A NON-INTERVENTIONAL STUDY PROTOCOL (NI)

Information on the study

Title	**ReFLECT** **National Observatory on use of Inflectra® under real-life conditions.**
Protocol number	**C1231004**
Identifier of protocol version	**Amendment NO. 3 - Version 6.0 final**
Date of latest version of the protocol	**22/June/2018**
Active substance	**Infliximab**
Medicinal product	**Inflectra®**
Question and objectives of the study	Primary Objective To describe under real-life conditions of use: - The response to treatment, - The profile of patients treated with Inflectra® Secondary objectives - To describe in routine practice: o The conditions for use of Inflectra® o The safety and tolerability to Inflectra® - To determine factors predictive of response to treatment - To describe the profile of immunogenicity of Inflectra® - To measure anxiety, stress and patient mistrust at time of announcement of switch and impact of the psychological profile on patient follow-up in terms of efficacy, safety and continuation of the biosimilar product - To evaluate the course of anxiety and of stress of patients after the switch
Author	**Pfizer PFE France**

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LIST OF ABBREVIATIONS

Abbreviation	Definition
6-MP	6-mercaptopurine
AE	Adverse event
AZA	Azathioprine
BMI	Body Mass Index
CCTIRS	Consultative Committee for Data processing in Scientific Research
CDEIS	Crohn's Disease Endoscopic Index of Severity
CEPS	Economic Committee on Health Products
CNIL	National Commission on Data Processing and Freedoms
CNOM	French National Medical Council
CRA	Clinical Research Associate
CRO	Contract Research Organization
CRF	Case Report Form
DMARD	Disease-modifying anti-rheumatoid drug
DNA	Deoxyribonucleic acid
eCRF	electronic Case Report Form
FDA	Food and Drug Administration (US)
HAS	French National Authority for Health
IgG	type G immunoglobulin
MA	Marketing Authorisation
NYHA	New York Heart Association
RA	Rheumatoid arthritis
SAE	Serious adverse event
SmPC	Summary of Product Characteristics
TNF	Tumour Necrosis Factor
UCEIS	Ulcerative Colitis Endoscopic Index of Severity

1. RESPONSIBLE PARTIES

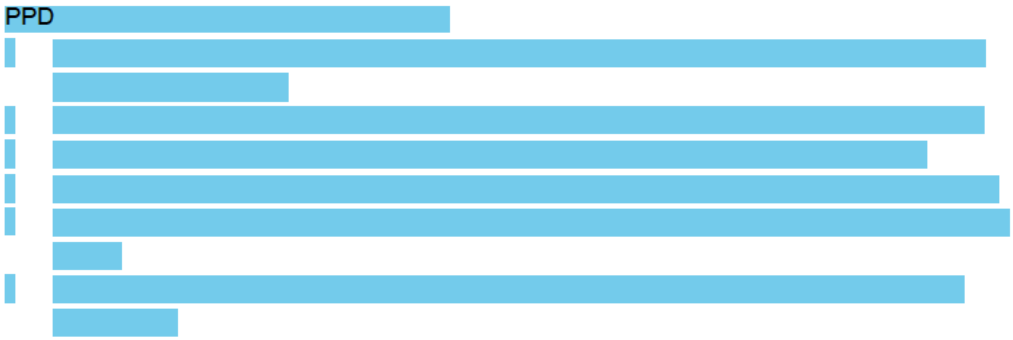
Experts in the Scientific Committee

Name	Title	Establishment	Address
PPD			
PPD			
PPD			
PPD			
PPD			
PPD			(Department of Hepato-gastro-enterology and digestive oncology) PPD

Coordinator of the Scientific Committee

Name	Title	Establishment	Address
PPD			

2. SUMMARY

Study title	**ReFLECT: National Observatory of use of Inflectra® under real-life conditions**
Sponsor	**Pfizer PFE France (Pfizer Group)**
Coordinator	**Prof. BOUHNIK Yoram**
Scientific Committee	**Coordinator** 
Participating centres and Doctors	- France (metropolitan) - Rheumatologists, gastroenterologists and internists in public or private Hospital establishments which have referenced Inflectra®,
Rationale	Infliximab is a chimeric monoclonal antibody directed against Tumour Necrosis Factor alpha (TNF-α) used in treatment of inflammatory auto-immune diseases. Infliximab, initially marketed under the name Remicade™, has been approved by the US Food and Drug Agency (Food and Drug Administration – FDA) in treatment of psoriasis, of Crohn's disease, of ulcerative colitis, of ankylosing spondylitis, of psoriatic arthritis and of rheumatoid arthritis. The first marketing authorisation (MA) was granted to Remicade™ by the FDA in August 1998 for the treatment of Crohn's disease. Remicade™ is marketed 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 requirements can be considered as a therapeutic alternative to the reference biological product. A phase III, randomised clinical trial conducted with double-blind design on 606 patients with rheumatoid arthritis (RA) made it possible to demonstrate the therapeutic equivalence of Inflectra® to Remicade™. In this study, 73.4% of patients treated with Inflectra® showed an improvement of at least 20% in symptoms of RA based on the ACR20 score 30 weeks versus 69.7% of patients treated with Remicade™. In this same study, 42.3% of patients in the Inflectra® group showed an improvement in symptoms of at least 50% in comparison to 40.6% of patients in the Remicade™ group. Data on comparable safety and tolerability between the two groups have confirmed the equivalence of Inflectra® to Remicade™. Furthermore, there was no significant difference concerning the immunogenicity profile at 54 weeks between the two treatments and the impact of the anti-medicinal product antibody on efficacy and safety was also comparable. Inflectra® was approved by the European Commission in September 2013.

	Beyond the economic aspect, it would be useful to collect data on use of Inflectra® under real-life conditions, data which currently do not exist. The present observatory is set up in order to meet this objective and to collect data concerning use of Inflectra® under real-life conditions. Moreover, and as with other biotherapies indicated in the management of psoriasis, the French National Authority for Health (HAS) has asked for the set up of a follow-up of a cohort representative of patients with psoriasis. For this purpose, the decision has been taken to become part of an ongoing register, the PSOBIOTEQ register. In order to avoid having two competing studies, patients with psoriasis therefore will not be included in the present observatory. Lastly, patient mistrust with regard to biosimilar medicinal products in general, and in particular, in a switch from the biological treatment of reference to its biosimilar and their impact on follow-up of the patient in terms of the nocebo effect have been the subject of recent publications. This new problem requires that elements of response be provided with the aid of observational prospective data.
Study objectives	Primary Objective To describe under real-life conditions of use - The response to treatment, - The profile of patients treated with Inflectra® Secondary objectives - To describe in routine practice: • The conditions for use of Inflectra® • Safety of Inflectra® - To determine the factors predictive of response to treatment - To describe the profile of immunogenicity of Inflectra® - To measure anxiety, stress and mistrust of the patient at time of announcement of the switch and the impact of the psychological profile on follow-up of the patient in terms of efficacy, safety and continuation of the biosimilar product - To assess the course of anxiety and of stress in patients after the switch
Population concerned	**Inclusion criteria** - Adult patients treated with Inflectra® on date of inclusion, whatever the phase of treatment or adult patients who have been informed of a switch from infliximab reference product to Inflectra®, in one of the following indications and in conformity with the SmPC: Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis or psoriatic arthritis. - Paediatric patients (children and adolescents 6 to 17 years of age) treated with Inflectra®, whatever the phase of treatment, from the time that Inflectra® is prescribed in conformity with indications mentioned in the SmPC: Crohn's disease or ulcerative colitis - Patients (or their legal representatives) who received the information (oral and written) concerning the study and who accept to participate - Patients who gave their agreement for access to their clinical data and to their medical dossier by signing the consent form. Patients must have signed the consent form at the latest prior to their discharge from the hospital (first administration of

	Inflectra® after inclusion in the study). **Non-inclusion criteria** - Patients who refused to provide access to their medical dossier for collection of their personal medical data. - Patients not treated with Inflectra® - Patients treated with Inflectra® for psoriasis - Patients with a history of hypersensitivity to infliximab, other murine proteins or one of the excipients of Inflectra®. - Patients with tuberculosis or presenting with any other severe infection such as sepsis, an abscess or an opportunistic infection. - Patients presenting with moderate to severe heart failure (NYHA III/IV)
Study design and methodology	**Study design** An observational, national, prospective, multi-centre study. **Methodology** Doctors practicing in hospitals participating in this observatory will systematically inform eligible patients to whom they prescribe Inflectra® of the existence of the study and will give them an information leaflet. Once the patient has been included, data of interest in the patient's medical dossier will be recorded in the electronic case report form (eCRF) every 6 months during the first two years of follow-up. The participating doctor therefore should connect at least 5 times to the data case report form of each patient. In this regard, a reminder message will be sent automatically to doctors every 6 months after inclusion of each patient. If necessary, a clinical study technician may assist the participating doctor for data entry of each patient in the eCRF. Moreover, if the sponsor considers it necessary, a Clinical Research Associate (CRA) will perform regular monitoring visits on-site. Patients will be managed according to the usual practices of each centre. No special follow-up of patients is required by the protocol.

Data collected	**Data collected at the <u>inclusion visit</u>**
	• Age, sex, weight, height or body mass index (BMI) if available, status as a smoker (yes/no), use of contraception, if applicable
	• Medical speciality of the prescriber: gastroenterologist/rheumatologist/dermatologist/other, to be specified
	• Indication for which Inflectra® is prescribed: Crohn's disease/ulcerative colitis/rheumatoid arthritis/ankylosing spondylitis/psoriatic arthritis/other, to be specified
	• Date or year of diagnosis
	• Severity of the disease:
	  o Mild/moderate/severe
	  o Activity index specific of the disease
	• For patients initiating treatment with Inflectra®, a pre-treatment assessment prior to initiation of the anti-TNFα: completed/not completed
	• Comorbidities: yes/no/if yes, list them
	• For patients already under treatment with Inflectra®, date of first prescription of Inflectra®
	• Previous treatments: corticosteroids/immuno-suppressants/biotherapy/surgery/other (yes/no/unknown; if yes, list them)
	  o Patient naïve for biotherapy (never treated with biotherapy): yes/no; if no, specify:
	  ▪ Previous biotherapy prescribed: anti-TNFα (infliximab/ adalimumab/etanercept/golimumab), selective immuno-suppressant (vedolizumab/abatacept), interleukin inhibitor (anakinra/ustekinumab/tocilizumab), other (specify)
	  ▪ Dates of first and of last administration of previous biotherapy
	  ▪ Number of doses administered of a previous biotherapy
	  ▪ Last dose administered of a previous biotherapy
	  ▪ If the previous biotherapy is not Inflectra® (switch), reason why treatment was changed in favour of Inflectra®: no response with previous treatment/insufficient response with previous treatment/problem of tolerability with previous treatment/other
	• Results of immunogenicity, if available:
	  o Infliximab residual serum levels (IRL),
	  o Anti-infliximab antibody serum levels
	• Data relating to stress, anxiety and to mistrust (solely in patients who have been informed of a switch from infliximab reference to Inflectra®):
	  o Cook-Medley Questionnaire (8 items), also called the cynical mistrust rating scale
	  o GAD7 Questionnaire (7 items)
	  o Questionnaire on stress perceived relative to the switch (3 items)
	
	Data collected every 6 months
	• Data concerning each administration of Inflectra®:
	  o Administration performed: yes/no, if yes specify:

- Date of administration
- Posology or dose administered
- Duration of infusion
- Duration of monitoring of patient in the hospital after administration
- Treatment phase: induction/maintenance/re-administration

- Concomitant treatments:
  - Corticosteroids
  - Disease-modifying anti-rheumatic treatments (DMARDs)
  - 5-aminosalicylic acid derivative
  - Immuno-suppressants
  - Alkalising agents
  - Biotherapy
- Adverse events including adverse events of specific interest related to Inflectra®:
  - Reactions related to the infusion, including acute and delayed onset hypersensitivity reactions
  - Infections including serious infections, tuberculosis, opportunistic infections, hepatitis B
  - Congestive heart failure (CHF),
  - Intestinal and perianal abscess,
  - Malignant disease, leukaemias, lymphomas,
  - Demyelinating disorders
  - Lupus syndrome, disseminated lupus erythematosus
  - Hepato-biliary disorders
  - Sarcoidosis, sarcoidosis-like reactions
- Situations involving exposure to a medicinal product in the study, including:
- Exposure in pregnancy
- Exposure in breastfeeding
- Medicinal product errors
- Cases of an overdose
- Cases of misuse
- Extravasation,
- Lack of efficacy,
- And occupational-related exposure

- Results of immunogenicity testing, if available:
  - Infliximab residual serum levels (IRL),
  - Anti-infliximab antibody serum levels
- Patient's status:
  - In remission: yes/no
  - lost to follow-up: yes/no
  - Deceased: yes/no
  - The patient discontinued his/her treatment with Inflectra® permanently: yes/no
  - Disease severity:
    - According to assessment by the doctor: mild/moderate/severe
    - According to the specific activity index of the disease

	Data collected at time of each infusion (solely in patients who have been informed of the switch from infliximab of reference to Inflectra®) o GAD7 Questionnaire (7 items) **Data collected at 6 months and one-year follow-up** (solely in patients who have been informed of a switch of infliximab of reference to Inflectra®) o Questionnaire on stress perceived relating to the switch (3 items) **End of study visit:** • Reason and date of end of study: o Patient died, date of death o Patient lost to follow-up, date of last contact o Withdrawal of consent concerning access to the medical dossier and to collection of data, date of withdrawal of consent o Permanent discontinuation of treatment with Inflectra®: ▪ Specify: discontinuation of treatment with an anti-TNFα/switch to another infliximab (Remicade™/Remsima ™)/switch to another anti-TNFα therapy, specify which one ▪ Reason for discontinuation of treatment with Inflectra®: no response with Inflectra®/insufficient response with Inflectra®/problem of safety with Inflectra®/Inflectra® is no longer available in the hospital/stable condition of patient in remission/other, specify o Date of permanent discontinuation of treatment with Inflectra®
Duration of study and schedule	- Total duration of study: 4 years - Duration of inclusion period: 2 years - Duration of follow-up per patient: 2 years
Method of analysis **Data analysis**	Appropriate methods of descriptive statistics will be used in order to analyse the primary assessment end point. Characteristics of patients and of the switch will be described with their per cent and their 95% confidence interval, or by the mean, standard deviation, median, minimum and maximum value, depending on type of variable. The indication for prescription of Inflectra® and severity of the disease will be prescribed by a per cent and with its 95% confidence interval (CI). Lastly, the response to treatment will be expressed by the responder rate and the non-responder rate with their 95% confidence interval, overall and in each sub-group. Appropriate statistical methods (mean, standard deviations, median, minimum and maximum values, 95% confidence interval) will be used to describe conditions of use of Inflectra®. Concerning assessment of safety and tolerability to treatment, the overall per cent of AEs and per cent AEs of specific interest will be expressed with their 95% confidence interval. For each indication, factors predictive of a response to treatment will be analysed by a logistic regression model. Univariate analysis will be performed in order to select factors which then will be taken into account in the multi-variate model. It is planned to perform several interim analyses on data collected throughout the duration of the study. The final analysis will be performed when the study has been completed, with all data collected.

Number of patients	Except for patients with psoriasis, all adult and paediatric patients treated with Inflectra® in one of the participating French centres, whatever the treatment phase, will be included in the observatory, unless they explicitly express their refusal concerning access to their medical dossier for purposes of collection of personal information. Based on an estimate of the number of patients naïve for therapy treated each year, it is estimated that about **1,200 patients** will be treated with Inflectra® during the first **two years** corresponding to the inclusion period (600 patients over 12 months). Inclusions will be stopped if the level of 1,200 patients is reached prior to the end of the planned inclusion period; these 1,200 patients would make it possible to have an accuracy of ± 2.8% in the estimated responder rate. Concerning the objective related to stress and anxiety, the following hypotheses are considered: o Per cent discontinuations of treatment at one year: 25% o Per cent discontinuations in anxious patients (GAD>7):30% o Per cent discontinuations in non-anxious patients (GAD<8): 20% o Missing data on discontinuations of treatment due to patients lost to follow-up: 10% A sample size of 300 patients is necessary in order to calculate a 95% two-sided confidence interval of the odds ratio of the variable discontinuation of treatment not containing the value 1. Therefore, with these hypotheses, the odds ratio may be 0.58 and its confidence interval [0.35; 0.99]. Taking into account 10% of missing data, 300/0.9=330 patients will have to be included after implementation of amendment no. 3. Therefore, 330 adult patients who have been informed of a switch from infliximab of reference to Inflectra® will have to be included in order to achieve this secondary objective.
Regulatory approaches	- Submission to the CCTIRS (Consultative Committee for Data Processing): early February 2016 - Submission to the CNIL (National Committee on Data Processing and Freedoms): end of April 2016 - Submission to the CNOM (French National Medical Council): June 2016 - Submission of amendment No. 3 (Version 5) for information of CNIL: June 2018 - Implementation of amendment No. 3 (Version 5): June 2018 - Entry into application of the reference methodology No. 3 (MR003): June 2018

3. AMENDMENT

French-specific protocol

Amendment number	Date	Substantial or administra-tive amendment	Section(s) changed in protocol	Summary of amendment(s)	Reason
Initial protocol Version 2.0	19 April 2016	NA	NA	NA	NA
Amendment no. 1 Version 3.1	23 August 2016	Administrative	All	- Pfizer Template - Updating of PV paragraph	Updating in conformity with Pfizer procedures.
Amendment No. 2 Version 4.0	20/Nov/2017	Administrative	All	Change to participating doctors and schedule	
Amendment No. 3 Version 6.0	22/June/2018	Non-substantial	All	- Addition of data on stress, anxiety, and mistrust - Addition of two new members in the scientific committee - Updating of RGPD (General Regulation on Data Protection	New scientific publications

Possible protocol amendments will be reported to the CNIL and to the CNOM. Each participating doctor should be informed of each change to the protocol and agree to comply with the protocol and its amendments, which are an integral part of the protocol.

4. DECISIVE STAGES

The decisive stages are presented in the following.

Decisive stage	Planned date
Recruitment of doctors	End of May 2016
Start of data collection: - 1st patient included	September 2016

- Last patient included	December 2018
End of data collection: - 1st patient included - last patient included	 September 2018 December 2020
Interim report	Each year starting from December 2016
Study final report	At latest January 2021

5. JUSTIFICATION AND CONTEXT

The objective of this non-interventional study is to describe under real-life conditions of use, the response to treatment, as well as the profile of patients treated with Inflectra®

5.1. Medical Context

Although combined in the same category, auto-immune diseases are of a highly heterogeneous nature: over 80 of them exist [1]. In 2009, the world-wide prevalence of auto-immune diseases was 8% [2]. The pathophysiological mechanisms at the origin of these diseases are heterogeneous also: genetic factors, environmental and immunological factors can be involved. For example, psoriatic arthritis is characterised by specific mutations, while auto-antibodies can be detected in rheumatoid arthritis [1]. Psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, Crohn's disease and ulcerative colitis are classified among inflammatory type auto-immune diseases. In 2013, almost 431,000 persons in France were suffering from a long-duration disorder (ALD) associated with one of these diseases for which, therefore, they received total reimbursement of expenditures associated with their disease [3]. One of the characteristics of inflammatory auto-immune diseases is an increase in levels of Tumour Necrosis Factor alpha (TNF-α). Therefore, TNF-α inhibition is to be considered in treatment of the diseases. It is in this manner that infliximab acts. This monoclonal antibody binds to the soluble and transmembrane forms of TNF-α receptors, thus preventing interaction with the ligand. This results in blockade of activation of cellular signalling pathways responsible for production and release of cytokines. The result is a decrease in the immune and inflammatory responses [1,4].
Infliximab, initially marketed under the name Remicade™, was approved by the US Food and Drug Administration Agency (FDA) for treatment of Crohn's disease in August 1998 [5] and was authorised in Europe in 1999. Today, Remicade™ is also indicated in treatment of psoriasis, of ulcerative colitis, of ankylosing spondylitis, of RA and of psoriatic arthritis. Inflectra®, the first biosimilar of Remicade™, was approved by the European Commission in 2013 [4]. Inflectra® has been developed in conformity with European requirements and can be considered as a therapeutic alternative to Remicade™ [6]. In fact, its equivalence to Remicade™

has been demonstrated in a clinical study conducted on 606 patients with RA and in a pharmacokinetic study conducted on patients with ankylosing spondylitis [4]. In a phase III randomised trial, 73.4% of patients treated with Inflectra® showed an improvement of at least 20% in symptoms of RA based on the ACR20 score at 30 weeks versus 69.7% of patients treated with Remicade™. In this same study, 42.3% of patients in the Inflectra® group showed an improvement of symptoms of at least 50% in comparison to 40.6% of patients in the Remicade™ group. Comparable data on safety and tolerability between the two groups confirmed the equivalence of Inflectra® to Remicade™. Furthermore, there was no significant difference concerning the immunogenicity profile at 54 weeks between the two treatments, and the impact of anti-medicinal product antibodies on efficacy and safety was also comparable. Based on bioequivalence with Remicade™, the indications for Inflectra® have been expanded to all indications of Remicade™ [4].

5.2. Rationale of the Observatory

In 2013, European sales of Remicade™ amounted to almost 2 billion euros [7]. The introduction of the first biosimilar for Remicade™ on the European market may enable the European health systems to generate over 20 billion euros of savings between now and 2020 [8]. The introduction of Inflectra® on the European market therefore has a definite economic advantage. Beyond the economic aspect, it would be useful to collect data on use of Inflectra® under real-life conditions, data which currently do not exist.
The present observatory has been set up in order to achieve this objective and to collect data on the use of Inflectra® under real-life conditions.
Moreover, and as with other biotherapies indicated in management of psoriasis, the French National Authority for Health (HAS) has requested that the follow-up of a cohort representative of patients with psoriasis be set up. For this purpose, the decision has been taken to become part of an ongoing register, the PSOBIOTEQ register, dedicated to patients with psoriasis. In order to avoid having two competing studies, patients with psoriasis therefore will not be included in the present observatory.
Lastly, patient mistrust with respect to biosimilars in general, and in particular, at time of the switch from the reference biological treatment to its biosimilar product and their impact on follow-up of patients in terms of the nocebo effect have been the subject of recent publications (16-17). This new problem requires that elements of response be provided with the aid of observational prospective data.

5.3. Treatment

5.3.1. Description

Inflectra® (infliximab) is a medicinal product biosimilar to Remicade™. It is an IgG1 human-murine chimeric monoclonal antibody produced in murine hybridoma cells by recombinant DNA technique. Inflectra® is marketed as a powder for solution to be diluted for infusion is the dose of 100 mg.

5.3.2. Therapeutic indications in the setting of the study

The therapeutic indications of Inflectra® in adults which are considered in the setting of the study are described in the SmPC as follows:

- **Rheumatoid arthritis**: Inflectra®, in combination with methotrexate, is indicated for reduction of signs and symptoms, but also improvement of functional capacities in:
    - Adult patients with active disease when the response to DMARDs, including methotrexate, has been inappropriate;
    - Adult patients with active, severe, and progressive disease, not previously treated with methotrexate nor with other DMARDs.

  In these populations of patients, slowing of joint destruction, measured by X-rays, has been demonstrated.
- **Crohn's disease**: Inflectra® is indicated in:
    - Treatment of moderate to severe active Crohn's disease in adult patients who have not responded in spite of appropriate and well-conducted treatment with a corticosteroid and/or an immunosuppressant; or in whom this treatment is contra-indicated or is poorly tolerated;
    - Treatment of fistulising active Crohn's disease in adult patients who have not responded in spite of appropriate and well-conducted conventional treatment (including antibiotics, surgical drainage and immuno-suppressant therapy).
- **Ulcerative colitis:** Inflectra® is indicated in treatment of active, moderate to severe ulcerative colitis in adult patients who have not responded adequately to conventional treatment consisting of corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or in whom this treatment is poorly tolerated or contra-indicated.
- **Ankylosing spondylitis:** Inflectra® is indicated in treatment of active, severe ankylosing spondylitis in adults who have not responded adequately to conventional treatment.
- **Psoriatic arthritis**: Inflectra® is indicated in treatment of active and progressive psoriatic arthritis in adult patients when the response to previous treatment with DMARDs has been inadequate. Inflectra® should be administered
    - In combination with methotrexate
    - Or alone in patients who have shown intolerance to methotrexate or in whom methotrexate is contra-indicated.

In conformity with conditions of the SmPC, the indications for Inflectra® in children are:

- **Crohn's disease**: Inflectra® is indicated in treatment of severe, active Crohn's disease in children and adolescents 6 to 17 years of age, who have not responded to conventional treatment consisting of a corticosteroid, an immuno-modulator and first-line nutritional treatment; or in whom these treatments are poorly tolerated or contra-indicated. Infliximab has been studied solely in combination with immuno-suppressant conventional treatment.
- **Ulcerative colitis:** Inflectra® is indicated in treatment of severe, active ulcerative colitis in children and adolescents 6 to 17 years of age, who have not responded adequately to conventional treatment consisting of corticosteroids and 6-MP or AZA, or in whom these treatments are poorly tolerated or are contra-indicated.

5.3.3. Posology and administration

This observational study does not have the aim of changing or influencing medical practices concerning prescription and use of Inflectra®. Patients will be managed according to the usual practice of each centre.

In conformity with the SmPC, treatment with Inflectra® should be initiated under control of qualified doctors experienced in diagnosis and treatment of RA, of inflammatory bowel disease (IBD), of ankylosing spondylitis and of psoriatic arthritis. Inflectra® should be administered by intravenous dosing. Infusions of Inflectra® should be administered by qualified healthcare professionals experienced in detecting any infusion-related complication. Patients treated with Inflectra® should receive the patient leaflet, as well as the treatment reporting card.

The dosages for Inflectra® in adults are described as follows in the SmPC:

- **Rheumatoid arthritis:** 3 mg/kg administered in intravenous infusion followed by additional infusions of 3 mg/kg at weeks 2 and 6 after the first infusion and then every 8 weeks. Inflectra® should be administered in combination with methotrexate.
  Available data suggest that a clinical response usually is obtained within 12 weeks of treatment. If a patient obtains an inadequate response or no longer responds after this period, a dose increase by increments of about 1.5 mg/kg can be considered, up to a maximum of 7.5 mg/kg every 8 weeks. Alternatively, administration of 3 mg/kg, as often as every 4 weeks, can be considered. If an adequate response is obtained, patients should be maintained at the dose or the frequency of administration selected. Continuation of this treatment should be reconsidered attentively in patients for whom no therapeutic benefit has been demonstrated during the first 12 weeks of treatment or after adjustment of the dose.

- **Active, moderate to severe Crohn's disease**: 5 mg/kg administered by intravenous infusion, followed by an additional infusion of 5 mg/kg 2 weeks after the first infusion. If a patient does not respond after 2 doses, no additional treatment with infliximab should be administered. In responder patients, alternative strategies for continuation of treatment are as follows:
  - Maintenance therapy: an additional infusion of 5 mg/kg at week 6 after the initial dose, followed by infusions every 8 weeks, or
  - Re-administration: an infusion of 5 mg/kg if signs and symptoms of the disease recur.
- **Fistulised active Crohn's disease**: 5 mg/kg administered by intravenous infusion, followed by additional infusions of 5 mg/kg at weeks 2 and 6 after the first infusion. If the patient does not respond after 3 doses, no additional treatment with infliximab should be administered. In responder patients, alternative strategies for continuation of treatment are as follows:
  - Maintenance therapy: additional infusions of 5 mg/kg every 8 weeks or

    - 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 administered by intravenous infusion, followed by additional infusions of 5 mg/kg at weeks 2 and 6 after first infusion, and then every 8 weeks.
- **Ankylosing spondylitis**: 5 mg/kg administered by intravenous infusion, followed by additional infusions of 5 mg/kg at weeks 2 and 6 after first infusion, and then every 6 to 8 weeks. If a patient does not respond at week 6, no additional treatment with infliximab should be administered.
- **Psoriatic arthritis:** 5 mg/kg administered by intravenous infusion, followed by additional infusions of 5 mg/kg at weeks 2 and 6 after first infusion, and then every 8 weeks.
- **Re-administration for Crohn's disease and rheumatoid arthritis:** if signs and symptoms of the disease recur, infliximab can be re-administered within the 16 weeks following the last infusion. In clinical studies, delayed onset hypersensitivity reactions have been infrequent and have occurred after intervals without infliximab of less than 1 year. Safety and efficacy of re-administration after an infliximab-free interval of more than 16 weeks have not been established.
- **Re-administration for ulcerative colitis and psoriatic arthritis:** Safety and efficacy of re-administration, other than every 8 weeks, are not established.
- **Re-administration for ankylosing spondylitis:** Safety and efficacy of re-administration, other than every 6 to 8 weeks, have not been established.

The dosages of Inflectra® in children are described as follows in the SmPC:

- **Crohn's disease:** 5 mg/kg administered by intravenous infusion, followed by additional infusions of 5 mg/kg at weeks 2 and 6 after the first infusion, and then every 8 weeks.
- **Ulcerative colitis:** 5 mg/kg administered by intravenous infusion, followed by additional infusions of 5 mg/kg at weeks 2 and 6 after the first infusion, and then every 8 weeks.

5.3.4. Concomitant treatments

Considering that this study is observational and does not aim to change medical practice, no measure to be taken is required concerning use of concomitant treatments. Doctors are asked to refer to the SmPC of Inflectra® to ensure safety of patients.

6. OBJECTIVE OF THE STUDY

6.1. PRIMARY OBJECTIVE

The primary objective is to describe under real-life conditions of use:

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

6.2. Secondary objectives

The secondary objectives are:

- To describe in routine practice:
  - The conditions for use of Inflectra®
  - The safety of Inflectra®
- To determine factors predictive of response to treatment
- To describe the immunogenicity of Inflectra®
- To measure anxiety, stress and mistrust of patients at time of announcement of a switch and impact of psychological profile on follow-up of patients in terms of efficacy, safety and continuation of the biosimilar product
- To assess the outcome of anxiety and of stress of patients after the switch

7. ASSESSMENT END POINT

7.1. Primary assessment end points

Response to treatment will be described indirectly and expressed by the per cent of patients without therapeutic failure during the 2 years' follow-up. Therapeutic failure is defined as permanent discontinuation of Inflectra® because of intolerance and/or permanent discontinuation of Inflectra® due to lack of response to treatment based on the doctor's assessment.
The response to treatment will be described in the general population, but also in adults and in children. It will also be described based on severity of disease, assessed by specific rating scales of each disease and assessed by the doctor.

The profiles of adult patients and of paediatric patients who received prescription of Inflectra® will be described based on information collected by the participating doctor during the inclusion visit. The following data will be collected:

- Characteristics of patients
  - Age,
  - Sex,
  - Weight, height,
  - Contraception, if applicable
  - Pre-treatment assessment prior to initiation of anti-TNFα therapy
- In adults, in the indication for which Inflectra® is prescribed:
  - Gastroenterology: Crohn's disease, ulcerative colitis
  - Rheumatology: psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis
- In children and adolescents, indication for which Inflectra® is prescribed:
  - Gastroenterology: Crohn's disease, ulcerative colitis
- Date of diagnosis of the disease
- Severity of the disease: (annex 3)
  - Assessed by the participating doctor on the 3-point Likert scale: "mild", "moderate" or "severe".
  - Described by the specific activity index of the disease:
    - Rheumatoid arthritis: ACR or DAS28

        - Ankylosing spondylitis: BASDAI or BASFI
        - Psoriatic arthritis: ACR or DAS28
        - Ulcerative colitis: Mayo score/PUCAI for paediatric patients/UCEIS
        - Crohn's disease: Harvey-Bradshaw index/CDEIS
- For patients who discontinue the biotherapy for which they are treated to initiate treatment with Inflectra®, characteristics of this switch will be described as follows:
    - Previous biotherapy
    - Reason for which the switch was performed
    - Dates of first and last administration of previous biotherapy
    - Number of doses administered for the previous biotherapy
    - Last dose administered of previous biotherapy
    - Response of patient to the previous biotherapy

In conformity with new recommendations of the French health authorities (May 2016), patients naïve for infliximab or treated with Remicade™ can be treated with infliximab biosimilar product.

7.2. Secondary assessment end points

Data on prescription of Inflectra® during the 2 years' follow-up:

- Date of administration
- Posology or dose administered
- Duration of infusion
- Duration of monitoring of patient in the hospital after administration
- Treatment phase: induction/maintenance/re-administration
- Concomitant treatments: corticosteroids/disease-modifying anti-rheumatoid drugs DMARDs/immuno-suppressants/5-aminosalicylic acid derivative/alkalising agents/biotherapy

Tolerability to treatment will be expressed by the per cent of adverse events (AE) reported. The nature, severity and seriousness of each AE will be described. Adverse events specific to Inflectra® will be also be sought and described.

Statistical analysis will be performed in order to determine **factors predictive of response** to Inflectra®. Factors tested will be chosen among data collected and are detailed in the paragraph "statistical analyses" (page 35).

Maintenance under treatment will be determined at end of follow-up of each patient.

The **immunogenicity profile** of Inflectra® will be described by serum assay measurement of infliximab residual serum levels (IRL) and anti-infliximab antibody levels.

Data related to **stress, anxiety and to mistrust** (solely in patients who have been informed of a switch from infliximab of reference to Inflectra®) will be as follows:

- Cook-Medley Questionnaire (8 items), also called the cynical mistrust rating scale

- GAD7 Questionnaire (7 items)
- Questionnaire on stress perceived related to switch (3 items)

In order to measure the impact of announcement of a switch on duration of treatment and per cent discontinuation of treatment, patients will be categorised depending on their psychological profile at time of switch:

- For anxiety:
  - GAD>7 versus GAD<8
  - Or raw values in GAD7 score
- For mistrust:
  - Median in Cook-Medley questionnaire (>median: propensity to mistrust <median confidence in another person)
  - Or raw values in Cook-Medley score
- For stress:
  - Median in questionnaire on stress (>median: stress present <median stress absent)
  - Or raw values of scores in the questionnaire on stress

8. STUDY METHODS

8.1. Study

This observational, prospective, national, multi-centre study is aimed at eligible patients in whom Inflectra® is prescribed in conformity with the conditions contained in the SmPC, in one of the participating centres. The hospitals which take part in the study are part of the French hospital establishments which have referenced Inflectra®.

Total duration of the study is estimated to be 4 years: 2 years' inclusion period and 2 years' follow-up per patient. If needed, duration of the inclusion period can be modified.

Pfizer PFE France (Pfizer Group), sponsor of the study, has entrusted the logistics of conduct to the CRO Axonal-Biostatem (92000, Nanterre).
All members of the staff of the CRO in charge of follow-up of the study are required to complete Pfizer requirements in terms of training in: "Your Reporting Responsibilities: Monitoring the Safety, Performance and Quality of Pfizer Products (version in force)" (Pfizer) as well as all additional training considered useful. Such training will be provided at all members of staff of the CRO prior to start of the study. All trainings include a "certificate of training" (signed by the person trained) as the certificate of training, which should be kept in accessible format. Copies of all training certificates signed should be provided by Pfizer.

8.1.1. Recruitment of participating centres

All rheumatologists, gastroenterologists and internists practicing in a public or private hospital which have referenced Inflectra® will be invited to take part in this study.

Prior to start of the study, the departments concerned in these hospitals will be informed by postal mail of the set up of the observatory. Selection of centres which desire to participate will be performed.

8.1.2. Set up of centres by the CRO

A contract will be established for each participating doctor. Prior to set up of the centre performed by phone by a CRA in the CRO, a kit containing the protocol, the information leaflet and consent form, the register of non-inclusion, the study early permanent discontinuation forms and adverse event reporting forms will be sent to centres.

8.1.3. Recruitment of patients

Except for patients with psoriasis, all patients for whom Inflectra® is prescribed in conformity with conditions of the SmPC in one of the participating centres will be included in this study, unless they explicitly express their refusal concerning access to their medical dossier and to collection of their personal data. Doctors who prescribe Inflectra® in participating centres must systematically give patients the information leaflet. Patients who accept that their personal medical data be collected for purposes of this study will notify their agreement by signing the consent form. For minor patients, a decision on participation in this study will be left to one of their legal guardians.

We estimate that about 1,200 patients will be treated with Inflectra® during the 24 months of the recruitment period (600 patients over 12 months).

After a centre is set up, all patients receiving the administration of Inflectra® and who satisfy screening criteria are eligible to participate in the study. It is at time of this administration that patients will be invited to participate and that they will sign the consent form. Consent must be signed at latest prior to the discharge of the patient from the hospital. Both patients initiating Inflectra® and patients already under treatment with Inflectra® are eligible.

The participating doctor or the team in charge of the study will give to eligible patients and who have accepted to participate in this study by signature of the consent form, self-questionnaires as well as an envelope, in order to be completed. After completing it, the patient should then place the-questionnaire in a sealed envelope and then give it to the participating doctor or team in charge of the study.

The sealed envelope containing the patient's completed self-questionnaires will be sent by the participating doctor or the team in charge of the study, to the CRO in charge of the study, via a dedicated transporter.

The participating doctor or the team in charge of the study will not be made aware of responses to the self-questionnaires.

In each centre, a paper register will be made available to participating doctors in order to list patients eligible but who have not been included: reason for non-inclusion, age, sex and disease. Only an order number will be used to designate these patients in the manner so that they cannot be identified.

At the end of the study, this list will be recovered by the CRA. Patients not included will be compared to patients included based on characteristics reported, in order to verify the absence of a selection bias or of an inclusion bias.

8.1.4. Study schedule

	Inclusion	Month 6	Month 12	Month 18	Month 24	At each infusion
Distribution of the information leaflet	X					
Verification of inclusion and non-inclusion criteria	X					
Description of patient profile	X					
Description of conditions for use of Inflectra®		X	X	X	X	
Assessment of response to treatment		X	X	X	X	
Description of tolerability to treatment		X	X	X	X	
Description of immunogenicity profile of Inflectra®	X	X	X	X	X	
Cook-Medley* Questionnaire	X					
GAD7 Questionnaire* (7-item)	X					X
Questionnaire on stress*	X	X	X			

*: solely in patients who have been informed of the switch from infliximab reference to Inflectra®

8.1.5. Tentative study schedule

The tentative study schedule at time of regulatory submission is as follows:

- Submission to the CTIRS: early February 2016
- Submission to the CNIL: end of April 2016
- Submission to the CNOM; June 2016
- Set up of centres: September 2016
- Inclusion period: October 2016 – December 2018
- End of follow-up of patients: December 2020
- Interim analysis: Each year starting from December 2016
- Final analysis: December 2020
- Interim clinical report: Each year starting from December 2016
- Final clinical report: January 2021

8.2. Context

8.2.1. Inclusion criteria

- Adult patients treated with Inflectra® on day of inclusion, whatever the treatment phase or adult patients who have been informed of the switch from infliximab reference to Inflectra®, in one of the following indications and in conformity with the SmPC: Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis or psoriatic arthritis.
- Paediatric patients (children and adolescents 6 to 17 years of age) treated with Inflectra®, whatever the treatment phase, from the time that Inflectra® is prescribed in conformity with the indications mentioned in the SmPC: Crohn's disease or ulcerative colitis.
- Patients (or their legal representatives) who have received information (oral and written) concerning the study and who accept to participate.
- Patients who gave their agreement for access to their clinical data and to their medical dossier by signing the consent form. Patients should sign the consent form at latest prior to their discharge from the hospital (first administration of Inflectra® after inclusion in the study).

8.2.2. Non-inclusion criteria

- Patients who refuse access to their medical dossier for collection of their personal medical data.
- 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 with tuberculosis or presenting with any other severe infection such as sepsis, an abscess or an opportunistic infection.
- Patients presenting with moderate to severe heart failure (NYHA III/IV)

8.2.3. Exclusion criteria

Patients included who withdraw their consent will be excluded from the study. They will decide if their personal medical data collected may be used in the interim analysis and in the final analysis in so far as the latter have not been performed at time of their withdrawal from the study.

8.2.4. Study withdrawal

Reasons for withdrawal from the study will be indicated in the page of the e-CRF planned for this purpose. The date of end of study visit will be noted.
Study withdrawals prior to scheduled end of follow-up will be classified according to the following categories:

- Patient lost to follow-up
- Non-compliance with study procedures (inclusion or non-inclusion criteria not complied with)

- Withdrawal from study desired by patient (if yes, specify reason invoked by patient)
- Withdrawal from study for an adverse event which resulted in discontinuation of treatment (if yes, specify type)
- Serious adverse event which resulted in discontinuation of treatment (if yes, specify type)
- Death (cause and date)
- Other reason (if yes, specify)

8.3. Variables

The e-CRF is the tool for data collection which will make it possible to achieve the objectives of the study. Data will be collected from time of inclusion up to end of study, scheduled end or not.

8.3.1. Data at inclusion

Characteristics of patients will be collected and recorded in the electronic case report form (eCRF) during the inclusion visit:

- Age, sex, weight, height or body mass index (BMI) if available, smoker (yes/no), contraception if applicable
- Indication for which Inflectra® is prescribed: Crohn's disease/ulcerative colitis/rheumatoid arthritis/ ankylosing spondylitis/psoriatic arthritis/other, to be specified
- Date or year of diagnosis
- Severity of the disease:
    - Mild/moderate/severe
    - Specific activity index of the disease
- For patients initiating treatment with Inflectra®, a pre-treatment assessment prior to initiation of anti-TNFα: completed/not completed
- For patients already under treatment with Inflectra®, date of first prescription of Inflectra®
- Previous treatments: corticosteroids/immuno-suppressants/biotherapy/surgery/other (yes/no/unknown; if yes, list)
    - Patient naïve for biotherapy (never before treated with biotherapy): yes/no; if not, specify:
        - Previous biotherapy prescribed: anti-TNFα (infliximab/adalimumab/etanercept/golimumab/ Rituximab), selective immuno-suppressant (vedolizumab/abatacept), interleukin inhibitor (anakinra/ustekinumab/tocilizumab), Anti-integrin (Vedolizumab) other (specify)
        - Dates of first and of last administration of the previous biotherapy
        - Number of doses administered of previous biotherapy
        - Last dose administered of previous biotherapy
        - If the previous biotherapy is not Inflectra® (switch), reason for which treatment has been changed in favour of Inflectra®: no response with previous treatment/insufficient response with previous treatment/problem of tolerability with previous treatment/other
- Results of immunogenicity, if available:

  - Reason and date of assay
  - Infliximab residual serum levels (IRL),
  - Anti-infliximab antibody serum levels

- Data relating to stress, anxiety and to mistrust (solely in patients who have been informed of a switch from infliximab of reference to Inflectra®):
  - Cook-Medley Questionnaire (8 items), so-called cynical mistrust rating scale
  - GAD7 Questionnaire (7 items)
  - Questionnaire on stress perceived relating to switch (3 items)

8.3.2. Follow-up visit data

Data collected and recorded in the eCRF every 6 months:

- Data concerning each administration of Inflectra®:
  - Administration performed: yes/no, if yes specify:
    - Date of administration
    - Posology or dose administered
    - Duration of infusion
    - Duration of monitoring of patient in the hospital after administration
    - Treatment phase: induction/maintenance/re-administration
  - Concomitant treatments:
    - Corticosteroids
    - Disease-modifying anti-rheumatic treatments (DMARDs)
    - 5-aminosalicylic acid derivatives
    - Immuno-suppressant agents
    - Alkylating agents
    - Biotherapy
  - Adverse events including adverse events of specific interest related to Inflectra®:
    - Infusion-related reactions, including acute and delayed onset hypersensitivity reactions
    - Infections including serious infections, tuberculosis, opportunistic infections, hepatitis B
    - Congestive heart failure,
    - Intestinal and perianal abscess
    - Malignant disorders, leukaemias, lymphomas
    - Demyelinating disorders
    - Lupus syndrome, disseminated lupus erythematosus
    - Hepatobiliary disorders
    - Sarcoidosis, sarcoidosis-like reactions
  - Situations involving exposure to one of the study medicinal products, including:
  - Exposure in pregnancy,
  - Exposure in breastfeeding
  - Medicinal product errors,
  - Cases of an overdose,

  - Cases of misuse,
  - Extravasation,
  - Lack of efficacy,
  - Occupational exposure

- Immunogenicity results, if available:
  - Infliximab residual serum levels (IRL),
  - Anti-infliximab antibody serum levels
- Patient status:
  - In remission: yes/no
  - Lost to follow-up: yes/no
  - Deceased: yes/no
  - The patient discontinued his/her treatment with Inflectra® permanently: yes/no
  - Severity of the disease:
    - According to the doctor's assessment: mild/moderate/severe
    - According to specific activity index of the disease

In case of death, permanent discontinuation of Inflectra® or patient lost to follow-up, please complete the early permanent discontinuation form.

If the patient withdrew consent concerning access to his/her medical dossier and collection of personal data, please complete the early permanent discontinuation form.

Data collected at time of each infusion (solely in patients who have been informed of a switch from infliximab reference to Inflectra®)

- GAD7 Questionnaire (7 items)

Data collected at 6 months and one year (solely in patients who have been informed of a switch from infliximab reference to Inflectra®)

- Questionnaire on stress perceived relating to the switch (3 items)

8.3.3. Data on withdrawals from study

The early withdrawal from study form should be completed with the following elements:

- Reason and date of withdrawal from study:
  - Patient died, date of death
  - Patient lost to follow-up, date of last contact
  - Withdrawal of consent regarding access to medical dossier and collection of data, date of withdrawal of consent
  - Permanent discontinuation of treatment with Inflectra®:
    - Specify: discontinuation of treatment with an anti-TNFα/switch to another infliximab (Remicade™/Remsima ™)/switch to another biotherapy.
    - Reason for discontinuation of treatment with Inflectra®: no response with Inflectra®/insufficient response with Inflectra®/problem of tolerability with Inflectra®
      / Inflectra® is no longer available in the hospital/patient is stable in remission/other, specify

- Date of permanent discontinuation of treatment with Inflectra®

In case of problems of tolerability with Inflectra® or of death, please complete the adverse event/serious adverse event report form (annex 1).

8.4. Sources of data

Data of interest will be recorded in a case report form in electronic format (eCRF). If necessary, a clinical study technician may assist the participating doctor in patient data entry in the eCRF. For each patient included, the participating doctor is asked to collect data in the eCRF at the inclusion visit and then at least every 6 months during the 2 years of follow-up. At each connection to the eCRF, all data of interest in the previous 6 months will be recorded, including all information describing administrations of Inflectra®. For this purpose, an automatic reminder message will be sent to doctors a few days before planned date of connection.

The CRO service provider is responsible for creation and maintenance of eCRFs. Only the first letter of the patient's surname and first letter of his/her first name will be recorded in the eCRF. No data marked by a patient name will be collected. At time of individual set up of a centre, the CRO will assign a 3-figure composite code to each centre: this code corresponds to the centre number.

The patient number will consist of the centre number (out of 4 figures) followed by a 3 figure code assigned in increasing order to inclusions: for example, patient number 0009002 corresponds to second patient in centre 9. Data collected will be confidential and covered by medical secret.

8.5. Size of study

In conformity with new recommendations by the French health authorities (May 2016), patients naïve for therapy or treated with Remicade™ can be treated with Inflectra®. Based on current prescribing data, it is estimated that about 1,200 patients will be treated with Inflectra® during the two years corresponding to the inclusion period (600 patients over 12 months).
Calculation of sample size is based on accuracy of the estimate with a confidence interval for each proportion of patients treated with Inflectra®. The number of patients required depends on the expected per cent, the necessary accuracy and the alpha risk.
In the absence of data available under real-life conditions, in the most unfavourable hypothesis, i.e.: a proportion of 50% with a 95% two-sided confidence interval, the following formula makes it possible to calculate the sample size necessary based on proportion (p) and accuracy (i) as follows:

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

Proportion

			Proportion		
Accuracy	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

Based on the applied formula, 1,200 patients would make it possible to have an accuracy of between 2.5% and 3.0% in the treatment responder rate.

Concerning the objective related to stress and to anxiety: the per cent of treatment discontinuations at one year is estimated at 25%, whatever the level of anxiety. The Nocebo effect is included in this percentage for about 10% and may differ depending on level of anxiety.
Thus, the following hypotheses are considered:

- Per cent discontinuation of treatment at one year: 25%
- Per cent discontinuation in anxious patients (GAD>7): 30%
- Per cent discontinuation in non-anxious patients (GAD<8): 20%
- Missing data in discontinuation of treatment due to patients lost to follow-up: 10%

A sample size of 300 patients (150 GAD>7 and 150 GAD<8) is necessary in order to calculate a 95% two-sided confidence interval of the odds ratio of the variable treatment discontinuation not containing the value 1. Therefore, under these hypotheses, the odds ratio may be 0.58 and its confidence interval [0.35; 0.99]. By taking into account 10% missing data, 300/0.9=330 patients will have to be included after implementation of amendment no. 3. Thus, 330 adult patients having been informed of a switch from infliximab reference to Inflectra® will have to be included to achieve this secondary objective (Pass software version 15.0.4). The inclusion period may be changed depending on the progression of inclusions in order to achieve this objective.

8.6. Data management

A Data Management plan will be drafted which will describe all activities of Data Management performed during this study, as well as a Data Validation Plan which will describe all tests of consistency, obvious corrections (SECs) and listings of inconsistencies performed in this study, as well as messages of requests for corrections sent to the participating doctor which have to be approved by the Sponsor prior to start of inclusions.

Use of the e-CRF makes it possible to use pre-tests (tests of consistency executed online which enable to immediately correct differences between participating doctors) enables to decrease the number of requests for correction.

Once the pages have been entered and monitored, the Data Manager will initiate execution of tests of consistency programmed under Clinsight® version 7.0, inconsistencies will be resolved by participating doctors online.

Once all possible corrections have been made to the database, the Data Management Report written by the Data Manager and a request for authorisation of locking of the database by the Sponsor. Once the database has been locked, the final version of the Data Management Report and a certificate confirming locking of the database will be sent to the Sponsor.

8.6.1. Case report form and data collection

As used in the protocol, the term CRF (Case Report Form) should be taken as referring to a paper medium or to an electronic record of data, or both, depending on method of data collection used in this study.
Data of interest will be recorded in a case report form in electronic format (e-CRF).

A CRF is required and should be completed for each patient included. Original CRFs duly completed are the exclusive property of Pfizer and must not be made available to any third parties in whatever form except to authorised representatives of Pfizer or of the competent regulatory authorities, without written authorisation from Pfizer. The participating doctor must ensure that the CRFs are kept in a secure manner on the study site in encrypted electronic or paper form and will be password protected or secured in a locking room to prevent access by unauthorised third parties.

The participating doctor is responsible in the last resort for collection and reporting of all clinical data, safety and tolerability and biological data between the CRF and any other medium for data collection (source documents) and make certain that they are accurate, authentic, original, attributable, complete, consistent, legible and available (if necessary).

The CRF should be signed by the participating doctor or by an authorised member of staff to ensure the authenticity of data entered in the e-CRF. All corrections made to documents entered in the e-CRF or source documents must be dated, initialled and explained (if necessary) and must not conceal the original data entered.

In the majority of cases, source documents are comprised of hospital dossiers or of the doctor’s dossiers. In this case, data collected in the e-CRF should correspond to these dossiers.

In certain cases, the CRF can also be used as a source document. In such a case, a document available on-site and at Pfizer should clearly identify the data which will be recorded in the e-CRF and for which the CRF will comprise the source document.

8.6.2. Data storage

In order to enable evaluations and/or inspections/audits by the regulatory authorities or by Pfizer, the investigator agrees to keep the dossiers, including the identity of all participating patients (sufficient information to establish the link with the dossiers, for example, CRF[/ORD] and hospital dossiers), all signed original informed consent documents, copies of all CRFs, pharmacovigilance report forms, source documents, detailed dossiers on treatment allocation and adequate documentation of relevant correspondence (for example, letters, meeting minutes and phone call reports). Dossiers should be kept by the participating doctor in conformity with local regulation or according to specifications of an agreement established for the study according to the longest duration.

The participating doctor should ensure that dossiers continue to be stored in a secure manner for as long as they have to be stored.

If the participating doctor is no longer able, for whatever reason, to continue to keep the study dossiers during the required period (for example: if he/she retires, or if the participating doctor moves away from the site), the participating doctor should inform Pfizer. The study dossiers should be transferred to a person designated after acceptance by Pfizer, such as another participating doctor, another institution or to an independent third party designated by Pfizer PFE France (Pfizer Group).

The participating doctor’s dossiers should be kept for a minimum duration of 15 years after the end (last visit of last patient) or discontinuation of the study or for longer if necessary, whenever local regulations so require. The participating doctor should obtain written authorisation from Pfizer before disclosing the contents of any dossier, even if requirements for storage have been satisfied.

8.6.3. Channel of CRFs

Data collected from a participating doctor at time of inclusion and of follow-up visits of patients will be recorded directly by the participating doctor in the eCRF of the study.

Adverse events will be collected *via* the eCRF by doctors at consultations on usual follow-up, for all patients in the study. Whenever applicable, requests for additional information from the PFIZER PFE France pharmacovigilance department (Pfizer Group) will be sent to the person who reported the event (participating doctor). All reports (initial and follow-up reports) will be collected via the centre number and the patient number.

Self-questionnaires, as well as an envelope will be given to patients by the participating doctor or the team in charge of the study in order to be completed. They should then be given in a sealed envelope to the participating doctor or the team in charge of the study.

The sealed envelope containing completed patient self-questionnaires will be sent by the participating doctor or the team in charge of the study, to the CRO in charge of the study, via a dedicated transporter.

8.6.4. Construction of the database

An annotated questionnaire will be prepared by the CRO in charge of data management. This document will contain the names of tables and names of variables. Each variable will be associated with its type, its length, and its possible format. The annotated questionnaire will be submitted to Pfizer PFE France (Pfizer Group) for validation.

The CRO then will build a database using its own software. The structure of the database will be documented and verified on listings by comparing the attributes of variables in the database with specifications recorded in the annotated questionnaire.

Prior to entry of real data, the structure of the database and the data entry screens will be tested and validated in agreement with Standard Operating Procedures of the CRO and those of Pfizer PFE France (Pfizer Group). To do this, fictitious questionnaires will be completed and entered. Validation will be done by a case-by-case review on listing of these data and then on their comparison with data recorded in the questionnaires. A validation report will be written and sent to Pfizer PFE France (Pfizer Group). The final structure of the database should be submitted to Pfizer PFE France (Pfizer Group) for validation prior to data entry of real data.

An audit file will be created in order to record all changes made to the database. The original data, the modified data, the date and time of the change, the person who made the change and the reason for the change will be recorded in the audit file. Functioning of the audit file will be tested by the change to fictitious data. A report will be written and sent to Pfizer PFE France (Pfizer Group).

8.6.5. Control of data

A list of controls of consistency enabling detection of inconsistencies and of aberrant responses present in questionnaires will be edited by the CRO and validated by Pfizer. Such controls will be scheduled with the CRO’s own software and then tested with fictitious data. These fictitious data and documentation relating to tests will be kept in the study binder by the CRO and available for review by Pfizer PFE France firm (Pfizer Group).

After data entry, controls will be executed continuously, a specific request for each inconsistency will be generated electronically by the data control system. In order to limit the number of requests to submit to participating doctors, a guide to obvious corrections prepared by the CRO and validated by Pfizer may be compiled.

The CRO will make available the documentation on data control upon simple request from Pfizer PFE France (Pfizer Group). Periodic progress reports on data control will be edited by the CRO and sent to Pfizer PFE France (Pfizer Group).

8.6.6. Access to data

The databases and servers on which they are stored will be located in locking facilities. Only staff dedicated to the study will have access to the databases.

8.6.7. Locking of database

Locking of the database will be performed only after data entry, data control and possible coding have been completed by the CRO. Locking of the database will be performed in agreement with the Pfizer PFE France procedure (Pfizer Group). After validation by Pfizer PFE France (Pfizer Group), the database will be locked by the CRO and ready for statistical analysis.

8.6.8. Data management report

A data management report will be edited by the CRO after locking of the database and sent to Pfizer PFE France (Pfizer Group).

8.7. Data analysis

Statistical analyses will be performed by a CRO under the responsibility of Pfizer PFE France (Pfizer Group).

The detailed methodology of statistical analysis of data collected in the setting of the study will be documented in the statistical analysis plan (SAP), which will be dated, recorded and administered by Pfizer PFE France (Pfizer Group). The SAP can modify the plans described in the protocol; all major changes to definitions of the primary assessment end point or of their analyses will be reflected in a protocol amendment**.**

8.7.1. Statistical Method

The statistical analyses will be performed by the CRO Service Provider independently of **Pfizer PFE** France firm (Pfizer Group).

A statistical analysis plan (SAP) will be complied after approval of the protocol and validated before locking of the database. This document will present a comprehensive list of analyses which will be performed, as well as the methodologies used and rules on derivations of variables. This document will have value as a reference for statistical analyses.

8.7.2. General methodology

Quantitative data will be described by their sample size, their mean, standard deviation, median and their range.
Qualitative data will be described by their sample size and their per cent. 95% two-sided confidence intervals will be provided whenever considered relevant. Missing data will not be taken into account in calculation of per cents.
The statistical tests will be two sided with a 5% risk of error.
Since the primary objectives of this study are descriptive, no imputation of missing data is planned if only for certain dates (missing days will be replaced by 15 and missing months by 6).
No readjustment of visits is planned.
Sub-group analyses will be performed for each objective, by differentiating adult and paediatric populations.
Moreover, all analyses will be repeated in the sub-group of patients who have been informed of a switch from infliximab reference to Inflectra®.

8.7.3. Descriptive analysis

General characteristics of patients, as well as characteristics of prescribing doctors at time of inclusion will be described. In criteria available, subjects who accepted to participate will be compared to those who refused. Withdrawals from study will also be described and will be illustrated in the study flowchart.

8.7.4. Primary assessment end points

- Response to treatment:

Response to treatment will be described indirectly and expressed by per cent of patients who are not in therapeutic failure during the 2 years' follow-up. Therapeutic failure is defined as permanent discontinuation of Inflectra® because of intolerance (an adverse event related to Inflectra®) and/or permanent discontinuation of Inflectra® because of absence of a response to treatment according to the doctor's assessment (see chap. 7.1). The per cent of patients without a therapeutic failure will be described with its 95% confidence interval, overall and then by the following sub-groups:

- Paediatric and adult population
- The indication for which Inflectra™ was prescribed
- Severity of the disease according to the Likert scale
- The activity index specific for each disease
- Level of anxiety

- Profiles of patients

The demographic characteristics (such as: age, sex, etc.), clinical (duration of the disease, diseases, co-morbidity, previous treatments, etc.) will be described by differentiating paediatric and adult populations.

Special attention will be paid to the sub-population of patients who are in a therapeutic switch (as defined in chap. 7.1).
Profiles of patients as described in the abovementioned will be produced in this sub-population by adding the duration of previous biotherapy, the number of doses administered, the time between the last dose and initiation of Inflectra™, as well the patient's response.
If sample sizes so permit, this sub-population will be described according to the following:

- Previous biotherapy used
- Reasons for the switch
- Patient's level of anxiety

8.7.5. Secondary assessment end points

- Conditions on use of Inflectra®

Data relating to prescription (posology/dose, duration of infusion, duration of monitoring, post-treatment, treatment phase and concomitant treatment) will be described at each time: D0, M6, M12, M18 and M24 and overall according to the following sub-groups:

- Paediatric and adult population
- Indication for which Inflectra™ was prescribed
- Severity of the disease according to the Likert scale
- The activity index specific for each disease

The cumulative doses and durations of treatment will be presented and also described.

- Safety and tolerability to Inflectra®

At the outset, coding of AE will be performed according to the MedDRA dictionary.
The following tables will be presented according to adult and paediatric populations:

- Proportion of patients who reported at least one AE
- Proportion of patients who reported at least one un SAE
- Proportion of patients who reported at least one specific AE (as described in chap. 8.2)

A description of AEs will be performed based on:

- Paediatric or adult population
- Seriousness (mild, moderate, severe)
- Relation with Inflectra™
- Severity
- Type of disease
- Duration of disease
- Naïve of therapy characteristics of the patient with respect to biotherapies
- Responder status or not

An individual listing of AEs and specific AEs (description, type, date of start and date of end, intensity, treatment, etc.) will be provided.

- Factors predictive of response to treatment

For each indication, factors predictive of response to treatment will be analysed by a logistic regression model. Univariate analysis will be performed in order to select factors which then will

be taken into account in the multi-variate model. The following list presents non-exhaustively certain variables which may be tested:

- Demographic data
  - Age,
  - Sex,
  - BMI,
  - Smoker status
- Clinical and laboratory data
  - Severity (described qualitatively and quantitatively),
  - Duration of the disease,
  - Concomitant treatments,
  - History of treatment with a biotherapy,
  - History of treatment with infliximab,
  - Infliximab residual serum level (IRL) after 14-week induction therapy in patients treated for acute episodes,
  - anti-infliximab antibody serum levels after 14-week induction therapy in patients treated for acute episodes
  - Cumulative dose
  - Duration of treatment with Inflectra™
  - Anxiety profile of patient
  - Cynical mistrust rating scale
  - Stress score

- Inflectra® immunogenicity profile

IRL and anti-infliximab antibody levels will be described at each time and according to:

- Dose or posology administered
- Naïve status for biotherapy
- Indication
- Severity of the disease

- Data relating to stress, anxiety and to mistrust (solely in patients who have been informed of a switch from infliximab of reference to Inflectra®):

A detailed plan of analysis will present the analyses relating to these data.

GAD7 questionnaire is an anxiety state questionnaire with 7 items on the experience of the last two weeks.

The patient's anxiety profile will be defined as follows: GAD (Anxious >7; not anxious <8)
The best categorisation may be chosen with methods of sensitivity/specificity with the variable discontinuation of treatment.

The outcome (absolute difference of scores from time of inclusion visit) over time of GAD7 scores will be analysed with a repeated measure mixed model of analysis of covariance including at least as explanatory variables the initial value, as well as the variable for stopping of treatment

at one year (or 2 years). The LS Means will be estimated at each time in this model with their 95% two-sided confidence interval. The time x discontinuation of treatment interaction will also be explored in this model. For patients anxious at the outset (score>7), the time necessary for return to a non-anxious state (GAD≤7) will be analysed with analysis of survival methodology.

The Cook-Medley 8-item questionnaire, also called cynical mistrust scale will be described and may also be correlated with the GAD7 questionnaire, as well as the response and duration of treatment.

The questionnaire on stress perceived with relation to a switch to the biosimilar contains three questions and the score is obtained by addition of the three scores (on emotional reactivity, syndrome of repetition and tendency to avoidance) in order to obtain an overall score. This score may be correlated with the GAD7 questionnaire, as well as response and duration of treatment. The outcome of scores at the 3 times will be analysed as for GAD7. Since this questionnaire has not been validated, a working validation may be planned (sensitivity to change, etc.).

8.7.6. Schedule of analyses

It is planned to perform several interim analyses, mainly descriptive, based on data collected throughout the duration of the study. The final analysis will be performed when the study has been completed with all data collected.

8.8. Quality control

8.8.1. Set up of participating doctors

Participating doctors will be asked to participate in this study. This participation will be evidenced by signature of the financial agreement. Upon validation of the latter, a visit to set up on-site or by phone will be organised by the Clinical Research Associate in order to present the study and all afferent documents to the participating doctor, as well as to members of his/her staff that will have been designated, if applicable.

8.8.2. Logistics and monitoring of participating centres

Throughout this study, participating doctors will be contacted in order to ensure their understanding and compliance with the protocol and of the electronic questionnaire. All contacts will be documented.

If the sponsor considers it necessary, in light of the progress in completing eCRFs, CRAs may perform monitoring visits on-site. During these visits, CRAs from the CRO will check the quality of data collected. In order to do this, they should refer to the patient's medical dossiers. Participating doctors therefore should ensure that the CRAs can have access to patient dossiers

The CRAs involved in monitoring procedures do not intervene in data collection. The frequency of on-site visits will depend on the number of patients included in each centre.

Key indicators in proper conduct of the study (number of active centres, number of patients included, number of follow-ups performed, etc.) will be generated using the study database. This database will enable to edit study progress reports which will enable to manage reminders from centres.

8.8.3. Quality and accuracy of data

The participating doctor will be responsible for collection and reporting of all clinical data, safety and laboratory data entered in the eCRF and/or other forms of data collection (source documents), and must make certain that they are accurate, authentic, attributable to the patient, complete, consistent, legible, contemporaneous and available if needed.

In order to enable controls and/or audits by the regulatory authorities or by PFIZER PFE France (Pfizer Group), the participating doctor agrees to keep registers, including the identify of all participating patients (sufficient information to connect dossiers (ex.: eCRF and hospital medical dossiers). The participating doctor will keep all original informed consent forms, copies of reports of adverse events, source documents, and medical results leading to therapeutic decisions.

8.9. Limits of methods of research

This protocol has been built in a manner so as to best achieve the objectives set for this observational study. However, it has certain limits which should be discussed and taken into account at time of implementation of the study and utilisation of results, such as for example:

Measures taken to limit patient's lost to follow-up and missing data

Since this study does not aim to influence or to modify usual practices, participating doctors will have the ability to note "not done" or "not applicable" in collection of data. In case of missing data, without one of these notations, the CRA will make every effort to collect corresponding information with the aid of the participating doctor. Nevertheless, if data are still missing at time of the analysis, they will not be replaced and they will be processed such as the following:

In case of patients lost to follow-up, the participating doctors will accept to call the patient, one of their family members or their family doctor in order to retrieve sufficient data to close the dossier.

In case of death, the doctor will investigate its cause.

8.10. Other aspects

8.10.1. Data collection

After signature of the contract and a visit to set up the study, the participating doctors and each person participating in the centre, should return to the CRO the form on awareness of the protocol, the certificate of training in the eCRF and the certificate of training in pharmacovigilance. Participating doctors will then receive the web link with their identifier and their access code number to the e-CRF.

These codes are personal, each person participating in the centre will receive his/her identifier and his/her code number.

The participating doctors will complete the questionnaire for each patient included at time of regular consultations scheduled when such consultations coincide with the study visits. A one-month time period before and after the theoretical date will be tolerated for visits to be entered in the eCRF.

If the patient discontinues the study during the follow-up, the doctor will complete the end of study questionnaire and will provide the reason for withdrawal from the study (Section -).

Participating doctors agree to exhaustive collection of data for each patient.

8.10.2. Archiving

Participating doctors will keep questionnaires up to 15 years after the last visit of the last patient

The study management centre will keep all documentation related to the study up to 15 years after last visit of the last patient.

Then, all documents will be returned to the sponsor of the study.

9. PROTECTION OF PATIENTS

9.1. Information of the patient

All parties will comply with legislation in force, in particular, by implementation of organisation and technical measures in order to ensure protection of personal data of patients. These measures will include the omission of names of patients or of other data enabling to identify them directly in all reports, all publications and all other disclosures, except for requirements imposed by legislation in force.
Personal data will be stored on the study site (in encrypted electronic and/or paper format) and will be password protected and/or secured in a locking room in order to ensure that only authorised

study staff has access to it. The participating centre will set up appropriate technical and organisational measures in order to ensure that personal data may be retrieved in case of an accident. In the eventuality of a potential violation of personal data, the participating centre will be responsible for determining if this violation has really occurred and if so, to perform the notifications required by law.

In order to protect the rights and freedoms of physical persons with regard to processing of personal data, when study data are compiled in order to be transferred to Pfizer and to other certified parties, names of patients will be removed and replaced by a unique, specific numerical code, based on a numbering system defined by Pfizer.

All other data enabling identification of patients which will be transferred to Pfizer or to other certified parties will be identified by this specific unique code for each patient. The centre of the participating doctor will retain a confidential list of patients who participated in the study, with a link between the numerical codes for each patient and the actual identity of each of them.

In case of transfer of data, Pfizer will maintain high standards of confidentiality and of protection of personal data of patients, in conformity with conditions of the contract established for the study and laws on protection of personal data.

9.2. Consent

Consent documents and all materials intended for recruitment of patients must comply with regulatory requirements and local legislation, in particular, laws in force on respect of personal data.

Informed consent documents used in the process for obtaining informed consent and all materials enabling recruitment of patients must be examined and approved by Pfizer, approved by the Committee for the Protection of Persons (CPP- Ethics Committee) (if applicable) prior to their use and should be available for their inspection.

The participating doctor must ensure that all patients in this study or their legal representative or relative(s) or parent(s) or legal guardian(s) (when this involves a minor) are fully informed of the nature and the objectives of the study, of communication of data related to the study and of possible risks associated with their participation, in particular, risks associated with processing of a patient's personal data.

The participating doctor must ensure that all patients in this study or their legal representative or their relative(s) or parent(s) or legal guardian(s) (when it involves a minor) are fully informed of their rights of access and of correction of their personal data and of their right of withdrawal of consent for processing of their personal data.

When consent is obtained from a legal representative/parent) or from a patient's legal guardian, the consent of the patient (affirmative agreement) must then be obtained when the patient is able to provide consent according to modalities determined by the CPP (if applicable). If the participating doctor determines that the decision-making capacity of a patient is too limited so that he/he, in particular, may be consulted then, if this is authorised by the CPP (if applicable) and in conformity with regulatory requirements and local registration, an exemption from patient consent is possible by mentioning in the source documentation the reason why consent was not obtained.

If the patient does not provide his/her own consent, the source documents should mention why the patient did not provide consent (for example, a minor, an adult with impaired decision-making capacity), how the participating doctor determined that the person signing the consent form was the patient's legal representative, the relationship between the signatory of the consent form and the patient participating in the study (for example, parent, spouse) and the fact that consent from the patient was obtained or that an exemption was granted. If consent is obtained orally, it should be documented in the source documents.

If the study includes minors who reach the age of adulthood during this study, as defined by local legislation, they should repeat their consent in their capacity as adults in order to remain in the study. If inclusion of emancipated minor children is authorised by study criteria relating to age, the CPP (if applicable) and local legislation, they should provide documentation of their civil state in order to provide their consent without the permission of a parent or of a legal guardian.

The participating doctor, or a person designated by the participating doctor, will obtain written informed consent from each of the patients, or from the patient's legal representative, from one or both parents, or from the legal guardian and consent of the patient is applicable before any specific part of the study is performed. The participating doctor will retain the original informed consent document from each patient.

9.3. Early discontinuation by a patient

Patients can withdraw early from this study at any time at their own request or they can be excluded from it at any time at the discretion of the participating doctor or the sponsor for reasons of safety, behaviour or administrative problems. In all cases, every effort should be made to document the outcome of the patient, if possible. The participating doctor should inquire to find the reason for the early withdrawal and follow-up of the patient regarding all unresolved adverse events.

If a patient withdraws early from the study and he/she also withdraws his/her consent for disclosure of future information, no other assessment should be performed and no additional data should be collected. The sponsor can keep and continue to use all data collected prior to the so-called withdrawal of informed consent.

9.4. Regulatory aspects

9.4.1. Committee for the Protection of Persons (CPP -Ethics Committee)/Public Health Code Law "2004- 806 of 9 August 2004"

This is an observational study which does not change in any manner the usual medical management of persons entering into the study, does not produce any change to physical or psychological integrity and does not require a specific follow-up visit for persons entering in this study. All procedures are performed and products are used as usual, with no additional or unusual procedure for diagnosis or follow-up.

Under these conditions, this study does not fall within the scope of application of the law of programme no. 2006-450 of 18 April 2006 for research nor under law no. 2004-806 of 9 August 2004 article 88 chapter II article L1121-1 and therefore the project does not come under the heading of submission to the French National Agency for Medicines and Health Products Safety (ANSM), nor to the Committee for the Protection of Persons (Ethics Committee - CPP).

Regulation no. 2016-800 of 16 June 2016 relating to research involving the human person stipulates in its article 8 that research regularly reported or authorised as of date of entry in force of the application decision (application decision of the so-called Jardé law no. 2016-1537 of 16 November 2016) continued during five years in conformity with legislation which was initially applicable to them.

At the end of this 5-year period, they will be subject to another examination by the Committee for the Protection of Persons (CPP-Ethics Committee), and if applicable, by ANSM (French National Agency for Medicines and Health Products Safety under conditions stipulated by the public health code.

In the case in point, for an opinion which was delivered prior to 16 November 2017, the Committee for the Protection of Persons (Ethics Committee (CPP) is not competent for substantial changes involving this project.

9.4.2. French National Council of Doctors

Participating doctors and scientific committee experts will be compensated for their participation in this study. The study protocol and the financial agreements will be submitted to the French National Medical Council, section H (article L4113-6 of the Public Health Code and articles R4113-104 and R4113-105).

Each participating doctor and scientific expert must send to the Departmental Board of the Medical Council a copy of his/her contract (articles L4113-9, L4113-10 and L4163-10 of the Public Health Code).

9.4.3. Data protection: National Commission on Data Processing and Freedoms "CNIL"

In conformity with law 78-17 of 6 January 1978 relating to data processing, files and freedoms as modified by law 2004-801 of 6 August 2004 relating to protection of physical persons with regard to processing of personal data, this protocol has been the subject of a request for an opinion from the Consultative Committee on data processing in the area of research in the field of health (CCTIRS). Upon receipt of a favourable opinion from this committee, the computer file used in order to conduct the present study has been the subject of a request for authorisation from the National Commission on Data Processing and Freedoms (CNIL). This computer file can be implemented only upon receipt of authorisation from the CNIL.

Since this involves the potential competence of the Consultative committee on data processing in the area of research in the field of health (CCTIRS) which was eliminated on 5 May 2017, the date of the decision which mentioned creation of a Committee of Experts for Research, Studies and Evaluations in the field of Health (CEREES) in application of French law no. 2016-41 in modernisation of the health system of 26 January 2016, and the decision on application of the so-called Jardé law no. 2016-1537 of 16 November 2016, the departments of the minister of research are no longer competent to analyse corrections made to research projects.

Also, in conformity with law 78-17 of 6 January 1978 relating to data processing, files and freedoms as modified by law 2004-801 of 6 August 2004 relating to protection of physical persons with regard to processing of personal data, the protocol has been the subject of a declaration of conformity with a reference methodology to the National Commission on Data Processing and Freedoms (CNIL).

Data collected will correspond strictly to the field of application of the methodology of reference MR-003 of CNIL and Pfizer agrees to follow this methodology, which will be added to the study documents.

9.5. Ethical conduct of the study

The study will be conducted in conformity with legal and judicial requirements, as well as the objective, the scientific value and rigour and in compliance with generally accepted research practices described in the recommendations on Good pharmaco-epidemiological practices (GPP) published by the *International Society for Pharmaco-epidemiology* (ISPE), recommendations on Good epidemiology practice (GEP) published by the *International Epidemiological Association* (IEA), Good practices of research on results published by the *International Society for Pharmacoeconomics and Outcomes Research* (ISPOR), the international ethical recommendations for epidemiological research published by the *Council for International Organizations of Medical Sciences* (CIOMS), the European network of centres of pharmaco-epidemiology and pharmacovigilance (ENCePP) and the European Medicines Agency (EMA),

the Guide of methodological standards in pharmaco-epidemiology, and guidance of the FDA for industry: Good pharmacovigilance and pharmaco-epidemiological assessment (*Good Pharmacovigilance and Pharmacoepidemiologic Assessment*), directives of the *Food and Drug Administration* (FDA) and for the pharmaceutical industry and staff of the FDA: Good practice of conduct and of reporting of pharmaco-epidemiological safety studies using all electronic medical data, guidelines for industry: Measures of outcome noted by the patient: Use in development of medical products to support the labelling of the label and/or equivalent.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS

10.1. Requirements in terms of pharmacovigilance

The following table summarises the requirements for recording of adverse events in the electronic case report and for reporting adverse events via the adverse event report form of non-interventional studies in Pfizer pharmacovigilance (NIS AEM Report Form). These requirements are defined by three types of events:

(1) Serious adverse events (SAE)
(2) Non-serious adverse events (AE) (if applicable), and
(3) Situations involving exposure to a medicinal product, including exposure in pregnancy, exposure in breastfeeding, medicinal product errors, overdose, misuse, extravasation, and occupational exposure. These events are defined in the section entitled “Definition of an adverse event”.

	Recorded in the electronic eCRF of the study	**Reported via the NIS AEM *Report Form* in Pfizer Pharmacovigilance within 24 Hr. following awareness of the event**
SAE	All	All
Non-serious AE	All	Reactions related to the infusion, including acute and delayed onset hypersensitivity reactions, infections including serious infections, tuberculosis, opportunistic infections, hepatitis B, Congestive heart failure, intestinal and peri-anal abscess, malignant disease, leukaemias and lymphomas, demyelinating disorders, Lupus syndrome, disseminated lupus erythematosus, hepatobiliary disorders, sarcoidosis, sarcoidosis-like reactions
Situations involving exposure to a medicinal product of the study including exposure in pregnancy, exposure during breastfeeding, medicinal product errors, overdose, misuse, extravasation, lack of efficacy and occupational exposure.	All (independently of the existence of an associated AE), **except occupational exposure**	All (independently of the existence of an associated AE)

For each AE, the participating doctor must look for and obtain sufficient information both to determine the outcome of the adverse event and to assess if it meets criteria for classification as an SAE (see section "serious adverse events" in the following).

Adverse events must be reported to Pfizer within 24 hours after the participating doctor becomes aware of the event, whether the event has been considered as related or not to the study medicinal product by the participating doctor.

In particular, if the serious adverse event is fatal or life-threatening, the event should be reported to Pfizer immediately, whatever the information available on the adverse event. This time period also applies to all new information (follow-up) relating to reports of adverse events previously sent. In rare cases, where the participating doctor is not immediately informed of the outcome of an adverse event, the participating doctor should report the event within 24 hours after he/she became aware of it and provide information on the time when he/she became aware of this adverse event for the first time.

For adverse events considered as serious or identified in the right column of the abovementioned table which are to be reported to Pfizer within 24 hours of awareness of them, the participating doctor is required to look for and provide all information to Pfizer in conformity with this time period of 24 hours. Furthermore, Pfizer can request to obtain urgently from the participating doctor specific additional information on follow-up. Such information can be more detailed than that reported in the study case report. Generally, such information will include a sufficiently detailed description of the adverse event in order to enable a complete medical evaluation of the case and an independent determination of the possible causal relationship. All relevant information regarding the event such as concomitant treatments or disorders must be provided. In case of death of a patient, a summary of available results of an autopsy should be sent as soon as possible to Pfizer or to its certified representative.

10.2. Period of reporting

For each patient, the period of reporting of adverse events starts with the time when the patient received the first dose of the study medicinal product or from the date on which the patient provided his/her informed consent if he/she has already been exposed to the study medicinal product and ends with the end of the period of observation of the study, i.e. at least at the end of a period of 28 calendar days after the last dose of the medicinal product of the study. A report should be sent the PFIZER Pharmacovigilance or its certified representative for all types of adverse events listed in the abovementioned table and which occurred during this period. If the patient received the study medicinal product on the last day of the observational period, the period of reporting will be extended 28 calendar days after the end of the observational period.

In cases where the patient provided his/her consent but was never included in the study (for example: the patient changed his/her mind on participation; failure in screening criteria), the period of reporting ends with date of decision on non-inclusion of the patient.

If the participating doctor becomes aware of a serious adverse event which occurred at any time after the end of the observational period and that he/she considers related to a study medicinal product, this serious adverse event should also be reported to the Pfizer Pharmacovigilance department.

10.3. Evaluation of causal relationship

The participating doctor must assess and report the causal relationship. For all adverse events, sufficient information must be obtained by the participating doctor in order to determine the causal relationship of each adverse event. For AE considered as related to a study medicinal product, the participating doctor is required to perform follow-up until resolution or stabilisation of the event and/or of its sequelae at a level considered acceptable by the participating doctor and that Pfizer agrees with this evaluation.

The evaluation of the causal relationship by the participating doctor is the determination of the fact that a reasonable possibility exists that a study medicinal product has caused or contributed to an adverse event. If final determination of the causal relationship is "unknown" and that the participating doctor cannot determine if a study medicinal product has caused the event, then the event should be reported within 24 hours.

If the participating doctor cannot determine the aetiology of the event, but that he/she has determined that no study medicinal product was the cause of the event, this should be clearly mentioned in the case report form and in the adverse event report form in non-interventional studies.

10.4. Definition of an adverse event

10.4.1. Adverse event

An adverse event is any untoward manifestation which occurs in a patient in whom a medicinal product was administered and the event does not necessarily have a causal relationship with this treatment or its use. Examples of adverse events include, without this list being limited to, the following:

a. Abnormal test results (see in the following for circumstances in which an abnormal test result constitutes an AE);
b. Clinically significant symptoms and signs,
c. Changes to results of a clinical examination,
d. Hypersensitivity reactions,
e. Progression/worsening of an underlying disorder;
f. Lack of efficacy;
g. Medicinal product abuse;
h. Medicinal product dependence.

Furthermore, for medicinal products, they can include signs or symptoms resulting:

a. From an overdose;
b. From withdrawal;
c. From misuse;
d. From off-label use (off-label use in the Marketing Authorisation);
e. Medicinal product interactions;
f. Of extravasation;
g. Of exposure in pregnancy;
h. Of exposure during breastfeeding;
i. Of a medicinal product error;
j. Of occupational exposure.

Abnormal test results

Criteria enabling to determine if an abnormal result of an objective test must be reported as an adverse event are as follows:

- The test result is associated with symptoms, and/or
- The test result requires additional diagnostic investigation or medical/surgical intervention, and/or
- The test result leads to a change in posology or to withdrawal of a patient from the study, the administration of a significant additional concomitant treatment or to another treatment, and/or
- The test result is considered as an adverse event by the participating doctor or the sponsor.

The simple repetition of an abnormal test result, in the absence of one of the abovementioned conditions, does not constitute an adverse event. Any abnormal test result which proves to result from an error does not need to be reported as an adverse event.

10.4.2. Serious adverse events

A serious adverse event is defined as any untoward manifestation in a patient receiving a medicinal product or a nutritional product, whatever the dose, or using a medical device, and:

- Which causes death;
- Is life-threatening;
- Requires hospitalisation of the patient or prolongation of hospitalisation (see following for circumstances in which this does not constitute an adverse event);
- Results in permanent or important disability or incapacity (important alteration of capacity to perform actions of daily life);
- Results in a congenital anomaly or a malformation.

An event will be defined as a medically important event based on medical and scientific judgement. A medically important event may not be immediately life-threatening and/or resulting in death or hospitalisation. However, if it is established that the event can be life-threatening and/or require an intervention in order to avoid one of the abovementioned outcomes, the medically important event must be reported as serious.

Events which, for example, enter into this category of medically important events are allergic bronchospasm requiring intensive care in a hospital emergency room or in the patient's home, bleeding disorders, seizures which have not resulted in hospitalisation, or development of medicinal product dependence or medicinal product abuse.

Furthermore, all suspicion of transmission of an infectious agent, pathogenic or not, by a Pfizer product is considered as a serious adverse event. This event can be suspected by clinical symptoms or test results indicating an infection in a patient exposed to a Pfizer product. The terms "suspicion of transmission" and "transmission" are considered as synonymous.

Such cases are considered as unexpected and should be managed as serious cases by the Pfizer Pharmacovigilance department. These cases can also be reported as a product defect, if applicable.

Hospitalisation

Hospitalisation is defined as any initial admission (even for a duration of less than 24 hours) in a health establishment or any prolongation of an admission.

An admission also includes the transfer within the hospital to an intensive care unit (for example, from a psychiatry department to a medical department, from a medical department to the coronary care unit, from the neurology department to a medical unit for tuberculosis).

A consultation in the emergency room does not necessarily constitute a hospitalisation; however, an event which leads to a consultation in the emergency room (ER) should be evaluated as medically important.

A hospitalisation in the absence of an adverse event does not constitute an adverse event in itself and does not require to be reported. For example, the following reasons for hospitalisation without AE that are not be reported.

- Social admission (for example, the patient has no place to sleep)
- An administrative admission (for example, for an annual check-up)
- An optional admission not associated with a triggering AE (for example, for a scheduled cosmetic surgery procedure)
- Hospitalisation for observation in the absence of an AE

- Admission for treatment of a pre-existing condition not associated with development of a new AE nor worsening of a pre-existing condition (for example, for an assessment following persistence of abnormal laboratory test data pre-existing prior to treatment)
- Admission planned by the protocol during a clinical study (for example, for a procedure required by the study protocol).

10.5. Situations requiring reporting to Pfizer Pharmacovigilance within 24 hours.

Situations involving exposure in pregnancy, exposure during breastfeeding, a medicinal product error, an overdose, misuse, extravasation, lack of efficacy and occupational-related exposure are described in the following.

Exposure in pregnancy (or exposure in utero)

Exposure in pregnancy occurs if:

1. A woman becomes pregnant or it turns out that she is pregnant while she is receiving or is exposed to a medicinal product of the study (for example, environmental exposure), or a woman becomes pregnant or it turns out that she is pregnant after having discontinued and/or having been exposed to the medicinal of the study (maternal exposure);
   An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (for example, a nurse reports that she is pregnant and has been exposed to chemotherapy products).
2. A man has been exposed, in the setting of a treatment or of environmental exposure to a medicinal product of the study before or around the period of conception and/or has been exposed during pregnancy of his partner (paternal exposure).

Generally, cases of prospective and retrospective exposure during pregnancy, whatever the source, are to be reported, whether a concomitant adverse event is present or not, according to the procedure for reporting serious adverse events.

If a female patient in the study or the partner of a male patient in the study becomes pregnant or it turns out that she is pregnant during treatment of a patient in the study with a medicinal product in the study, the participating doctor must report this information to Pfizer, whether an adverse event has occurred or not, by completing the adverse event report form for non-interventional studies, as well as the additional form “Exposure in pregnancy”.

Furthermore, information relating to environmental exposure to a medicinal product of the study of a pregnant female patient (for example, a patient reports that she is pregnant and that she has been exposed to a cytotoxic product by inhalation or after accidentally spilling the product) must be reported to Pfizer, whether an adverse event has occurred or not, by completing the adverse event report form for non-interventional studies, as well as the additional form “Exposure in pregnancy”.

The information sent should include the planned date of term of pregnancy (in the following for information concerning term of pregnancy).

Follow-up should be implemented in order to obtain general information on pregnancy.

Furthermore, follow-up should be initiated to obtain information on the outcome of pregnancy for all cases which are the subject of reporting of exposure in pregnancy whose outcome is unknown.

A pregnancy should be followed up to term or up to termination of pregnancy (for example, voluntary termination of pregnancy) and Pfizer must be informed of its outcome.

This information will be provided as follow-up to the initial report on exposure in pregnancy. In case of the birth of a baby, the structural integrity of the neonate can be evaluated at time of birth.

In case of termination of pregnancy, the reason must be specified and, if possible clinically, the structural integrity of the foetus must be evaluated by visual inspection (unless results of tests performed prior to the procedure have concluded in a congenital anomaly and these results have been reported).

If the outcome of pregnancy corresponds to criteria of an SAE (for example, an ectopic pregnancy, a spontaneous abortion, foetal death in utero, neonatal death, a congenital anomaly [for a live birth, an aborted foetus, foetal death in utero, or neonatal death]), procedures for reporting SAE must be followed.

Additional information on the outcome of pregnancy which are reported as an SAE are as follows:

- A spontaneous abortion which includes a miscarriage and retention of the foetus;
- Neonatal death which occurs within a month after birth must be reported, whatever the causal relation as an SAE. Furthermore, the death of an infant more than 1 month of age must be reported as a SAE when the participating doctor assesses the death of the baby of a very young age as related or possibly related to exposure to the studied product.

Additional information on exposure in pregnancy can be requested. Follow-up on outcome at birth will be processed on a case-by-case basis (for example, follow-up of pre-term neonates of low gestational age in order to identify developmental retardation).

In case of paternal exposure, a form for reporting information intended for pregnant partners will be given to the patient participating in the study for his partner. It must be documented that this document has been given to the patient participating in this study for transmission to his partner.

<u>Exposure during breastfeeding</u>

Situations of exposure during breastfeeding must be reported, independently of existence of an associated AE.

Reporting of exposure during breastfeeding should not be performed when a Pfizer product specifically indicated for use in a breastfeeding woman (ex.: vitamins) is administered in agreement with the MA.

However, if the infant presents an AE associated with administration of a such a medicinal product, the AE must be reported with exposure during breastfeeding.

Medicinal product error

A medicinal product error means any unintentional error in prescribing, dispensing or administration of a medicinal product, which can cause or lead to inappropriate use of a medicinal product or to harm for the patient while the latter is under the control of the healthcare professional, the patient or the consumer. These events can be related to professional practice, the products, the procedures and to systems in particular: prescribing, transmission of an order; product information, packaging and nomenclature of the product, composition, dispensing, distribution, administration, training in the product, monitoring and use.

Medicinal product errors include:

a. Near-accidents, involving or not a patient directly (for example, inadvertent administration/error, which is accidental use of a product outside of the indication or the prescription by a healthcare professional or a patient/consumer);
b. Confusion concerning the name of the patient (for example, commercial name, tradename);

The participating doctor must report the following medicinal product errors to Pfizer, independently of existence of a concomitant AE/SAE:

a. Medicinal product errors involving exposure of a patient to the product, whether the medicinal product error is accompanied by an adverse event or not.

b. Medicinal product errors not involving a patient directly (for example, potential errors or near adverse events). Whenever a medicinal product error does not involve exposure of a patient to a product, the following minimal criteria comprise a case of a medicinal product error:
    - An identifiable reporting party;
    - A suspect product;
    - A medicinal product error.

Overdose, Misuse, Extravasation

Cases of an overdose, misuse and extravasation associated with use of a Pfizer product must be reported to Pfizer by the participating doctor, independently of existence of a concomitant AE/SAE.

Lack of efficacy

Cases of lack of efficacy of a Pfizer product should be reported to Pfizer by the participating doctor independently of the existence of a concomitant AE/SAE or of indication of a Pfizer product.

Occupational exposure

Cases of occupational exposure to a Pfizer product should be reported to Pfizer by the participating doctor independently of existence of a concomitant AE/SAE.

10.6. Single reference document on safety

The reference document to use during this study is the Summary of Product Characteristics (SmPC) in force in France.

This single reference document on safety should be used by the participating doctor for prescribing information and recommendations.

11. PLANS ON COMMUNICATION OF STUDY RESULTS

Pfizer and the scientific committee aggress to send the study results to all doctors who participated in the study.

The list of participating doctors will be systemically associated in all publications.

At least one communication and one publication are planned at end of study.

11.1. Scientific committee

A qualified, multi-disciplinary Scientific Committee has been set up for the study. It consists of 2 rheumatologists and 2 gastroenterologists who participated in drafting of the protocol and in its validation and who will participate in validation of the statistical analysis plan and in drafting of the clinical report. The scientific committee also has the mission of proposing and/or of validating changes to the protocol once the study is ongoing.

11.2. Access to source data

Source data means all documents or an original object enabling to prove the existence or accuracy of data or of a fact recorded during the study, in particular, medical dossiers of patients included.

Participating doctors will make available documents and individual data strictly necessary to data collection in the setting of the study, follow-up of the study, quality control and an audit of a biomedical research study, the disposition of persons having access to documents in conformity with legislative and regulatory conditions in force (articles L.1121-3 and R.5121-13 of the public health code).

11.3. Confidentiality

In conformity with legislative conditions in force (articles L.1121-3 and R.5121-13 of the public health code), persons with direct access to source data will take all necessary precautions in order to ensure confidentiality of information relating to investigational medical devices, a research study, persons who are subjects in it and, in particular, concerning their identity as well as the results obtained. Such persons, in the same capacity as participating doctors themselves, are subject to professional secrecy.

During the research study or at its end, data collected on persons who are subjects in it and sent to the sponsor by participating doctors (or all other specialised participants) will be made anonymous. In any case, they must not clearly reveal the names of persons concerned nor their address.

No data by name concerning the patient will be collected.

The sponsor (or its representative) will make certain that each person who is a subject in the research study has given his/her agreement for access of individual data concerning him/her and strictly necessary in quality control of the study.

11.4. Property of data

PFIZER PFE France (Pfizer Group) will retain the right of property of all forms in the case reports, data analyses and reports which result from this study.

11.5. Communication and publication

All information obtained based on this study will be considered as confidential, up until the analysis and final review by PFIZER PFE France (Pfizer Group) and by members of the scientific committee have been performed.

Results of this study can be edited or presented by members of the scientific committee after revision and agreement of PFIZER PFE France (Pfizer Group), and such that the confidential

information or industrial property is not disclosed. Prior to publication or presentation, a copy of the final text should be sent by members of the scientific committee to Pfizer PFE France (Pfizer Group), for comment. Such comments will aim to ensure the scientific content of publications and/or presentations proposed and to ensure that the data and the material relating to products and activities of PFIZER PFE France (Pfizer Group) receive a just, precise and reasonable presentation.

11.6. Communication of problems

In the eventual case of prohibition or a restriction imposed (for example, suspension of the study) by a competent authority responsible in whatever region of the world, or if the participating doctor becomes aware of new information which could influence the evaluation of benefits and risks of a PFIZER PFE France (Pfizer Group) product, PFIZER PFE France (Pfizer Group) must immediately be informed of it.

Furthermore, the participating doctor will immediately inform PFIZER PFE France (Pfizer Group) of all urgent measures of safety taken by the participating doctor in order to protect patients in this study against all immediate hazard and all serious violations of this protocol of a non-interventional study for which the participating doctor is aware of.

11.7. Financing of the Study

Conduct of this observatory is paid for by PFIZER PFE FRANCE (PFIZER GROUP).

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