Date: 02/11/2021
Version 3.1

Study: REFLECT

STATISTICAL ANALYSIS PLAN

NATIONAL OBSERVATORY ON REAL-WORLD USE OF INFLECTRA®

SPONSOR

Pfizer SAS
23-25 avenue du Dr Lannelongue
75668 Paris cedex 14

Contract Research Organization

PPD

PROJECT MANAGER

PPD
Tel: PPD
E-mail: PPD

BIOSTATISTICIAN

PPD
Tel: PPD
E-mail: PPD

1. VERSION HISTORY

Version	Date	Nature(*)	Description
1.0	05/08/2016	C	SAP creation
1.1	16/08/2016	M	Updated according the feedback of PPD and PPD (Pfizer)
1.2	19/08/2016	M	Updated according the feedback of PPD (Pfizer)
1.3	24/08/2016	M	Updated following the amendment to the protocol
1.4	10/11/2016	A+D+M	Updated according the changes in the eCRF (version 2.1, dated 14/10/2016): - Addition of data during the 1st injection in the case where treatment was started before inclusion (laboratory tests, endoscopy, disease activity…), and addition of data on Inflectra® administration at baseline - Deletion of Salicylates for the follow-up visits - Change in the definition of AE of special interest related to Inflectra®
1.5	10/01/2018	A+M	Updated on the interim analyses
1.6	01/03/2019	M	Modification of the subpopulation « Patient switching treatment » by « Biologics experienced patients »
2.0	28/01/2020	A	Updated following protocol amendment, with new data on stress and anxiety
2.1	11/03/2020	M	Updated on the interim analyses in 2020
2.2	23/11/2020	M	Updated according the feedback of PPD (Pfizer)
2.3	21/05/2021	M	Updated according the feedback of Pfizer
3.0	18/10/2021	M	Updated according the feedback of Pfizer for the final analyses in 2021
3.1	02/11/2021	M	Updated according the feedback of Pfizer for the final analyses in 2021 - Final version

(*) C: Creation, M: Modification, A: Addition, D: Deletion

2. VALIDATION OF THE PLAN

Date:

Author of analysis plan: PPD

Signature:

Review and validation by AXONAL-BIOSTATEM:

Function	Name	Date / Signature
Biostatistician	PPD	[redacted]
Project Manager	PPD	[redacted]

[redacted]

[redacted]

3. TABLE OF CONTENTS

4. STUDY SYNOPSIS

Title	National observatory on real-world use of Inflectra®
Study design	National, multicenter, prospective, observational study.
Sponsor	REFLECT: Pfizer SAS
Study rationale	Infliximab is a chimeric monoclonal antibody directed against Tumor Necrosis Factor alpha (TNF-α). It is used in the treatment of inflammatory autoimmune diseases. Infliximab, initially marketed under the name Remicade™, was approved by the American drug authority (Food and Drug Administration – FDA) in the treatment of psoriasis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis, and rheumatoid arthritis. Remicade™ was granted its first Marketing Authorization (MA) by the FDA in August 1998 for the treatment of Crohn's disease. Remicade™ has been approved in Europe since 1999. Inflectra® (infliximab) is a biosimilar of the reference product, Remicade™. It is the first biosimilar monoclonal antibody approved by the European Commission. In fact, a biosimilar whose development complies with European guidance can be considered as a therapeutic alternative to the reference biologic. A randomized, double-blind phase III trial in 606 patients with rheumatoid arthritis (RA) demonstrated therapeutic equivalence of Inflectra® to Remicade™. In this trial, 73.4% of patients treated with Inflectra® achieved at least 20% improvement in RA symptoms based on ACR20 response at week 30 versus 69.7% of those on Remicade™. In this same trial, 42.3% of patients in the Inflectra® arm had at least 50% symptom improvement compared with 40.6% of Remicade™ patients. The comparable safety and tolerance data between the two arms confirmed the equivalence between Inflectra® and Remicade™. Furthermore, there were no marked differences in the immunogenicity profile of the two products up to 54 weeks and the impact of anti-drug antibodies on efficacy and safety was also comparable. Inflectra® was approved by the European Commission in September 2013. Beyond the economic aspects, it would be interesting to collect data on the real-world use of Inflectra®, since currently such data are lacking. The present observatory is being created to meet this objective and to collect data on the real-world use of Inflectra®. In addition, and like the other biotherapies indicated in the treatment of psoriasis, the Haute Autorité de Santé (HAS) has requested that a representative cohort be set up for the monitoring of patients with psoriasis. To this end, it was decided to become part of the existing PSOBIOTEQ registry. To avoid having two competing studies, patients with psoriasis will therefore not be included in the present observatory.
Study population	With the exception of psoriasis patients, all adult and pediatric patients treated with Inflectra® in one of the participating French centers, regardless of treatment phase, will be included in the observatory, unless they explicitly refuse to allow access to their medical record for the purpose of collecting personal information. Based on the estimated number of naïve patients treated each year, we estimate that approximately **1200 patients** will be treated with Inflectra® during the **two-year** inclusion period (600 patients per 12 months). Inclusions will be stopped if 1200 patients accrue before the end of the planned inclusion period; this sample size will allow calculation of an estimated response rate with a precision of ± 2.8%. Regarding the objective related to the stress and anxiety, the following hypotheses are considered • Proportion of patients with treatment permanent discontinuation: 25%

	• Proportion of patients with treatment permanent discontinuation among anxious patients (GAD>7): 30% • Proportion of patients with treatment permanent discontinuation among non- anxious patients (GAD<8): 20% • Missing data on treatment permanent discontinuation due to lost to follow-up: 10% A sample size of 300 patients is necessary to calculate a two-sided 95% confidence interval of the odds-ratio of the variable "treatment permanent discontinuation", not including 1. With these hypotheses, the odds-ratio would be 0.58 with a 95% confidence interval of [0.35-0.99]. Taking into account the 10% of lost to follow-up, 300/0.9=330 patients would be needed.
Description of the treatment	Inflectra® (infliximab) is a chimeric human-murine IgG1 monoclonal antibody produced in murine hybridoma cells by recombinant DNA technology. **Posologies in adults**: • **Rheumatoid arthritis**: 3 mg/kg given as an intravenous infusion followed by additional 3 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. Inflectra® must be given concomitantly with methotrexate. • **Moderately to severely active Crohn's disease**: 5 mg/kg given as an intravenous infusion followed by an additional 5 mg/kg infusion 2 weeks after the first infusion. If a patient does not respond after 2 doses, no additional treatment with infliximab should be given. In responding patients, the alternative strategies for continued treatment are: o Maintenance: Additional infusion of 5 mg/kg at 6 weeks after the initial dose, followed by infusions every 8 weeks, or o Re-administration: Infusion of 5 mg/kg if signs and symptoms of the disease recur. • **Fistulising, active Crohn's disease**: 5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusions at 2 and 6 weeks after the first infusion. If a patient does not respond after 3 doses, no additional treatment with infliximab should be given. In responding patients, the alternative strategies for continued treatment are: o Maintenance: Additional infusions of 5 mg/kg every 8 weeks or o Re-administration: Infusion of 5 mg/kg if signs and symptoms of the disease recur followed by infusions of 5 mg/kg every 8 weeks • **Ulcerative colitis**: 5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. • **Ankylosing spondylitis**: 5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 6 to 8 weeks. If a patient does not respond by 6 weeks, no additional treatment with infliximab should be given. • **Psoriatic arthritis**: 5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. **Posologies in children:** • **Crohn's disease:** 5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter.

	• **Ulcerative colitis**: 5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter.
Primary objective	Describe in real-world conditions of use: • Response to treatment, • Profile of patients treated with Inflectra®
Secondary objectives	• Describe in routine practice: o Conditions of use of Inflectra® o Tolerance/safety of Inflectra® • Identify predictive factors of response to treatment • Describe immunogenicity profile of Inflectra® • Measure anxiety, stress and distrust of the patient after the switch announcement (from infliximab to Inflectra®), and the impact of the psychological profile on the follow-up of the patients in terms of efficacy, tolerance and continuation of biosimilar • Evaluate the evolution of anxiety and stress of patients after the switch from infliximab to Inflectra®
Inclusion criteria	• Adult patients treated with Inflectra®, regardless of treatment phase, in one of the following indications and in accordance with the SPC: Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, or psoriatic arthritis. • Pediatric patients (children and adolescents aged 6 to 17 years old) treated with Inflectra®, regardless of treatment phase, as long as Inflectra® is prescribed in accordance with the indications stated in the SPC: Crohn's disease or ulcerative colitis. • Patients (or legal representatives) who received oral and written information about the study and gave their consent to participate. • Patients who gave their authorization for access to their clinical data and their medical record by signing the consent. Patients must sign the consent no later than when they leave the hospital (first Inflectra® infusion after inclusion in the study).
Exclusion criteria	• Patients refusing access to their medical record for collection of their medical information. • Patients not treated with Inflectra®. • Patients treated with Inflectra® for psoriasis. • Patients with a history of hypersensitivity to infliximab, to other murine proteins or to one of the excipients of Inflectra®. • Patients diagnosed with tuberculosis or any other severe infection such as sepsis, abscess or opportunistic infections. • Patients with moderate to severe heart failure (NYHA III/IV)
Study design	– Study duration: 4 years – Inclusion period: 2 years – Follow-up per patient: 2 years Hospital physicians participating in this observatory will systematically inform eligible patients to whom they prescribe Inflectra® of the existence of this study and will give them the information notice. After the patient has been enrolled in the observatory, data of interest in the medical record will be reported in an electronic case report form (eCRF) every 6 months during the two-year follow-up. The physician must therefore login to the eCRF at least five times for each patient. To this end, a reminder will be automatically sent to the physicians every six months after inclusion of each patient. If necessary, a clinical study technician can assist the physician in entering the patient's data in the eCRF.

	In addition, if the sponsor considers it necessary, a Clinical Research Associate (CRA) will carry out periodic on-site monitoring visits. Patients will be managed according to each center's usual practices. No special monitoring is required by the protocol.
Number of centers	Hospitals attached to the AGEPS (20 hospitals) and to UNI.HA (36 hospitals), for a total of 56 centers.
Statistical methods	Appropriate descriptive statistics will be used to analyze the primary endpoint. Characteristics of patients and treatment switches will be described with percentages and the 95% confidence interval, or else by the mean, standard deviation, median, minimum and maximum, depending on the type of variable. The indication for the Inflectra® prescription and severity of disease will be described as a percentage with the 95% confidence interval. Lastly, the response to treatment will be expressed as the responder and non-responder rate with the 95% confidence interval, overall and in each subgroup. Appropriate statistical methods (mean, standard deviation, median, minimum and maximum, 95% confidence interval) will be used to describe the conditions of use of Inflectra®. For the safety assessment, the overall incidence of AEs and the incidence of AEs of special interest will be expressed with their 95% confidence interval. For each indication, predictive factors of the response to treatment will be analyzed by a logistic regression model. A univariate analysis will be performed to identify factors to be incorporated into the multivariate model. Several interim analyses are planned on the data collected as the study progresses. The final analysis will be done when the study has ended, after all the data have been collected.
Scientific committee	○ 2 rheumatologist experts, ▪ PPD ▪ PPD ○ 2 gastroenterologist experts ▪ PPD ▪ PPD ▪ PPD ○ 1 psychiatrist expert ▪ PPD
Observatory logistics	[redacted]
Time line	• Submission to CCTIRS: early February 2016 • Submission to CNIL: late April 2016 • Submission to CNOM: June 2016 • Center set-up: July 2016 • Inclusion period: September 2016 – September 2018 • End of follow-up period: September 2020 • Interim analysis: Every year from December 2016 • Final analysis: December 2020 • Interim clinical report: Every year from December 2016 • Final clinical report: January 2021

5. ABBREVIATIONS

6-MP	6-mercaptopurine
Ab	Antibody
ACR	American College of Rheumatology
AE	Adverse event
AGEPS	Agence Générale des Équipements et des Produits de Santé *(General Agency for Health Products and Equipment)*
Anti-CPP	Anti-cyclic citrullinated peptide antibody
ASDAS	Ankylosing Spondylitis Disease Activity Score
AV	Absolue Variation
BMI	Body mass index
CCTIRS	Comité Consultatif pour le Traitement de l'Information en matière de Recherche Scientifique (*French Advisory Committee on Information Processing in Material Research in the Field of Health)*
CD	Crohn's disease
CDEIS	Crohn's Disease Endoscopic Index of Severity
CNIL	Commission Nationale Informatique et Libertés *(Data Protection Authority)*
CNOM	Conseil National de l'Ordre des Médecin *(French National Medical Council)*
CR	Critical
CRA	Clinical Research Associate
CRP	C reactive protein
DMARD	Disease-modifying antirheumatoid drug
DNA	DeoxyriboNucleic Acid
eCRF	electronic Case Report Form
FDA	Food and Drug Administration
HAQ	Health Assessment Questionnaire

HAS	Haute Autorité de Santé
HR	Hazard Ratio
IFX-TL	Infliximab Trough Level
IgG	Immunoglobulin G
MA	Marketing Authorization
MedDRA	Medical Dictionary for Regulatory Activities
NC	Non Critical
NYHA	New York Heart Association
OR	Odds Ratio
PA	Psoriatic arthritis
PT	Preferred Term
RA	Rheumatoid arthritis
RV	Relative Variation
SAE	Serious adverse event
SAS	Statistical Analysis Software
SD	Standard Deviation
SDAI	Simple Disease Activity Index
SOC	System Organ Class
SpA	Ankylosing Spondylitis
SPC	Summary of Product Characteristics
TNF	Tumor Necrosis Factor
UC	Ulcerative colitis
UCEIS	Colitis Endoscopic Index of Severity
UNI.H.A	Union des Hôpitaux pour les Achats *(university hospital purchasing agency)*

The purpose of this document is to describe the statistical analyses to be carried out for the REFLECT study, based on the study protocol (Amendment No 1, Version 3.1, dated 23/08/2016).

6. MODIFICATIONS OF THE ANALYSES SPECIFIED IN THE PROTOCOL

The analyses of the study endpoints according to physician-assessed disease severity will not be done for patients with Crohn's disease (CD) or ulcerative colitis (UC). This global disease assessment by the physician for patients with rheumatoid arthritis (RA), ankylosing spondylitis (SpA) and psoriatic arthritis (PA) was not evaluated with a Likert scale but on a 10-point scale which will have to be categorized.

For RA and PA patients, the analyses according to ACR score will not be performed because this score was not collected.

7. DERIVED VARIABLES

Section concerned	Derived variables	Calculation
Patient status	Time between inclusion visit and follow-up visits (months)	(Date of visit X – Date of inclusion visit) / 30.44 X = {M6, M12, M18, M24}
	Duration of follow-up (months)	(Date of study withdrawal- Date of inclusion visit) / 30.44 If the study withdrawal date is not provided (in particular during the interim analyses), the calculation is made from the date of the last follow-up visit.
	Duration of treatment with Inflectra (months)	(Date of the last follow-up visit- Date of the first administration of Inflectra) / 30.44
Populations and subgroups studied	Analysis set	Patients excluded from the analysis will be identified during the data review.
	Adult and pediatric populations	"Adult" = age > 17 years "Pediatric" = age ≤ 17 years
	Physician-assessed disease severity (category)	○ ≤3 ○]3-7[○ ≥7
	DAS28 (category) (1)	If patient RA or PA: ○ In remission: DAS28 ≤ 2.6 ○ Mildly active: 2.6 < DAS28 ≤ 3.2 ○ Moderately active: 3.2 < DAS28 ≤ 5.1 ○ Very active: DAS28 >5.1
	SDAI (category) (2)	If patient RA: ○ In remission: SDAI ≤ 3.3 ○ Mildly active: 3.3 < SDAI ≤ 11 ○ Moderately active: 11 < SDAI ≤ 26 ○ Very active: SDAI > 26
	HAQ (category) (3)	If patient RA : ○ Existence of functional disability: HAQ > 0.5 ○ Absence of functional disability: HAQ ≤ 0.5
	BASDAI (category) (4)	If patient SpA: ○ SpA active: BASDAI > 4 ○ SpA inactive: BASDAI ≤ 4
	BASFI (category) (4)	If patient SpA: ○ Significant functional impairment: BASFI > 4 ○ Mild functional impairment : BASFI ≤ 4

	ASDAS (category) [5]	If patient SpA: o SpA inactive: ASDAS < 1.3 o SpA mildly active: 1.3 ≤ ASDAS < 2.1 o SpA moderately active: 2.1 ≤ ASDAS ≤ 3.5 o SpA very active: ASDAS > 3.5
	Mayo score (category) [6]	If patient UC: o UC inactive: Mayo score ≤ 2 o Mild UC: 3 ≤ Mayo score ≤ 5 o Moderate UC: 6 ≤ Mayo score ≤ 10 o Severe UC: Mayo score > 11 Mayo score = Frequency of bowel item + rectal bleeding item + overall assessment of gravity + Rectosigmoidoscopy item
	PUCAI (category) [7]	If pediatric patient and UC: o UC in remission: PUCAI < 10 o Mild UC: 10 ≤ PUCAI < 35 o Moderate UC: 35 ≤ PUCAI < 65 o Severe UC: PUCAI ≥ 65
	Harvey-Bradshaw Index (category) [8]	If Crohn's disease: o Inactive disease: score < 4 o Active disease: 4 ≤ score ≤ 12 o Very active disease: score > 12
	Biologics experienced patients	Discontinuation of any biotherapy for the initiation of Inflectra® : "Patient already treated with biotherapy other than infliximab before inclusion (other than Inflectra®)" = YES +
	Patient switching from Remicade™ to Inflectra®	"Patient already treated with biotherapy before inclusion (other than Inflectra®)" = YES + Last biotherapy="REMICADE"
	Patient naive to biotherapy	Patient naive to biotherapy if: "Patient already treated with biotherapy before inclusion (other than Inflectra®)" = NO + Last biotherapy="REMICADE
Primary endpoints	Response to treatment	o Treatment failure = definitive discontinuation of Inflectra® for "Loss of efficacy" or "Intolerance", or AE related to Inflectra® resulting in death o Without treatment failure = if study withdrawal as per protocol or definitive discontinuation due to unavailability of treatment or other reason Lost to follow-up, withdrawal of consent, patient's decision to withdraw, or other reason for study withdrawal will be considered in a second step as "without treatment failure".
	Time to response (months)	<u>If treatment failure (not censored):</u> (Date of treatment stopped (or date of death) – Date of 1st infusion +1) /30.44 <u>If without treatment failure (censored):</u> (Date of study withdrawal (or last news or withdrawal of consent or treatment stopped) - Date of 1st infusion +1) / 30.44
	BMI (kg/m²)	Weight (kg) / (Height (cm)/100)²
	Duration of disease (years)	(date of first administration of Inflectra – date of diagnosis) / 365.25
	Time since endoscopy	Date of first administration of Inflectra – Date of endoscopy To be divided by 30.44 days if expressed in months To be divided by 365.25 days if expressed in years
	CDEIS (category)	If Crohn's disease: o Endoscopic remission: CDEIS ≤ 7 o Absence of endoscopic remission: CDEIS > 7
	Endoscopic Mayo score (category 1)	If patient UC: o Complete endoscopic remission: Rectosigmoidoscopy item = 0 o Absence of complete endoscopic remission: Rectosigmoidoscopy item > 0

	Endoscopic Mayo score (category 2)	If patient UC: ○ Endoscopic remission: Rectosigmoidoscopy item < 2 ○ Absence of endoscopic remission: Rectosigmoidoscopy item ≥ 2
	Clinical Mayo score (category)	If patient UC: ○ Clinical remission: partial Mayo score ≤ 2 AND rectal bleeding item ≤1 ○ Absence of clinical remission: partial Mayo score > 2 OR rectal bleeding item >1 Partial Mayo score = Frequency of bowel item + rectal bleeding item + overall assessment of gravity
	Time since appendicectomy	(date of first admiration of Inflectra – date of appendicectomy) / [30.44 or 365.25] 30.44 days if expressed in months 365.25 days if expressed in years
	Time since resection	(Date of first admiration of Inflectra – date of resection) / [30.44 or 365.25] 30.44 days if expressed in months 365.25 days if expressed in years
	Number of colon segments involved	Number of colon segments involved (0 to 6 colon segments ticked)
	Involved colon segments (association)	Associations of colon segments will be described. Example: None Caecum + Right Colon Caecum + Left Colon + Rectum Rectum ….
	Time since last laboratory result For tests: {Rheumatoid factor, CRP, anti-CPP Ab, Hemoglobin, Fecal calprotectin}	Date of first admiration of Inflectra® – Date of laboratory test To be divided by 30.44 days if expressed in months To be divided by 365.25 days if expressed in years
	Time since 1st Inflectra® infusion	(Date of inclusion – date of 1st Inflectra® infusion) / [7 or 30.44] 7 days if expressed in weeks 30.44 days if expressed in months
	Previous or concomitant treatment (association)	Associations of previous or concomitant treatment will be described. Example: Methotrexate Methotrexate + Ciclosporine ….
	Duration of previous treatment	If ongoing not ticked: (Stop date of previous treatment – start date of previous treatment) / [30.44 or 365.25] 30.44 days if expressed in months 365.25 days if expressed in years For Methotrexate, Aziatropine, Ciclosporine previous treatment
	Duration of previous biotherapies	Duration of biotherapy X = cumulative durations of biotherapies X received (Stop date of biotherapy X1 – start date of biotherapy X1) + (Stop date of biotherapy X2 –start date of biotherapy X2) +… / [30.44 or 365.25] 30.44 days if expressed in months 365.25 days if expressed in years
	Number of previous biotherapies	Sum of previous biotherapies
	Duration of last biotherapy	(Stop date of last biotherapy – Start date of last biotherapy) / [7 or 30.44] 7 days if expressed in weeks 30.44 days if expressed in months
	Time from last treatment to start of Inflectra® (weeks)	If last previous treatment was not Inflectra®: (Date of 1st Inflectra® infusion – Stop date of last treatment) / 7

Secondary endpoints (Objective1)	Number of Inflectra ™ infusions listed	Number of pages of Inflectra® infusions returned by physician for each patient during the period in question. Calculated by taking the maximum value of the number of occurrences of infusions during the period in question.
	Mean posology administered (mg/kg)	Dose-posology conversion: Posology = dose (mg) / weight (kg) $\frac{Posology\ of\ infusion\ No.1 + \cdots + Posology\ of\ infusion\ No.X}{Number\ of\ infusions\ listed\ during\ period\ in\ question}$
	Mean dose administered (in mg)	Posology-dose conversion: Dose = Posology (mg/kg)*weight (kg) $\frac{Dose\ of\ infusion\ No.1 + \cdots + Dose\ of\ infusion\ No.X}{Number\ of\ doses\ listed\ during\ period\ in\ question}$
	Cumulative dose (mg)	Posology-dose conversion: Dose = Posology (mg/kg)*weight (kg) Cumulative dose = Sum of doses during period in question
Secondary endpoints (Objective1)	Mean infusion time (minutes)	$\frac{Duration\ of\ infusion\ No.1 + \cdots + Duration\ of\ infusion\ No.X}{Number\ of\ infusions\ times\ listed\ during\ period\ in\ question}$
	Mean post-infusion monitoring time at hospital (minutes)	$\frac{Duration\ of\ monitoring\ No.1 + \cdots + Duration\ of\ monitoring\ No.X}{Number\ of\ monitoring\ times\ listed\ during\ period\ in\ question}$
	Mean time between infusions (weeks)	$\frac{\sum_{i=1}^{x}(Date\ of\ infusion\ No.i - Date\ of\ infusion\ No._{i-1})/7}{Number\ of\ infusions\ listed\ during\ period\ in\ question\ -1}$
	Mean rheumatoid factor assay result (IU/mL)	If patient RA, SpA, PA: $\frac{Result\ No.1 + \cdots + Result\ No.X}{Number\ of\ assays\ done\ during\ period\ in\ question}$
	Mean CRP assay result (mg/L)	$\frac{Result\ No.1 + \cdots + Result\ No.X}{Number\ of\ assays\ done\ during\ period\ in\ question}$
	Mean anti-CCP Ab result (IU/mL)	If patient RA, SpA, PA: $\frac{Result\ No.1 + \cdots + Result\ No.X}{Number\ of\ assays\ done\ during\ period\ in\ question}$
	Mean hemoglobin assay result (g/dL)	If patient CD or UC: $\frac{Result\ No.1 + \cdots + Result\ No.X}{Number\ of\ assays\ done\ during\ period\ in\ question}$
	Mean fecal calprotectin assay result(µg/g)	If patient CD or UC: $\frac{Result\ No.1 + \cdots + Result\ No.X}{Number\ of\ assays\ done\ during\ period\ in\ question}$
	Absolute variation of mean result compared with baseline (and with first administration) Relative variation of mean result (and	*AV = Mean result of laboratory test during period in question – Result of laboratory test at baseline*

	with first administration) compared with baseline (and with first administration)	$RV = \frac{AV}{Result\ of\ laboraory\ test\ at\ baseline} * 100$ Laboratory test = {Rheumatoid factor, CRP, anti-CPP Ab, Hemoglobin, Fecal calprotectin}}
	Mean global disease assessment score	$\frac{Disease\ assessment\ No.1 + \cdots + Disease\ assessment\ No.X}{Number\ of\ disease\ assessments\ listed\ during\ period\ in\ question}$
Secondary endpoints (Objective1)	Absolute variation of mean global disease assessment compared with baseline (and with first administration) Relative variation of mean global disease assessment compared with baseline (%) (and with first administration)	$AV = Mean\ global\ disease\ assessment\ score\ during\ period\ in\ question - Global\ disease\ assessment\ score\ at\ baseline$ $RV = \frac{AV}{Global\ disease\ assessment\ score\ at\ baseline} * 100$
	Mean fatigue score	$\frac{Fatigue\ score\ No.1\ + \cdots + Fatigue\ score\ No.X}{Number\ of\ fatigue\ scores\ listed\ during\ period\ in\ question}$
	Absolute variation of mean fatigue score compared with baseline (and with first administration) Relative variation of mean fatigue score compared with baseline (%) (and with first administration)	$AV = Mean\ fatigue\ score\ during\ period\ in\ question - Fatigue\ score\ at\ baseline$ $RV = \frac{AV}{Fatigue\ score\ at\ baseline} * 100$
	Mean T score T = {DAS28, SDAI, HAQ, BASDAI BASFI, ASDAS, Mayo, PUCAI, Harvey-Bradshaw Index}	$\frac{T\ score\ No.1\ + \cdots + T\ score\ No.Y}{Number\ of\ T\ scores\ listed\ during\ period\ in\ question}$
	Absolute variation of mean T score compared with baseline (and with first administration) Relative variation of mean fatigue score compared with baseline (%) (and with first administration) T = {DAS28, SDAI, HAQ, BASDAI BASFI, ASDAS, Mayo, PUCAI, Harvey-Bradshaw Index}	$AV = Mean\ T\ score\ during\ period\ in\ question - T\ score\ at\ baseline$ $RV = \frac{AV}{T\ score\ at\ baseline} * 100$

	Absolute variation of endoscopic score compared with baseline (and with first administration) Relative variation of endoscopiv score compared with baseline (%) (and with first administration) Endoscopic score = {CDEIS, UCDEIS}	$AV = Endoscopic\ score\ at\ visit\ X - Endoscopic\ score\ at\ baseline$ $RV = \frac{AV}{Endoscopic\ score\ at\ baseline} * 100$ X = {M6, M12, M18, M24}
	At least one clinical remission	If patient UC: At least one partial Mayo score ≤ 2 AND rectal bleeding item ≤1
	At least one absence of clinical remission	If patient UC: At least one partial Mayo score > 2 OR rectal bleeding item >1
Secondary endpoints (Objective1)	At least one absence of clinical remission	If patient UC: At least one partial Mayo score > 2 OR rectal bleeding item >1
	At least one complete endoscopic remission	If patient UC: At least one rectosigmoidoscopy item = 0 during the period in question.
	At least one endoscopic remission	If patient UC: At least one rectosigmoidoscopy item < 2 during the period in question.
	At least one absence of endoscopic remission	If patient UC: At least one rectosigmoidoscopy item ≥ 2 during the period in question.
Secondary endpoints (Objective 2)	Age of physician (category)	To be defined according to the distribution of the data.
	Duration of practice (category)	To be defined according to the distribution of the data.
	Age of patients (category)	To be defined according to the distribution of the data.
	BMI (category)	To be defined according to the distribution of the data.
	Duration of disease (category)	To be defined according to the distribution of the data.
	Infliximab Trough level (IFX-TL) (category)	To be defined according to the distribution of the data.
	Cumulative dose (category)	To be defined according to the distribution of the data.
	Duration on Inflectra® (category)	To be defined according to the distribution of the data.
Secondary endpoints (Objective 3)	Time since IFX-TL assay	Date of first administration – Date of IFX-TL assay To be divided by 30.44 days if expressed in months To be divided by 365.25 days if expressed in years
	Time since anti-infliximab Ab assay	Date of first administration – Date of anti-infliximab Ab assay To be divided by 30.44 days if expressed in months To be divided by 365.25 days if expressed in years
	Number of immunogenicity assays done	Sum of immunogenicity assays done =YES
	Mean IFX-TL (µg/mL)	$\frac{IFX - TL\ no.1 + \cdots + IFX - TL\ no.X}{Number\ of\ immunogenicity\ assays\ done}$

	Mean administered dose (category)	MA-labeled dose vs. Optimized dose MA-labeled doses are: RA adult: 3mg/kg PA adult: 5 mg/kg SpA adult: 5 mg/kg CD adult: 5 mg/kg CD pediatric: 5 mg/kg UC adult: 5 mg/kg UC pediatric: 5 mg/kg In case of decimal value for the dose (Dose-posology conversion), intervals about the MA-labeled dose will be defined a posteriori. Optimized doses are doses that are adjusted from the standard MA-labeled dose (reduction to 6 weeks of the time between infusions and at least on 3 consecutive infusions or dose increase).
Secondary endpoints (Objective 5)	GAD7 (category)	• GAD7>7: anxious • GAD7<8: non-anxious A better categorization may be decided using specificity/sensitivity methodology with the variable of treatment permanent discontinuation
	Cook-Medley questionnaire (category)	Propension to distrust/trust in others, 2 categories based on median value of the score: • score>median: propension to distrust • score<median: trust in others
	Stress questionnaire	Presence or absence of stress, 2 categories based on median value of the score: • score>median: stress present • score<median: stress absent
	Absolute evolution of GAD7 score at each visit	*Evol GAD7 at visit i = GAD7 score at visit i – GAD7 score at baseline, for i=each visit with GAD7 score assessment after baseline*
	Time until a non-anxious state	If patient anxious at baseline (GAD7>7): *Time where GAD7 score drops below 8 - Time from first assessment of GAD7*
	Absolute evolution of stress score at each visit	*Evol stress at visit i = stress score at visit i – stress score at baseline, for i=each visit with stress score assessment after baseline*
	Time until absence of stress	If patient stressed at baseline (score of stress>median): *Time where stress score drops below median value - Time from first assessment of stress score*

These derived variables are identified in blue type with the mention "Variable [d]" in the remainder of the document.

8. STATISTICAL ANALYSES

8.1. STUDY POPULATION

8.1.1. PATIENT STATUS/GENERAL STUDY DATA

The following parameters will be described:

- Number of physicians participating in the study and the number of patients included per physician
- Number of patients included
- Inclusion period (Date of first-in and last-in, date of last follow-up visit)
- Number of patients who completed each visit (Inclusion, 6 months, 12 months, 18 months, 24 months)
- Time between follow-up visits and inclusion (months) [d]
- Total duration of patient follow-up in the study (months) [d]
- Number of premature study withdrawals, the reason (death, lost to follow-up, withdrawal of consent, patient's decision, definitive discontinuation of Inflectra®, other) and their duration of follow-up in the study.

Note: If the "End of study" form is not completed, the patients with a follow-up visit at M24 will be considered as having completed the study and the end date of the study will be the date at M24.
The patients without a follow-up visit at M24 will be considered as not having completed the study and the date of study withdrawal will be the date of the last follow-up visit.

8.1.2. PROTOCOL VIOLATIONS

Protocol violations will be summarized in tabular format for the overall population enrolled in the study with indication of the number of patients concerned for each type of violation.

Patients will be considered as a protocol violation if they do not meet one or more of the following criteria:

Inclusion criteria:

- Adult patients treated with Inflectra®, regardless of treatment phase, in one of the following indications and in accordance with the SPC: Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, or psoriatic arthritis
  OR
  Pediatric patients (children and adolescents aged 6 to 17 years old) treated with Inflectra®, regardless of treatment phase, as long as Inflectra® is prescribed in accordance with the indications stated in the SPC: Crohn's disease or ulcerative colitis.
- Patients (or legal representatives) who received oral and written information about the study and gave their consent to participate.
- Patients who gave their authorization for access to their clinical data and their medical record by signing the consent. Patients must sign the consent no later than when they leave the hospital (first Inflectra® infusion after inclusion in the study)

Non-inclusion criteria:

- Patients refusing access to their medical record for collection of their medical information.
- Patients not treated with Inflectra®.
- Patients treated with Inflectra® for psoriasis.
- Patients with a history of hypersensitivity to infliximab, to other murine proteins or to one of the excipients of Inflectra®.

- Patients diagnosed with tuberculosis or any other severe infection such as sepsis, abscess or opportunistic infection.
- Patients with moderate to severe heart failure (NYHA III/IV).

Minor/major protocol violations will be defined with the Sponsor and presented in the data review report.

Patients with a major protocol violation will be excluded from all analyses. The list of protocol violations will be presented.
Enrolled patients who withdraw their consent will be excluded from the study. They will decide whether their medical data that was collected can be used in the interim and final analyses, in so far as these analyses have not yet been done at the time of their withdrawal from the study.

8.1.3. POPULATIONS STUDIED

Physician population: All physicians participating in the study (who returned at least one case report form).

Population of enrolled patients: All patients enrolled in the study.

Analysis set: All enrolled patients with Inflectra® (=All enrolled patients without a major protocol violation).

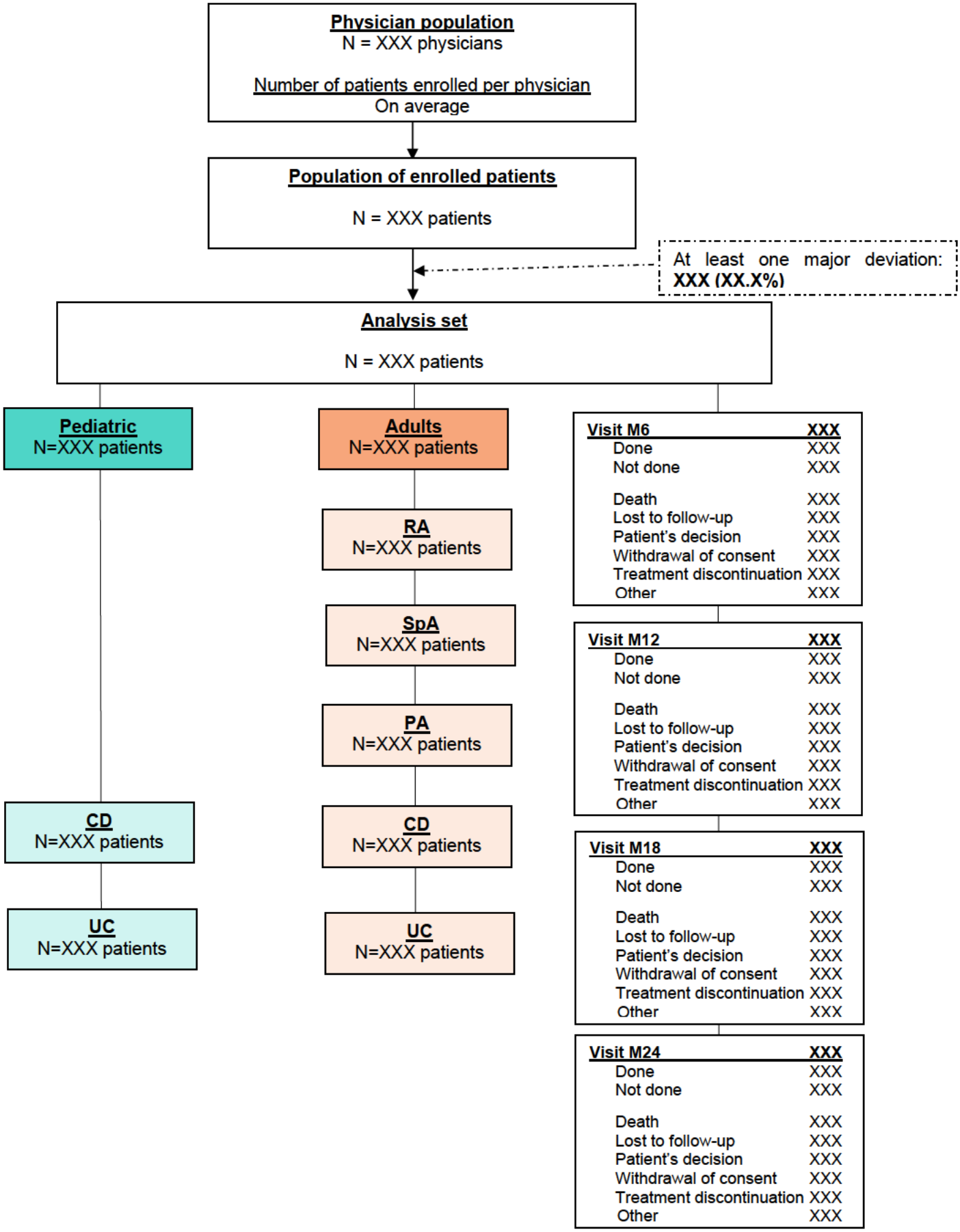
The following subgroups of interest will be identified and described:

- Pediatric and adult population [d]
- Indication for the Inflectra® prescription (CD; UC; RA; SpA; PA)
- Physician-assessed disease severity for RA, SpA and PA patients [d] (0-3; 4-6; 7-10)
- Specific activity index for each disease:
  - Rheumatoid arthritis (RA):
    DAS28 [d] (RA in remission; RA mildly active; RA moderately active; RA very active)
    SDAI [d] (In remission; Mildly active; Moderately active; Very active)
    HAQ[d] (Existence of functional disability; Absence of functional disability)
  - Ankylosing spondylitis (SpA):
    BASDAI [d] (SpA active; SpA inactive)
    BASFI [d] (Significant functional impairment; Mild functional impairment)
    ASDAS [d] (SpA inactive; SpA mildly active; SpA moderately active; SpA very active)
  - Psoriatic arthritis (PA):
    DAS28 [d] (PA in remission; PA mildly active; PA moderately active; PA very active)
  - Ulcerative colitis (UC):
    Mayo score [d] (UC in remission; Mild UC; Moderate UC; Severe UC)
    PUCAI [d] for pediatric patients (UC in remission; Mild UC; Moderate UC; Severe UC)
  - Crohn's disease (CD):
    Harvey-Bradshaw Index [d] (Inactive disease; Active disease; Very active disease)
- Subpopulation of biologics experienced patients [d] (= patients with biotherapy other than infliximab before the initiation of Inflectra®)
- Subpopulation of patient switch from RemicadeTM to Inflectra® [d]
- Subpopulation of biologics experienced patients in patient switched from RemicadeTM to Inflectra®(= patients with biotherapy other than infliximab before the initiation of Remicade)
- Subpopulation of patient naive to biotherapy [d] (= no biotherapy before the initiation of Inflectra®)

- Subpopulation of patient naive to biotherapy in patient switched from RemicadeTM to Inflectra® (= no biotherapy before the initiation of RemicadeTM)

The number and percentage of patients in each analysis set will be described.

The following flow-chart will be completed:


Physician population
N = XXX physicians
Number of patients enrolled per physician
On average
Population of enrolled patients
N = XXX patients
At least one major deviation: XXX (XX.X%)
Analysis set
N = XXX patients
Pediatric
N=XXX patients
Adults
N=XXX patients
RA
N=XXX patients
SpA
N=XXX patients
PA
N=XXX patients
CD
N=XXX patients
UC
N=XXX patients
CD
N=XXX patients
UC
N=XXX patients
Visit M6 XXX
Done XXX
Not done XXX
Death XXX
Lost to follow-up XXX
Patient's decision XXX
Withdrawal of consent XXX
Treatment discontinuation XXX
Other XXX
Visit M12 XXX
Done XXX
Not done XXX
Death XXX
Lost to follow-up XXX
Patient's decision XXX
Withdrawal of consent XXX
Treatment discontinuation XXX
Other XXX
Visit M18 XXX
Done XXX
Not done XXX
Death XXX
Lost to follow-up XXX
Patient's decision XXX
Withdrawal of consent XXX
Treatment discontinuation XXX
Other XXX
Visit M24 XXX
Done XXX
Not done XXX
Death XXX
Lost to follow-up XXX
Patient's decision XXX
Withdrawal of consent XXX
Treatment discontinuation XXX
Other XXX

8.1. DESCRIPTION OF PHYSICIANS

The following will be described:

- Number of physicians contacted
- Number and rate of physician refusals and agreements to participate (by differentiating active and non-active physicians)
- Reasons for non-participation

8.2. DESCRIPTION OF PATIENTS

8.2.1. CHARACTERISTICS OF ANALYSIS SET AT BASELINE

Baseline characteristics will be described globally for the **analysis set and according to the indication for the Inflectra® prescription:**

Patient sociodemographics

- Age (years)
- Gender (male; female)
  If female: menopausal (Yes; No)
  If not, use of contraception (Yes; No)
- Weight (kg), height (cm), BMI [d] (kg/m²)

Diagnosis and disease characteristics

- Physician specialty (Gastroenterologist; Rheumatologist; Internist; Other)
- Indication for Inflectra® (RA; SpA; PA; UC; Crohn's disease)
  The distribution of diseases will also be presented according to physician specialties.
- Duration of disease [d] (years)
- Physician global disease assessment for **RA, SpA and PA** (from 0 to 10)
- Baseline fatigue score for **RA, SpA and PA** (from 0 to 10)
- Granuloma for patients with **CD or UC** (Yes; No)

- Montreal classification:
  For CD patients
  - Age at diagnosis (< 16 years; 17-40 years; >40 years)
  - Location (Ileal; Colonic; Ileocolonic; Isolated upper digestive)
  - Phenotype (Inflammatory; Stenotic; Fistulising)
  - Ano-perineal involvement (Yes; No)
  - Perforating ano-perineal lesions (Yes; No; Unknown)
  - Extradigestive locations (Joints; Skin; Eye; Other)

  For UC patients
  - Age at diagnosis (< 16 years; 17-40 years; >40 years)
  - Location (Rectum; Left-sided; Pancolitis)
  - Extradigestive locations (Joints; Skin; Eye; Other)

- Endoscopic findings:
  For CD patients
  - Time since endoscopy (in days, months or years) [d]
  - CDEIS score continuous
  - CDEIS score by category [d] (Endoscopic remission; Absence of endoscopic remission)

  For UC patients
  - Time since endoscopy (in days, months or years) [d]
  - UCEIS score continuous

- Endoscopic Mayo score by category 1 [d] (Complete endoscopic remission; Absence of complete endoscopic remission)
- Endoscopic Mayo score by category 2 [d] (Endoscopic remission; Absence of endoscopic remission)

- Specific disease activity index:

RA:

- DAS28 score continuous
- DAS28 score by category [d] (In remission; Mildly active; Moderately active; Very active)
- SDAI score continuous
- SDAI score by category [d] (In remission; Mildly active; Moderately active; Very active)
- HAQ score continuous
- HAQ score by category [d] (Existence of functional disability; Absence of functional disability)

SpA:

- BASDAI score continuous
- BASDAI score by category [d] (SpA active; SpA inactive)
- BASFI score continuous
- BASFI score by category [d] (Significant functional impairment; Mild functional impairment)
- ASDAS score continuous
- ASDAS score by category [d] (SpA inactive; SpA mildly active; SpA moderately active; SpA very active)

PA:

- DAS28 score continuous
- DAS28 score by category [d] (In remission; Mildly active; Moderately active; Very active)

UC:

Pediatric patient (Yes; No)

For adult and pediatric patients:

- Mayo score continuous
- Mayo score by category [d] (UC inactive; Mild UC; Moderate UC; Severe UC)
- Clinical Mayo score by category [d] (Clinical remission; Absence of clinical remission)

For pediatric patients only :

- PUCAI score continuous
- PUCAI score by category [d] (UC in remission; Mild UC; Moderate UC; Severe UC)

CD:

- Harvey-Bradshaw Index continuous
- Harvey-Bradshaw Index by category [d] (Inactive disease; Active disease; Very active disease)

Antecedents

Patients with RA, SpA or PA:

- Smoking (Smoker; Nonsmoker; Ex-smoker)
- Personal history of autoimmune rheumatic disease (Yes; No)
  If yes, specify
- Family history of autoimmune rheumatic disease (Yes; No)
- If yes, specify
- Personal history of IBD (Yes; No)
- If yes, specify
- Family history of IBD (Yes; No)

- If yes, specify

Patients with UC or Crohn's disease:

- Smoking (Smoker; Nonsmoker; Ex-smoker)
- Appendicectomy (Yes; No)
  If yes, time since appendicectomy [d] (in months or years)
- Anterior intestinal resection (Yes; No)
  If yes,
  - Time since resection [d] (in months or years)
  - Type of resection (Middle small intestine; Terminal ileum; Ileo-colonic; Colonic)
  - Cumulative length of resections (cm)
  - Colonic segments involved (Caecum; Right colon; Transverse colon; Left colon; Sigmoid colon; Rectum)
    The number and associations of involved colonic segments [d] will be presented.
- Ano-perineal surgery (Yes; No)
- Family history of IBD (Yes; No)
  If yes, specify
- Personal history of autoimmune rheumatic disease (Yes; No)
  If yes, specify

Laboratory tests

For RA, SpA and PA patients

- Rheumatoid factors (Ticked; Not ticked)
  If ticked,
  - Time since result [d] (in days, months or years)
  - Result (IU/mL)
- CRP (Ticked; Not ticked)
  If ticked,
  - Time since result [d] (in days, months or years)
  - Result (mg/L)
- Anti-CPP Ab (Ticked; Not ticked)
  If ticked,
  - Time since result [d] (in days, months or years)
  - Result (IU/mL)

For CD and UC patients

- Hemoglobin (Ticked; Not ticked)
  If ticked,
  - Time since result [d] (in days, months or years)
  - Result (g/dL)
- CRP (Ticked; Not ticked)
  If ticked,
  - Time since result [d] (in days, months or years)
  - Result (mg/L)
- Fecal calprotectin (Ticked Not ticked)
  If ticked,
  - Time since result [d] (in days, months or years)
  - Result (µg/g)

Previous and concomitant treatments

- Corticosteroids during previous two months (Yes; No)
- Salicylates before inclusion (Yes; No)
- Other previous or concomitant treatments (Azathioprine/6-MP; Methotrexate; Cyclosporine) (Yes; No)
  - If yes,
    - Azathioprine/6-MP (Ticked; Not ticked)
    - Methotrexate (Ticked; Not ticked)

        - Cyclosporine (Ticked; Not ticked)
        - Associations of treatments [d]
        - Duration of each previous treatment (in months or years) [d]
        - Reason for stopping for each previous treatment (Loss of efficacy; Primary nonresponse; Intolerance; Other)
          Other reason will be listed.
    - If previous treatments,
        - Azathioprine/6-MP (Ticked; Not ticked)
        - Methotrexate (Ticked; Not ticked)
        - Cyclosporine (Ticked; Not ticked)
        - Associations of treatments [d]
    - If concomitant treatments,
        - Azathioprine/6-MP (Ticked; Not ticked)
        - Methotrexate (Ticked; Not ticked)
        - Cyclosporine (Ticked; Not ticked)
        - Associations of treatments [d]
- Biotherapy (other than Inflectra®) before inclusion (Yes; No)
  If yes,
    - Previous biotherapies:
        - Type ((Anti-TNFα (Remicade™/ Adalimumab/ Golimumab / Etanercept/ Rituximab); Anti-integrin (Vedolizumab); Immunosuppressant (Abatacept); Interleukin inhibitor (Anakinra / Tocilizumab); Anti IL12 and anti IL-23 (Ustekinumab); Other)
          Other reason will be listed.
        - Duration of previous biotherapies (in months or years) [d],
        - Number of previous biotherapies [d],
        - Reason for stopping (Loss of efficacy; Primary nonresponse; Intolerance; Other)
          Other reason will be listed.
    - Last biotherapy:
        - Type ((Anti-TNFα (Remicade™/ Adalimumab/ Golimumab / Etanercept); Anti-integrin (Vedolizumab); Immunosuppressant (Abatacept); Interleukin inhibitor (Anakinra / Tocilizumab); Anti IL12 and anti IL-23 (Ustekinumab); Other)
          Other reason will be listed.
        - Duration of last biotherapy (in months or years) [d],
        - Reason for stopping (Loss of efficacy; Primary nonresponse; Intolerance; Other)
          Other reason will be listed.
        - Last dose (units)
        - Number of doses administered
- Patient on Inflectra® before inclusion (Yes; No)
  If yes,
    - Time since 1st Inflectra® infusion [d] (in weeks or months)
    - Number of Inflectra® infusions since treatment initiation
    - Patient status at first infusion (Mildly active; Inflammatory exacerbation; Remission)
    - Laboratory tests at first infusion (as previously done at baseline)
    - Endoscopic findings at first infusion (as previously done at baseline)
    - Specific disease activity index at first infusion (as previously done at baseline)
- Check-list completed before starting anti-TNFα (Yes; No)

Individual data listings for the other treatments and Inflectra® infusions before inclusion will be presented.

<u>Inflectra® administration at baseline</u>

- Administered dose (in mg or mg/kg)
- Duration of infusion (minutes)
- Duration of patient monitoring at the hospital after infusion (minutes)

Baseline immunogenicity is a secondary endpoint and will be discussed in section 8.4.4. Baseline anxiety, stress and distrust levels are secondary endpoints and will be discusses in section 8.4.5 and 8.4.6.

8.3. PRIMARY OBJECTIVE

The primary objective is to describe in real-world conditions of use:

- Response to treatment,
- Profile of patients treated with Inflectra®

8.3.1. RESPONSE TO TREATMENT

The analyses will be carried out globally on the **analysis set** and also on the following subgroups:

- **Pediatric and adult population**
- **Indication for prescribing Inflectra®**
- **Physician-assessed disease severity for RA, SpA and PA patients**
- **Specific disease activity index**
- **Anxiety level**

The following will be described:

- Proportion of patients who permanently discontinued treatment with Inflectra®
- Reasons for Inflectra® treatment discontinuation (Remission; Loss of efficacy; Intolerance; Inflectra® no longer available; Other)
  If other, specify
- Discontinuations with or without a switch

Response to treatment[d] will be described indirectly and expressed as the percentage of patients without treatment failure during the 2-year follow-up, with the 95% confidence interval and the associated OR with the 95% confidence interval. Treatment failure is defined as permanent discontinuation of the treatment due to intolerance and/or absence of response according to the physician's assessment, or death of the patient related to Inflectra®.
Patients who are lost to follow-up, who withdraw their consent during the study, who decide to drop out of the study, who are withdrawn from the study for another reason will first be treated as missing data, and then as patients without treatment failure.

The proportion of patients without treatment failure will be calculated using the Kaplan-Meier method.
For patients who fail treatment, the duration of Inflectra® treatment will be calculated in months as follows:

(Treatment stop date (or date of death if patient died) – Date of 1st infusion +1) / 30.44

Patients lost to follow-up will be censored on the date of last news.
Patients who withdraw their consent (but agree to the analysis of data collected before withdrawal of consent) will be censored on the date of withdrawal of consent.
Patients who discontinued treatment for a reason other than intolerance or inefficacy will be censored on the date of treatment discontinuation.
Patients who complete the study as per the protocol, who decide to prematurely withdraw, or who are withdrawn for another reason will be censored on the date of study withdrawal.

If the date of last news, withdrawal of consent, or study withdrawal is missing, the date of the last visit will be used.

The proportion of patients without treatment failure in the different subgroups will be compared with a log-rank test.

8.3.2. PROFILE OF PATIENTS TREATED WITH INFLECTRA®

The profiles of patients treated with Inflectra® will be described from baseline characteristics (cf. *8.2.1 Characteristics of analysis set at baseline*) in the following subgroups:

- **Pediatric and adult population**
- **Subpopulation of patients who switched treatment versus patients who did not switch treatment**
  If numbers permit, this subpopulation will be described in terms of:
  - Previous biotherapy (Anti-TNFα; Anti-integrin; Immunosuppressant; Interleukin inhibitor; Anti IL12 and anti IL-23; Other)
  - Reason for the switch (Loss of efficacy; Primary nonresponse; Intolerance; Other)
  - Anxiety level of the patient

In the switch subpopulation, the following parameters will also be described in addition to the profile data mentioned in section *8.2.1*:

- Last biotherapy (Anti-TNFα (Remicade™/ Adalimumab/ Golimumab / Etanercept); Anti integrin (Vedolizumab); Immunosuppressant (Abatacept); Interleukin inhibitor (Anakinra / Tocilizumab); Anti IL12 and anti IL-23 (Ustekinumab); Other)
  Other biotherapies coded beforehand with WHODrug terminology will also be described.
- Number of administered doses of last biotherapy
- Last administered dose of last biotherapy
- Reason for discontinuation (Loss of efficacy; Primary nonresponse; Intolerance; Other)
  If other, specify
- Duration of last biotherapy [d] (in weeks or months)
- Time from last biotherapy to initiation of Inflectra® [d] (in weeks)

In accordance with the recommendations of the French health authorities, only patients naive to Remicade™ should be treated with Inflectra®. However, if there are notifications of patients who switch from Remicade™ to Inflectra®, the corresponding data will nonetheless be collected and analyzed.

8.4. SECONDARY OBJECTIVES

The secondary objectives are to:

- Describe in routine practice the conditions of use of Inflectra®
- Describe in routine practice the tolerance/safety of Inflectra®
- Identify predictive factors of response to treatment
- Describe the immunogenicity profile of Inflectra®
- Measure anxiety, stress and distrust of the patient after the switch announcement (from infliximab to Inflectra®), and the impact of the psychological profile on the follow-up of the patients in terms of efficacy, tolerance and continuation of biosimilar
- Evaluate the evolution of anxiety and stress of patients after the switch from infliximab to Inflectra®

8.4.1. DESCRIPTION OF CONDITIONS OF USE OF INFLECTRA®

The following prescription data will be described:

Prescription
- Number of Inflectra® infusions listed [d]
- Mean administered dose [d] (in mg/kg and mg)
- Cumulative dose [d] (in mg)
- Mean infusion time [d] (minutes)
- Mean duration of post-infusion monitoring at the hospital [d] (minutes)
- Mean time between infusions [d] (in weeks)
- Concomitant treatments:
    - Corticosteroids (Yes; No)
    - Another biotherapy received in addition to Inflectra® (Yes; No)

Note: the infusions will be classified at the corresponding visit from the date of infusion.

These data will be described overall and at the following time points:
- D0 (infusions since inclusion, in the case where treatment was started before the patient was included in the study)
- M6 (infusions from inclusion to visit M6)
- M12 (infusions between visit M6 and visit M12)
- M18 (infusions between visit M12 and visit M18)
- M24 (infusions between visit M18 and visit M24)

Prescription data will also be described during the induction phase, maintenance phase and re-administration phase.
The duration of treatment with Inflectra® [d] and of concomitant treatments (Azathioprine/6-MP; Methotrexate; Cyclosporine) will be described globally during the study.

Clinical and laboratory data will also be described at each follow-up visit:

Laboratory tests
For RA, SpA and PA patients
- At least one assay of rheumatoid factors (Yes; No)
  If yes,
    - mean result [d] (IU/mL)
    - Absolute and relative variation of mean result compared with baseline (and with first administration) [d]
- At least one assay of CRP (Yes; No)
  If yes,
    - mean result [d] (mg/L)
    - Absolute and relative variation of mean result compared with baseline (and with first administration) [d]
- At least one assay of anti-CCP Ab (Yes; No)
  If yes,
    - mean result [d] (IU/mL)
    - Absolute and relative variation of mean result compared with baseline (and with first administration) [d]

For CD and UC patients
- At least one assay of hemoglobin (Yes; No)
  If yes,
    - mean result [d] (g/dL)
    - Absolute and relative variation of mean result compared with baseline (and with first administration) [d]
- At least one assay of CRP (Yes; No)
  If yes,
    - mean result [d] (mg/L)

  - Absolute and relative variation of mean result compared with baseline (and with first administration) [d]
- At least one assay of fecal calprotectin (Yes; No)
  If yes,
  - mean result [d] (µg/g)
  - Absolute and relative variation of mean result compared with baseline (and with first administration) [d]

Disease activity

- Mean global physician-assessed disease activity for **RA, SpA and PA** (from 0 to 10) [d]
- Absolute and relative variation of mean global physician-assessed disease activity compared with baseline (and with first administration) for **RA, SpA and PA** [d]
- Mean fatigue score for **RA, SpA and PA** (from 0 to 10) [d]
- Absolute and relative variation of mean fatigue score compared with baseline (and with first administration) for **RA, SpA and PA** [d]
- Specific disease activity index:

  RA:
  - Mean DAS28 score [d]
  - Absolute and relative variation in mean DAS28 score compared with baseline (and with first administration) [d]
  - Mean SDAI score [d]
  - Absolute and relative variation in mean SDAI score compared with baseline (and with first administration) [d]
  - Mean HAQ score [d]
  - Absolute and relative variation in mean HAQ score compared with baseline (and with first administration) [d]

  SpA:
  - Mean BASDAI score [d]
  - Absolute and relative variation in mean BASDAI score compared with baseline (and with first administration) [d]
  - Mean BASFI score [d]
  - Absolute and relative variation in mean BASFI score compared with baseline (and with first administration) [d]
  - Mean ASDAS score [d]
  - Absolute and relative variation in mean ASDAS score compared with baseline (and with first administration) [d]

  PA:
  - Mean DAS28 score [d]
  - Absolute and relative variation in mean DAS28 score compared with baseline (and with first administration) [d]

  UC:

  For adult and pediatric patients:
  - Mean Mayo score [d]
  - Absolute and relative variation in mean Mayo score compared with baseline (and with first administration) [d]
  - At least one clinical remission [d] (Yes; No)
  - At least one absence of clinical remission [d] (Yes; No)
  - At least one complete endoscopic remission [d] (Yes; No)
  - At least one endoscopic remission [d] (Yes; No)
  - At least one absence of endoscopic remission [d] (Yes; No)

  For pediatric patients only:
  - Mean PUCAI score [d]
  - Absolute and relative variation in mean PUCAI score compared with baseline (and with first administration) [d]

CD:
- Mean Harvey-Bradshaw Index [d]
- Absolute and relative variation in mean Harvey-Bradshaw Index compared with baseline (and with first administration) [d]

- Patient status at last Inflectra® infusion administered (Mildly active; Inflammatory exacerbation; Remission)
- Surgery **for CD and UC patients** (Yes; No)
  If yes,
  - Appendicectomy (Yes; No)
  - Anterior intestinal resection (Yes; No)
    If yes,
    - Type of resection (Middle small intestine; Terminal ileum; Ileo-colonic; Colonic)
    - Cumulative length of resections (cm)
    - Colonic segments involved (Caecum; Right colon; Transverse colon; Left colon; Sigmoid colon; Rectum)

      The number and associations of involved colonic segments [d] will be presented.
  - Ano-perineal surgery (Yes; No)
- Endoscopic score:
  CD:
  - CDEIS score
  - Absolute and relative variation in CDEIS score compared with baseline (and with first administration) [d]

  UC:
  - UCEIS score
  - Absolute and relative variation in UCEIS score compared with baseline (and with first administration) [d]

The analyses will be carried out overall on the **analysis set** and also on the following subgroups:
- **Pediatric and adult population**
- **Indication for prescribing Inflectra®**
- **Physician-assessed disease severity for RA, SpA and PA patients**
- **Specific disease activity index**
- **Patient naive to biotherapy before Inflectra® initiation**
- **Patient who switch from Remicade™ to Inflectra®**
- **Psychological profiles after announcement of the switch (first assessment of each score):**
  - **Anxious/non-anxious**
  - **Stress absent/stress present**
  - **Propension to distrust/ Trust in others**

8.4.2. DESCRIPTION OF INFLECTRA® TOLERANCE

AEs will first be coded according to MedDRA terminology.

The following data will be presented for the **adult and pediatric populations**:
- Proportion of patients with at least one AE
- Proportion of patients with at least one SAE
- Proportion of patients with at least one non-SAE
- Proportion of patients with at least one AE of special interest related to Inflectra®:
  - Infusion reactions, including acute and delayed hypersensitivity reactions
  - Infections including severe infections, tuberculosis, opportunistic infections, hepatitis B
  - Congestive heart failure,

  - Intestinal or perianal abscess,
  - Malignant diseases, leukemias, lymphomas
  - Demyelinating disorders
  - Lupus-like syndrome, disseminated lupus erythematosus
  - Hepatobiliary disorders
  - Sarcoidosis, sarcoid-like reactions
  - Exposure during breastfeeding
  - Medication error
  - Overdose
  - Misuse
  - Extravasation
  - Lack of efficiency
  - Occupational exposure
- Proportion of patients with at least one thromboembolic event:
  - Pulmonary embolism
  - Deep vein thrombosis
  - Superficial vein thrombosis

    Any manifestation linked to arterial thromboembolism including acute arterial occlusion, occlusive peripheral arterial disease, ischemic stroke, transient ischemic attack, myocardial infarction and angina.

AEs will be described according to:

- Adult and pediatric population
- Type of disease (RA; SpA; PA; CD; UC)
- Severity (Mild; Moderate; Severe)
- Relationship to Inflectra® (Suspect; Non suspect)
- Seriousness (Serious; Nonserious)
- Duration of disease [d] (in categories according to the distribution of the data)
- Biotherapy status before Inflectra® initiation (Naive; Non-naive)
- Inflectra® status at baseline (Naive; Non-naive)
- Responder or non-responder status [d]
- Psychological profiles after announcement of the switch (first assessment of each score) :
  - Anxious/non-anxious
  - Stress absent/stress present
  - Propension to distrust/ Trust in others

An individual listing of specific AEs (description, start and end date, seriousness, severity, outcome, causal relationship to treatment, measure taken) will be provided.

8.4.3. IDENTIFICATION OF PREDICTIVE FACTORS OF RESPONSE TO TREATMENT

For each indication, predictive factors of response to treatment will be analyzed using a logistic regression model. A univariate analysis will be performed to identify factors significant at p=0.20, which will then be incorporated in the multivariate model.

The following baseline variables will be tested:

- Physician characteristics
  - Age,
  - Gender,
  - Size of place of practice
  - Type of practice
  - Type of patients

  - Duration of practice

- Patient demographic data
  - Age,
  - Gender,
  - BMI,
  - Smoking status

- Clinical and laboratory data
  - Personal and family history,
  - Disease activity index for each disease,
  - Duration of disease,
  - Concomitant treatments,
  - Naive or non-naive to biotherapy before Inflectra® initiation
  - Naïve or non-naïve to Inflectra® at baseline
  - Treatment switch from Remicade™ to Inflectra® or not
  - Serum infliximab trough level
  - Presence or not of anti-infliximab antibodies
  - Treatment phase at time of first infusion
  - Anxiety profile (anxious/ not anxisous) of the patient
  - Cynical distrust score
  - Stress score

The final model will be built using a stepwise selection of variables (with a p-value entry cutoff of 0.20 and removal cutoff of 0.05). Based on the final model, the Odds Ratios (OR) will be presented with their 95% confidence interval.

A Cox model will also be built using the same procedure as described previously, by also testing the cumulative dose, duration of Inflectra® treatment, and IFX-TL and the presence or not of anti-fliximab antibodies at 14th week for patient in induction treatment. Based on the final model, the Hazard Ratios (HR) will be presented with their 95% confidence interval.

8.4.4. DESCRIPTION OF THE IMMUNOGENICITY PROFILE OF INFLECTRA®

The immunogenicity profile of Inflectra® will be described at each time point:

<u>At 1st Inflectra® infusion and Inclusion:</u>
- Immunogenicity assayed (Yes; No)
  If yes,
  - Reason for assay (Loss of response; Primary nonresponse; De-escalation; Other)
    If Other, specify
  - Infliximab trough level assay (Available; Not available)
    If available,
    - Time since assay [d] (in days, months or years)
    - IFX-TL (µg/mL)
  - Anti-infliximab antibody assay (Available; Not available)
    If available,
    - Time since assay [d] (in days, months or years)
    - Presence of anti-infliximab antibodies (Yes; No)
      If yes, neutralizing antibodies (Yes; No; Not identified)

<u>Between each follow-up visit (M6, M12, M18, et M24):</u>
- Number of immunogenicity assays done [d]

If at least one was done,
- Reason for assay:
  - At least one loss of response (Yes; No)
  - At least one primary nonresponse (Yes; No)
  - At least one de-escalation (Yes; No)
  - At least one other reason (Yes; No)

  Other reasons will be listed.
- Mean IFX-TL [d] (µg/mL)
- At least one presence of anti-infliximab antibodies (Yes; No)
  If yes, at least one presence of neutralizing antibodies (Yes; No)

These data will be described on the following subgroups:
- **Pediatric and adult population**
- **Indication for prescribing Inflectra®**
- **Physician-assessed disease severity for RA, SpA and PA patients**
- **Specific disease activity index**
- **Mean dose or posology administered at visit in question [d]**
- **Naive or non-naive to biotherapy before Inflectra® initiation**
- **Naive or non-naive to Inflectra® at baseline**

8.4.5. MEASURE ANXIETY, STRESS AND DISTRUST OF THE PATIENT AFTER THE SWITCH ANNOUNCEMENT (FROM INFLIXIMAB TO INFLECTRA®), AND THE IMPACT OF THE PSYCHOLOGICAL PROFILE ON THE FOLLOW-UP OF THE PATIENTS IN TERMS OF EFFICACY, TOLERANCE AND CONTINUATION OF BIOSIMILAR.

The following data will be described and analyzed only among those who were informed of a switch from infliximab to Inflectra®:

For anxiety, the GAD7 questionnaire is a questionnaire of anxiety with 7 items, scoring from 0 to 3. The total score is calculated by adding together the scores for the seven items.
Anxiety profile will be defined categorizing the overall score as follows: overall score of GAD7>7: anxious, overall score of GAD7<8: non-anxious. A better categorization may be decided using specificity/sensitivity methodology with the variable of treatment permanent discontinuation. The following data will be described:
- Score of GAD7 categorized in two categories:
  - GAD7>7: anxious
  - GAD7<8: non-anxious
- Crude values of the GAD7 score

For distrust, the Cook-Medley questionnaire, also called cynical distrust scale, contains 8 items, scoring from 0 to 4. The total score of the questionnaire is calculated by adding together the scores for the 8 items. The Cook-Medley questionnaire would possibly be correlated to GAD7 score, response to treatment and time of treatment. The following data will be described:
- Score of Cook-Medley categorized in two categories using the median value:
  - score>median: propension to distrust,
  - score<median: trust in others
- Crude values of the Cook-Medley score

For stress, the questionnaire on stress perception after the switch to the biosimilar contain 3 items (emotional reactivity, repetition syndrome and tendency to avoid), each scoring from 0 to 4. The overall score of stress is calculated by adding together the scores for the 3 items. The stress questionnaire would possibly be correlated to GAD7 score, response to treatment and time of treatment. The following data will be described:

- Score of stress categorized in two categories using the median value:
  - Score<median: stress absent
  - score >median: stress present
- Crude values of the score of stress

8.4.6. EVALUATE THE EVOLUTION OF ANXIETY AND STRESS OF PATIENTS AFTER THE SWITCH FROM INFLIXIMAB TO INFLECTRA®

The evolution of anxiety and stress of patients after switch from infliximab to Inflectra® will be analyzed only among those who were informed of a switch from infliximab to Inflectra® (If the number of patients is not low):

The evolution (absolute difference in the score since inclusion visit) of the GAD7 score will be analyzed using an analysis of covariance with repeated measures. Model will include at least 2 dependent covariates: the initial value of GAD7 and the treatment discontinuation at 1 year (or 2 years), Least-square means will be estimated at each time, and presented with their two-sided 95% confidence interval. The interaction between time* permanent discontinuation of the treatment will be explored.
For patients anxious at baseline (initial score of GAD7>7), the time until a non-anxious state (GAD7<8) will be analyzed using time-to-event analysis, as described below.Time until a non-anxious state (GAD7<8) is defined as the time from the date of first assessment of GAD7 to the date where GAD7 score drops below 8. Patients will be censored following Table 1.

Table 1 Censoring for time until a non-anxious state

Situation	Date of non-anxious state or Censoring	Outcome
Non-anxious state achieved during study	Date of first exam showing non-anxious state	Event
Death before the end of the study, without reaching the non-anxious state	Date of death	Censored
Still anxious (GAD7>7) at the end of the study	Date of last contact with patient	Censored
Lost to follow-up	Date of last contact with patient	Censored

Time until a non-anxious state (GAD7<8) will be estimated by the Kaplan-Meier method.

The evolution of the score of stress will be analyzes similarly to GAD7. As this questionnaire is not yet validated, a process of validation may be considered.

8.5. INTERIM ANALYSIS

An interim analysis was performed in January 2017. This analysis was purely descriptive and described all the available baseline data.
Other interim analyses are planned each year. The analyses planned in the SAP will be performed on the available data. The subgroups defined in the SAP will be analyzed if the sample size is superior to 10 patients.

8.6. STATISTICAL METHODOLOGY AND PRESENTATION OF RESULTS

8.6.1. GENERAL POINTS

Depending on the nature of the variables, descriptive statistics will be as follows:

For qualitative data: number in sample, number of missing values, frequency and percentage for each modality of the variable (excluding missing data in the denominator). Two-sided 95% confidence intervals will be presented when considered relevant. Percentages will be expressed to the first decimal place.
Qualitative variables will be compared with a Chi2 or Fisher exact test when the theoretical sample is less than 5.

For quantitative data: number in sample, number of missing values, mean, standard deviation, median, quartiles, minimum and maximum. Data will be presented as follows: 1 more decimal place than the original variable for mean, standard deviation, median and quartiles, 0 for min and max.
Quantitative variables will be compared with a Student t test for normally distributed variables or otherwise with a Wilcoxon rank sum test.

All statistical analyses will be performed at 5% alpha risk without correction using a two-sided hypothesis.

No visits will be re-set.

Statistical analyses will be carried out on SAS® software, release 9.3 or later, SAS Institute, NC, Cary, USA.

8.6.2. HANDLING OF MISSING OR INCOHERENT DATA

All procedures performed on aberrant, missing or incoherent data found in the database will be described in the data review report.

As the primary objectives of the study are exclusively descriptive, no imputation of missing data will be done, except for certain partial dates:

- if the day is missing, it will be replaced by 15.
- if the day and the month are missing, the date will be replaced by 15/06.

Negative durations caused by imputation of partial dates will be considered as missing data.

To build the predictive model of treatment failure, simple or multiple imputation methods may be considered, according to the nature and frequency of missing data, on the covariates.

8.6.3. PRESENTATION OF RESULTS

The TFLs are presented in the results of the interim analysis in 2019 “TAB763 0.1 NL 02APR19.doc”. The tables will be presented in the following format:

Table 1 – Description of quantitative variables

		Group A N=xxx	Group B N=xxx	Total N=xxx	P-value
Variable 1 (unit)	N	xx	xx	xx	
	Mean ± SD	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x	
	Median	xx.x	xx.x	xx.x	0.xxx [d]
	Q1 ; Q3	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x	
	Min. ; Max.	xx ; xx	xx ; xx	xx ; xx	
	Missing	xx	xx	xx	
Variable 2 (unit)	N	xx	xx	xx	
	Mean ± SD	xx.x ± x.x	xx.x ± x.x	xx.x ± x.x	
	Median	xx.x	xx.x	xx.x	0.xxx [d]
	Q1 ; Q3	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x	
	Min. ; Max.	xx ; xx	xx ; xx	xx ; xx	
	Missing	xx	xx	xx	
[d]: name of test					

Table 2 – Description of qualitative variables

		Group A N=xxx	Group B N=xxx	Total N=xxx	P-value
Variable 1	N	xx	xx	xx	
	Missing	xx	xx	xx	
	Modality 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	0.xxx [a]
	Modality 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
Variable 2	N	xx	xx	xx	
	Missing	xx	xx	xx	
	Modality 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	0.xxx [a]
	Modality 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
[a]: name of test					

Table 3 - Description of AEs by SOC and PT

SOC and PT	Group A (N=xxx)			Group B (N=xxx)			Total (N=xxx)		
	EI (1)	n (2)	% (3)	EI (1)	n (2)	% (3)	EI (1)	n (2)	% (3)
TOTAL	xx	xx	xx.x	xx	xx	xx.x	xx	xx	xx.x
SOC 1	xx	xx	xx.x	xx	xx	xx.x	xx	xx	xx.x
PT 1	xx	xx	xx.x	xx	xx	xx.x	xx	xx	xx.x
PT 2	xx	xx	xx.x	xx	xx	xx.x	xx	xx	xx.x
….	xx	xx	xx.x	xx	xx	xx.x	xx	xx	xx.x
SOC 2	xx	xx	xx.x	xx	xx	xx.x	xx	xx	xx.x
PT 1	xx	xx	xx.x	xx	xx	xx.x	xx	xx	xx.x
PT 2	xx	xx	xx.x	xx	xx	xx.x	xx	xx	xx.x
….	xx	xx	xx.x	xx	xx	xx.x	xx	xx	xx.x

(1) Number of AEs
(2) Number of patients with at least one AE
(3) % of patients with at least one AE

8.6.4. IMPACT OF COVID-19 ON STUDY RESULTS

We must be prepared to identify the impact of Covid-19 (if any) on the results in terms of:

- Number of visits/patients/centres with possible impact of COVID-19 pandemic from 17 March 2020 to 11 May 2020
- Number of temporary and permanent discontinuations of study treatment due to Covid-19
- Number of temporary switches to another treatment (In this case, the name of treatment will be given)

9. SAMPLE SIZE CALCULATION

In accordance with the recommendations of the French health authorities, only patients naive to Remicade™ should be treated with Inflectra®. Based on current prescription data, it is estimated that approximately 1200 patients will be treated with Inflectra® during the two years corresponding to the inclusion period (600 patients per 12 months).
The sample size calculation is based on the precision of the estimated confidence interval for any proportion of patients treated with Inflectra®. The required number of patients is a function of the expected percentage, the required precision and the alpha risk.
In the absence of real-world data, under the least favorable hypothesis, namely: proportion of 50% with a two-sided 95% confidence interval, the following formula is used to calculate the required sample size based on the desired proportion (p) and precision (i)

$$n = z^2_{1-\alpha/2} \frac{p(1-p)}{i^2}$$

	Proportion				
Precision	10%	20%	30%	40%	50%
±2.5%	553	983	1291	1475	1536
±3.0%	384	683	896	1024	1067
±3.5%	282	502	658	753	784
±4.0%	216	384	504	576	600
±4.5%	171	304	398	455	474
±5.0%	138	246	323	369	384
±5.5%	114	203	267	305	317
±6.0%	96	171	224	256	267
±6.5%	82	145	191	218	227

According to this formula, 1200 patients would allow a precision between 2.5% and 3.0% on the rate of treatment response.

Regarding the objective related to the stress and anxiety, the following hypothesis are considered

- Proportion of patients with treatment permanent discontinuation: 25%
- Proportion of patients with treatment permanent discontinuation among anxious patients (GAD>7): 30%
- Proportion of patients with treatment permanent discontinuation among non- anxious patients (GAD<8): 20%
- Missing data on treatment permanent discontinuation due to lost to follow-up: 10%

A sample size of 300 patients is necessary to calculate a two-sided 95% confidence interval of the odds-ratio of the variable “treatment permanent discontinuation”, not including 1.

With these hypotheses, the odds-ratio would be 0.58 with a 95% confidence interval of [0.35-0.99]. Taking into account the 10% of lost to follow-up, 300/0.9=330 patients would be needed.

10. LEVEL OF ANALYSIS VALIDATION

The level of validation of the programming is defined by assessing the risk associated with the complexity of the program and the impact of an error.

3 levels of validation are defined:

- *Basic* = each time the program is run, the programmer ensures the validity of his programming. Firstly, the code has to be checked to ensure that it corresponds to the planned analyses. Secondly, no error messages should appear in the "log/journal" window. If this is not the case, the error must be corrected. Warnings and notes such as non-initialized variables, automatic replacement of missing data, data outside the graphics area, etc. must also be checked. Thirdly, the results output must be checked to ensure that the program does what it is supposed to do and that there are no errors in the presentation of results.

- *NC (non critical)* = The tables, listings and figures compiled in a single document will be checked against the study case report form and the SAP by a qualified person other than the program developer. Spot checks (numbers, mean, minimum, maximum, frequency, number of missing data) will be carried out. Comparisons with other data (eg., comparison of a figure with the source table) will be done.

- *CR (critical)* = A double programming and a comparison of the results must be done by a qualified person other than the program developer. If these controls reveal any discordance, the cause must be sought and the programming must be redone if the error is found to come from the first programming.

Analyses with a level of programming validation "Basic + CR"	SAP reference
- Status of patients - Protocol violations Analysis set and subgroups	Section 8.1 *« Study population »*
- Primary endpoint: Response to treatment	Section 8.3.1 *« Response to treatment »*

The other analyses and programs have a "Basic + NC" level of validation by default.

11. LITERATURE REFERENCES

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