**SYNOPSIS**

**Title:**

TREAtment Satisfaction, effectiveness and safety towards IBD patients initiating Ustekinumab: a 12-months REal-life study: TREASURE study

**Background and rationale:**

Inflammatory bowel disease (IBD) is a general term for chronic or remitting/relapsing inflammatory diseases of the intestinal tract, generally referring to ulcerative colitis (UC) and Crohn's disease (CD) [1]. Both pathologies lead to digestive disorders and inflammation in the digestive system, and have strong impact on quality of life (QoL). According to data from the French health authority (HAS), incidence rates are estimates in France around 5 per 100,000 person-years, and prevalence is estimates to 0.1%, for both pathologies [2, 3].

Ustekinumab is a fully human immunoglobulin G1 monoclonal antibody that blocks the p40 subunit of IL-12 and IL-23, precluding cytokine-mediated cellular activation [4]. Randomized clinical trials have demonstrated the clinical efficacy and safety of ustekinumab, in terms of response and clinical remission and of improve on health-related quality of life [4]. However, most patients with moderate-severe inflammatory bowel disease entering into clinical trials are not representative of those in usual practice [5]. Moreover, data from private centers are complementary to those from hospital referral centers where physicians manage the most severe forms of IBD [6]. Finally, limited data are available regarding the effects of ustekinumab on treatment satisfaction and on patient disability. In patient-centered care, patient-reported outcome (PRO) measures are central to evaluate healthcare [7].

This is why Janssen decided to conduct a prospective, non-interventional study in order to assess treatment satisfaction, effectiveness, use and safety of ustekinumab in adult IBD patients (CD or UC diagnosis). Eligible patients will be asked to participate in this study after the participating physician's decision to initiate a treatment with ustekinumab.

**OBJECTIVES AND HYPOTHESES**

**Primary objective:**

The primary objective will be to assess treatment satisfaction through the effectiveness domain of the TSQM-II questionnaire at the short term follow-up visit (V2)* on IBD patients initiating ustekinumab.

**The short term follow-up visit (V2) will occur between 10 and 20 weeks after inclusion visit (V1).*

Primary endpoint:

The primary endpoint will be the mean change between baseline and short term follow-up visit (V2) of the "effectiveness" domain of the TSQM-II questionnaire.

**Secondary objectives:**

- To assess treatment satisfaction through the TSQM-II questionnaire at the short term follow-up visit (V2) for the 3 following domains (side effects, convenience, and global satisfaction);
- To assess treatment satisfaction through the TSQM-II questionnaire at the long term follow-up visit (V3)* for all domains of the questionnaire (effectiveness, side effects, convenience, and global satisfaction);
- To assess the disability of patients through the IBD-disk at the short (V2) and long term (V3) follow-up visits;
- To assess the severity of symptoms through usual clinical scores; partial Mayo score (UC-DAI) for UC and Harvey-Bradshaw score for CD at the short (V2) and long term (V3) follow-up visits;
- To assess endoscopy scores through UCEIS score for UC and SES-CD score for CD at the short (V2) and long term (V3) follow-up visits;
- To describe patients' demographical characteristics at treatment initiation;
- To describe patients' clinical characteristics at treatment initiation and during the follow-up period;
- To describe physicians' characteristics;
- To describe treatment use (e.g. dose modifications, frequency of administration);
- To describe safety related parameters (collection of Adverse Events (AEs)).

**The long term follow-up visits (V3) will occur 12 months ± 1 month after inclusion visit (V1).*

Secondary endpoints:

- Mean change between baseline and short term follow-up visit (V2) for the three domains: side effects, convenience and global satisfaction of the TSQM-II questionnaire.
- Mean change between baseline and long term follow-up visit (V3) for the four domains: effectiveness, side effects, convenience and global satisfaction of the TSQM-II questionnaire.
- Mean change between baseline and short (V2) and long term (V3) follow-up visits of all scores of the 10 domains of the IBD-disk: abdominal pain, defaecation, social life, professional life, sleep, energy, anxiety, self-image, sexual functions, and joint pain;

- Mean change between baseline and short (V2) and long term (V3) follow-up visits of partial Mayo score (UC-DAI) for UC patients and Harvey-Bradshaw score for CD patients;
- Mean change between baseline and short (V2) and long term (V3) follow-up visits of UCEIS score for UC and SES-CD score for CD;
- Descriptive data of patient's demographical characteristics at baseline;
- Descriptive data of clinical characteristics at baseline including disease history, comorbidities, current disease status, laboratory parameters, previous therapy(ies) for CD/UC and concomitant drugs for CD/UC;
- Descriptive data of clinical characteristics during the follow-up period including current disease status, laboratory parameters, and concomitant drugs for CD/UC;
- Descriptive data of physicians' characteristics (e.g. age, type of structure, geographical repartition);
- Descriptive data treatment use (e.g. dose modifications, frequency of administration);
- Descriptive data of safety related parameters (e.g. all AEs, serious AEs (SAEs), their causal relationship with ustekinumab, and others safety related data as overdoses, misuse, abuse, off-label uses).

**STUDY DESIGN**

This is a prospective, non-interventional study in order to assess treatment satisfaction, effectiveness, use and safety of ustekinumab in adult IBD patients (CD or UC diagnosis) in real life setting in France. Eligible patients will be asked to participate in this study after the participating physician's decision to initiate a treatment with ustekinumab.

The decision of patients to participate in this study must not, in any way, impact upon the standard of care that they are receiving or any benefits to which they are otherwise entitled. The treatment decision must have been taken prior to and independently of the patient's inclusion in the study. All aspects of treatment and clinical management of patients will be in accordance with local clinical practice and applicable local regulations, and at the discretion of the participating physician. Only data available per clinical practice will be collected within this study. Additionally, participating physicians will be asked to obtain Patients Reported Outcomes (PRO) data from patients within this study.

Data will be collected during three visits: V1 (inclusion), V2 (between 10 and 20 weeks after V1), and V3 (12 months ± one month after V1). The maximum duration of a patient's participation in this study will be 12 months ± one month, according to allowed time windows.

The end of the study will be the last visit within the study for the last participating patient. To be noted, collection of AEs will be performed 90 days after the last administration within the study. With one year of expected period for patient's recruitment, the overall duration of the study, including recruitment and follow up, is expected to be 28 months.

A Scientific Committee (SC) will be in charge of the review and validation of the study protocol as well as the study results and Clinical Study Report (CSR).

An interim analyses is planned to be performed after the end the recruitment period.

**STUDY SETTING AND PATIENT POPULATION**

Physicians

Targeted sites are private centers with gastroenterologist specialists. A total of 40 centers will be activated.

Patients

Targeted patient population are adult patients initiating ustekinumab for the first time at inclusion for their diagnosed IBD: CD or UC. For the purpose of this non-interventional study, patients may enter to this study at the time of initiation of ustekinumab therapy. For these patients, start of ustekinumab therapy is considered as a maximum of 14 days after the patient's inclusion in the study. Patients who have initiated ustekinumab prior to enrollment in the study must not be enrolled in the study. Patients who had previously already initiated ustekinumab treatment in the past must not be included.

A total of 257 patients should be included in the study (see following sub-part STATISTICAL METHODS).

Each potential patient must satisfy the following criteria to be eligible for data collection in this study:

- Male or female adults (≥18 years of age);
- Must have a confirmed diagnosis of CD or UC according to physician's routine care clinical practice;
- Informed and having agreed to participate in the study;
- Initiating ustekinumab at inclusion (visit V1)*;
- Covered by healthcare insurance.

** Start of ustekinumab therapy is considered within a maximum of 14 days after patient inclusion in the study.*

Potential patients who meet any of the following criteria will not be eligible for this study:

- Patient deprived of liberty by a judicial or administrative decision, or who is under a measure of legal protection (e.g. guardianship or curatorship);
- Not able to read, understand and complete questionnaire in local language;
- Currently enrolled in an interventional study;
- Currently enrolled in a non-interventional study sponsored or managed by a Janssen company.

A non-inclusion patients log will be completed by each participating site directly into the electronic case report form (eCRF) on all eligible patients, with the reason for refusal of participation together with the patient age, gender, and year of CD or UC diagnosis to assess enrolled patient's overall representativeness.

Prior to data collection, all patients will have time to read the information note and must give their oral participation agreement allowing data collection and source data verification in accordance with local requirements and/or sponsor policy. This agreement must be documented in the patient's medical file by physician.

Participating sites will be encouraged to enroll patients in a consecutive manner when patients come for their regular consultation, in order to minimize bias in patient selection.

**DATA SOURCES AND COLLECTION METHODS**

The primary data source for this study will be the medical records of each patient. Source documentation should be in patients' medical records for all data entered into the eCRF. Additionally, PRO questionnaires will be recorded onto paper forms and will be considered as source data.

Measures of Treatment Effectiveness/Satisfaction and Patient-Reported Outcomes

Different validated PROs and clinician reported outcomes (ClinROs) questionnaires will be used in this non-interventional study.

*PROs*

Regarding the treatment satisfaction, the TSQM-version II (Treatment Satisfaction Questionnaire for Medication) is chosen because it is widely used in clinical studies, and especially in IBD area [8, 9]. This 11-item questionnaire completed by patients allows also to conclude separately on different domains related to the treatment' satisfaction and to have a specific assessment of treatment satisfaction among effectiveness, side effects, convenience, and global satisfaction [10].

Then, the IBD-disk was chosen for the assessment of IBD disease's impact on disability as evaluated by patients. This recent validated 10-item PRO 1 give an immediate visual representation of patient-reported IBD-related disability. Widely used in clinical practice, it is considered as a relevant tool to be used in non-interventional studies [11, 12].

Therefore, a total of 21 items will have to be completed by patients, representing about 10-15 minutes for completion, a duration not considered as burdensome.

*ClinROs*

The severity of symptoms will be assessed by physicians through usual clinical scores, the partial Mayo score (UC-DAI) for UC and the clinical score Harvey-Bradshaw score for CD [13].

Measures of Safety

In this non-interventional study, ustekinumab is a Janssen product. During the observational period, all adverse events (AEs) and special situations following exposure to ustekinumab are to be recorded in the eCRF and the patient's source records, regardless of seriousness or causality. AE collection should start with the first use within the study of a product under study and will apply to all adverse events, regardless of seriousness, that occur within 90 days after a patient's last use within the study of a product under study. All pregnancies following exposure to a product under study are to be recorded in the eCRF and in the patient's source records. All Serious Adverse Events (SAEs) following exposure to ustekinumab should be reported directly by the participating physician, within 24 hours of them becoming aware, to the local sponsor using a SAEs Report Form.

**STATISTICAL METHODS**

Sample size determination:

The statistical analysis of this study will be mainly descriptive. Therefore, the sample size was calculated to allow acceptable precision in estimating the primary endpoint. The required number of evaluable patients can be assessed using the standard formula:

$$n = \left(\frac{1.96 \times s}{e}\right)^2$$

with s = standard deviation and e = precision

Based on a recent study using the TSQM-II questionnaire in IBD patients [8], the standard deviation corresponding to the mean change between 3 months and baseline for the "Effectiveness" domain is equal to 37.23.

Assuming a similar result, 205 patients are required to obtain a 95% confidence interval with a precision of 5.1 points. Taking into account the range of the "Effectiveness" domain (from 0 to 100), a precision of 5.1 points is considered to be an acceptable precision.

Allowing a 20% rate of non-evaluable patients for the primary endpoint, 257 patients should be included in the study.

Table 1: Estimated sample size needed according to the precision

| Precision | Number of evaluable patients | % Of non-evaluable patients for the primary endpoint | Number of patients to include |
|---|---|---|---|
| 4 | 333 | 15% | 392 |
| 4 | 333 | 20% | 417 |
| 4 | 333 | 25% | 444 |
| 5 | 214 | 15% | 252 |
| 5 | 214 | 20% | 268 |
| 5 | 214 | 25% | 286 |
| 5.1 | 205 | 15% | 242 |
| **5.1** | **205** | **20%** | **257** |
| 5.1 | 205 | 25% | 274 |
| 6 | 148 | 15% | 175 |
| 6 | 148 | 20% | 185 |
| 6 | 148 | 25% | 198 |

Physicians, patients' characteristics and treatment characteristics and use

Descriptive statistics will be generated across all patients and by disease (CD and UC).

All continuous variables will be summarized using descriptive statistics, which will include the number of available and missing data, mean, standard deviation, median, minimum, maximum and quartiles. All categorical variables will be summarized using frequencies and percentages.

Where appropriate, 95% confidence intervals (95%CI) will be presented (Wald for the continuous variables, Agresti-Coull for the categorical variables).

Measures of Effectiveness/Satisfaction and Patient-Reported Outcomes

Effectiveness will be assessed through the PROs, and ClinROs:

- the four domains of the TSQM-II questionnaire (effectiveness, side effects, convenience, and global satisfaction);

- the 10 domains of the IBD-disk (abdominal pain, defaecation, social life, professional life, sleep, energy, anxiety, self-image, sexual functions, and joint pain);
- clinical scores for severity of symptoms; partial Mayo score for UC (UC-DAI) and Harvey-Bradshaw score for CD.

Data will be descriptively summarized across all patients and by disease (CD and UC). Change from baseline will be summarized and the associated 95%CI will be provided.

Safety

A summary table of AEs (number and percentage of patients who experience an adverse event and number of events) grouped by primary MedDRA System Organ Class (SOC) and Preferred Term (PT) will be provided. All documented adverse events will be included in the analysis.

For each adverse event, the percentage of patients who experience at least 1 occurrence of the given event will be summarized (presented as preferred term and categorized by system organ class). Where appropriate, additional summaries, listings, or narratives may be provided for any deaths, serious adverse events, or any adverse events of specific interest (AESI).

Descriptive data will be performed for safety related parameters (all AEs, SAEs, their causal relationship with ustekinumab, and others safety related data as overdoses, misuse, abuse, off-label uses).

**DATA COLLECTION SCHEDULE**

**Table 2: Data collection schedule**

| Data Collection | Visit 1<br>Baseline | Visit 2<br>Short term follow up<br>Between 10 and 20 weeks after V1 | Visits 3/End of study<br>Long term follow up<br>12 months (±1 month) after V1 |
|---|---|---|---|
| **Screening/Patient information** | | | |
| Patient information note/oral agreement to participate[a] | X | | |
| Eligibility criteria | X | | |
| **Demographics and other patient information**<br>*-Age at inclusion*<br>*-Gender*<br>*-Smoking status*<br>*-Weight, height (BMI)*<br>*-For women only : control of efficient contraceptive method* | X | | |
| **Medical history**<br>*-Current comorbidities (treated or not) among the following categories (psoriasis / renal impairment / hepatic impairment / spondyloarthritis / psoriatic arthritis / arthralgia / uveitis / others)*<br>*-Medical history of cancer (start/end dates associated)* | X | | |
| **Disease history**<br>*- Age of the patient at diagnosis*<br>*-Previous surgery (total number of surgery, date, and type of the last surgery)* | X | | |
| **Current disease status**<br>*- Location of the disease (Crohn's disease)*<br>*- Behaviour of the disease (Crohn's disease)* | X | X | X |

| Data Collection | Visit 1<br>Baseline | Visit 2<br>Short term follow up<br>Between 10 and 20 weeks after V1 | Visits 3/End of study<br>Long term follow up<br>12 months (±1 month) after V1 |
|---|---|---|---|
| *- Extent of the disease (Ulcerative colitis)*<br><br>*-Clinical scores (partial Mayo (UC-DAI) for UC / Harvey-Bradshaw for CD): scoring of severity symptoms by physicians (ClinROs)*<br>*-Biological markers (ferritin / albumin / hemoglobin / CRP / fecal calprotectin) (if available)* | | | |
| *-Endoscopic scores (UCEIS for UC / SES-CD for CD) & date of endoscopy (if available)* | X | | X |
| **Therapy(ies) for ulcerative colitis or crohn disease** | | | |
| **Previous therapy(ies) for CD/UC**<br>*-Name of treatment, start and end date of intake*<br>*-Main driver for initiation of ustekinumab among the following possibilities (primary failure of previous biotherapy / secondary failure of previous biotherapy / adverse events / contraindication or intolerance to others therapies / others)* | X | | |
| **Ustekinumab therapy for CD/UC**<br>*- Date, doses, methods and route of administration associated of all injections performed* | X | X | X |
| *-Timelines planned by physician between 2 injections (number of weeks)*<br>*-Potential delay regarding timelines initially planned by physician between 2 injections and associated reason for modification*<br>*-Number of visit(s) at general practitioner office since previous visits*<br>*-Date & reason for definite discontinuation* | | X | X |

| Data Collection | Visit 1<br>Baseline | Visit 2<br>Short term follow up<br>Between 10 and 20 weeks after V1 | Visits 3/End of study<br>Long term follow up<br>12 months (±1 month) after V1 |
|---|---|---|---|
| **Concomitant therapy(ies) for CD/UC**<br>*-Name of treatment, start and end date of intake* | X | X | X |
| **Patient-reported outcomes** | | | |
| **PRO medication satisfaction :** TSQM-II | X | X | X |
| **PRO 1** : IBD-disk | X | X | X |
| **Safety parameters** | | | |
| Adverse events[b] | X | X | X |

a. Before the start of data collection in this study, all patients must give orally their agreement to participate allowing data collection and source data verification in accordance with local requirements.

b. All adverse events and special situations following exposure to ustekinumab are to be recorded in the eCRF, regardless of seriousness or causality. Adverse event collection should start with the first use within the study of a product under study and will apply to all adverse events that occur within 90 days after a patient's last use within the study of a product under study.

*CD: Crohn Disease; SES-CD: Simple Endoscopic score for Crohn Disease; TSMQ-II: Treatment Satisfaction Questionnaire for Medication - version II; UC: Ulcerative colitis; UCEIS: Ulcerative Colitis Endoscopic Index of Severity; UC-DAI: Ulcerative Colitis Disease Activity Index*

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