRCI Pavillon Dauphiné – Rez-de-chaussée CS 10217 38043 GRENOBLE Cedex 9 Tel : 04 76 76 59 57

GLOSSAIRE

ANSM	:	Agence nationale de Sécurité du Médicament et des produits de santé
CHU	:	Centre Hospitalo-Universitaire
CPP	:	Comité de Protection des Personnes : structure chargée de l'évaluation des protocoles de recherche impliquant la personne humaine, préalablement à toute mise en œuvre
Investigateur	:	Personne qui dirige et surveille la réalisation de la recherche
Monocentrique	:	L'étude est réalisée dans un seul service clinique
Multicentrique	:	L'étude est réalisée dans plusieurs services cliniques
Promoteur	:	Responsable de la recherche et du traitement des données

Nous vous remercions d'avoir pris le temps de lire cette lettre d'information.

THÈSE SOUTENUE PAR : Loïc CABON

TITRE : A 12-MONTH REAL LIFE EFFICACY AND SAFETY STUDY OF IBD PATIENTS UNDER STABLE STEROID FREE CLINICAL AND BIOLOGICAL REMISSION SWITCHED FROM ADALIMUMAB ORIGINATOR HUMIRA® TO ONE OF ITS BIOSIMILARS : AMGEVITA®, HULIO®, HYRIMOZ® OR IMRALDI®. RHONESWITCH STUDY.

CONCLUSION :

Contexte : Les anti-TNF sont des médicaments efficaces dans le traitement d'induction et d'entretien des maladies inflammatoires chroniques de l'intestin (MICI) modérées à sévères, et sont un progrès incontestable dans leur prise en charge. Le brevet de l'adalimumab est tombé dans le domaine public en 2018, conduisant à l'arrivée de plusieurs biosimilaires de cette molécule, représentant ainsi une possibilité d'économie de santé et de réinvestissement dans la recherche. Si des études de non infériorité lors de switch vers les biosimilaires ont prouvé une efficacité et une sécurité équivalentes à l'Humira® dans le psoriasis et les pathologies rhumatismales inflammatoires, les données de vraie vie dans les MICI sont aujourd'hui attendues. Atténuer l'effet nocébo d'un switch est également un grand challenge pour les cliniciens à l'ère des biosimilaires.

Objectif : Rhoneswitch est un essai multicentrique prospectif observationnel d'un an évaluant des patients MICI en rémission chez qui l'on propose le switch de l'Humira® vers un de ses biosimilaires, suivis dans le cadre du soin courant. L'objectif primaire est de décrire l'amplitude de l'effet nocébo, les objectifs secondaires, le maintien de l'efficacité, la sécurité et les facteurs d'adhésion au switch pendant l'année de suivi.

Matériel et méthode : 200 patients MICI stables ambulatoires sans corticoïdes depuis au moins 3 mois sous Humira® se verront proposer de switcher vers l'un de ses biosimilaires lors d'une consultation interdisciplinaire dédiée, une information verbale et écrite leur sera délivrée sur les biosimilaires et l'effet nocébo. Après signature d'un consentement, ils rempliront des questionnaires, puis seront suivis tous les 3 mois pendant un an en consultation cliniquement et

avec dosage biomarqueurs de l'inflammation, tout en en remplissant les questionnaires BMQ, SATMED-Q et l'IBD Disk à chaque consultation.

Résultats : le critère principal de jugement est le pourcentage de patients qui repasseront, dans l'année du switch, à l'Humira®, ce « switch back » étant un marqueur indirect d'effet nocébo. Les critères secondaires de jugement : pourcentages de rémission clinique, biologique, réponse clinique, perte de réponse et effets indésirables à un an, seront recueillis. Les facteurs favorisant un effet nocébo seront explorés par les questionnaires BMQ, SATMED-Q, et l'IBD Disk tous les 3 mois un an.

Conclusion : Rhoneswitch est une étude innovante qui apportera les premières données françaises de vraie vie chez des patients MICI un an après leur « switch » de l'Humira® vers un de ses biosimilaires.

VU ET PERMIS D'IMPRIMER

Grenoble, le :

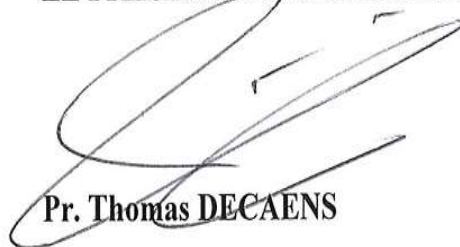
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LE DOYEN

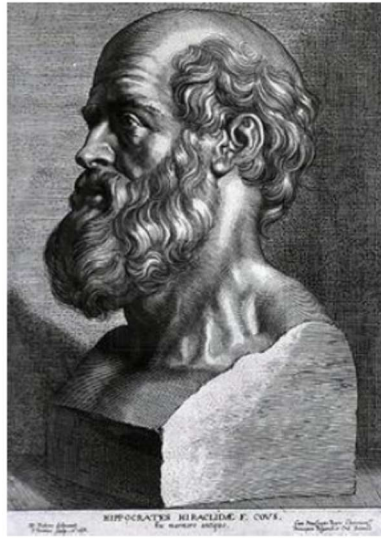


Pr. Patrice MORAND

LE PRÉSIDENT DE LA THÈSE



Pr. Thomas DECAENS



SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté, de mes chers condisciples et devant l'effigie d'HIPPOCRATE,

Je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuitement à l'indigent et n'exigerai jamais un salaire au dessus de mon travail. Je ne participerai à aucun partage clandestin d'honoraires.

Admis dans l'intimité des maisons, mes yeux n'y verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.

Je ne permettrai pas que des considérations de religion, de nation, de race, de parti ou de classe sociale viennent s'interposer entre mon devoir et mon patient.

Je garderai le respect absolu de la vie humaine.

Même sous la menace, je n'admettrai pas de faire usage de mes connaissances médicales contre les lois de l'humanité.

Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses.

Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque.