Janssen EMEA Medical Affairs*

Non-interventional Post-authorization Safety Study - Protocol

An Observational Post-authorization Safety Study to Describe the Safety of Ustekinumab and Other Crohn's Disease Treatments in a Cohort of Patients With Crohn's Disease

Protocol RRA-20745
AMENDMENT 1

STELARA (ustekinumab)

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EU PAS Register Number: Study Not Yet Registered.

Status:	Approved		
Protocol version:	6.0	**Version date:**	18 May 2021
Prepared by:	Janssen-Cilag Limited		
EDMS number:	EDMS-ERI-144442725, 9.0		

Compliance: This study will be conducted in compliance with the protocol and applicable regulatory requirements.

1. PASS INFORMATION

Title:	An Observational Post-authorization Safety Study to Describe the Safety of Ustekinumab and Other Crohn's Disease Treatments in a Cohort of Patients With Crohn's Disease
Protocol version:	6.0
Date of last version of the protocol:	14 May 2019
EU PAS Register No:	EUPAS21954
Active substance (INN common name):	Ustekinumab
Pharmaco-therapeutic group (ATC Code):	L04AC05
Medicinal product(s):	STELARA®
Product reference:	EMEA/H/C/000958
Procedure number:	EMEA/H/C/000958/MEA/045
Name of Marketing Authorization Holder(s)	Janssen-Cilag International NV
Joint PASS	No
Research question and objectives	The objective of this study is to evaluate the long-term safety of ustekinumab in adult patients treated for Crohn's disease by describing the risks of malignancies, serious infections, and VTE in cohorts of patients treated with ustekinumab, anti-TNFs or immunomodulators.
Countries of study	The study is proposed to be conducted in United Kingdom, France, Spain, Greece, Germany, Italy, Israel, Belgium, Portugal, Ireland, Hungary, Denmark, Sweden, Netherlands, Poland, Russia and Switzerland.
Author	PPD

2. MARKETING AUTHORIZATION HOLDER(S)

Name of Marketing Authorization Holder:	Janssen-Cilag International NV
Address:	Turnhoutseweg 30 B-2340 Beerse Belgium
Contact Details:	PPD
Qualified Person Pharmacovigilance:	Dr Laurence Oster-Gozet, PharmD, PhD
Signature:	[e-signature appended at the end of this document]
Date:	

3. RESPONSIBLE PARTIES

Coordinating Investigator:	PPD
Contact person for this protocol:	PPD
E-mail address or telephone number of contact person:	PPD

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AMENDMENTS AND UPDATES

Neither the investigator nor the sponsor will modify this protocol without a formal amendment. All protocol amendments must be issued by the sponsor, and will follow the review and approval process in accordance with local regulations.

Protocol Version	Date
Original Protocol	14 May 2019
Amendment 1	18 May 2021

Amendments below are listed beginning with the most recent amendment.

Amendment 1 (18 May 2021)

The overall reason for the amendment: The overall reason for the amendment is to correct the key milestones for the study.

Applicable Section(s)	Description of Change(s)
Rationale: The key milestones for the study were updated.	
4. Abstract; 5. Milestones.	The dates for the key milestones of the study are corrected.

4. ABSTRACT

Protocol Title: An Observational Post-authorization Safety Study to Describe the Safety of Ustekinumab and Other Crohn's Disease Treatments in a Cohort of Patients With Crohn's Disease (6.0, 18 May 2021)

Sponsor's Responsible Medical Officer: PPD (Main Author)

NOTE: The term "sponsor" used throughout this document refers to the entities listed in the contact information page(s), which will be provided separately.

Background and Rationale

Ustekinumab (STELARA®) is a fully human immunoglobulin G1 kappa monoclonal antibody to human interleukin (IL)-12/23p40 that binds with high affinity to the p40 subunit of human IL-12 and IL-23. By inhibiting interaction with the cell surface IL-12Rβ1 receptor protein, ustekinumab effectively neutralizes all IL-12 (T helper [Th]1) and IL-23 (Th17) mediated cellular responses. Abnormal regulation of IL-12 and IL-23 has been associated with multiple immune-mediated diseases including Crohn's disease (CD); therefore, inhibition of these and associated inflammatory pathways constitutes a novel mechanism of action for the treatment of CD. The therapeutic potential of this approach was demonstrated from the efficacy and safety results of a comprehensive Phase 2 and Phase 3, randomized double-blind, clinical studies for CD.

Ustekinumab (STELARA) was approved by the European Medicines Agency (EMA) for the treatment of adult patients with CD based on the results from the Phase 2 and Phase 3 clinical studies through Week 44 of maintenance treatment. A long-term extension of the patients enrolled in the Phase 3 clinical study is ongoing beyond Week 44 and is planned through Week 272. However, as part of the EMA regulatory approval for CD, the Marketing Authorization Holder committed to undertake a post-authorization safety study (PASS) in a cohort of patients with CD in the European Union (EU).

The goal of this study of adult CD patients is to address the postmarketing commitment to characterize the long-term safety profile of ustekinumab in adult patients with CD. This study will provide guidance to key stakeholders on key important risks associated with the use of ustekinumab, as described in Part III.5, 'Summary of the Pharmacovigilance Plan,' of the EU Risk Management Plan.

At the time of approval, ustekinumab had been studied beyond 52 weeks of continuous treatment in adult patients with CD in the IM-UNITI study, a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel group study, evaluating the efficacy and safety of ustekinumab maintenance therapy. At the time of approval, 2 years data was available for this study and included data from 397 patients who achieved a response to ustekinumab at Week 8 following an induction phase and were randomized to receive subcutaneous ustekinumab 90 mg every 8 weeks or every 12 weeks, or placebo during a maintenance (0–44 week) period, before entering the long-term extension (44–252 week) period. In this study, adverse events (per hundred subject years of follow-up) were similar between ustekinumab treated patients and placebo treated patients from Week 44 through to Week 96, and were similar in number to events reported in the blinded period of the maintenance period. However, the population in this study is small; therefore, there is still a need to further evaluate the long-term safety profile of ustekinumab in CD.

To address this need, a cohort of patients with CD who are receiving ustekinumab treatment, as well as cohorts of CD patients receiving anti-tumor necrosis factor (TNF) or immunomodulators and who are enrolled in the I-CARE study will be analyzed. The *source data* for this protocol will be the database of the *ongoing* and *independent* I-CARE cohort study. The I-CARE study is a European prospective, longitudinal, observational, multicenter cohort study, endorsed by the Groupe d'Etude Thérapeutique des Affections Inflammatoires Digestives (GETAID), the Europe Crohn's and Colitis Organisation (ECCO) and the European Federation of Crohn's and Ulcerative Colitis Associations (EFCCA). The objective of the

independent I-CARE study is to assess the presence and extent of safety concerns (malignancies and serious infections risks) among 10,000+ patients with an established diagnosis of inflammatory bowel disease (IBD) (CD, ulcerative colitis). Patients in I-CARE are enrolled into the following groups:

- IBD patients who have never received biological agents or immunomodulators;
- IBD patients receiving thiopurines alone;
- IBD patients treated with anti-TNF therapy alone (without any concomitant immunomodulators);
- IBD patients treated with anti-TNF therapy in combination with thiopurines or methotrexate;
- IBD patients treated with vedolizumab alone (without any concomitant immunomodulators);
- IBD patients treated with vedolizumab in combination with thiopurines or methotrexate;
- Crohn's disease patients treated with ustekinumab.

During the observational period in I-CARE, data collection is performed at least once yearly, at patient visits conducted within clinical practice. Additionally, where permitted per local regulations, patients complete an electronic-diary every month and an electronic-patient-reported outcomes (e-PRO) questionnaire on a yearly basis. The last visit is planned after 3 years of follow-up, at the end of the study, or at the time of early withdrawal from the study, if applicable.

The present study will use data collected in I-CARE to analyze the long-term safety of ustekinumab as observed in clinical practices across Europe.

Research Question and Objectives

The objectives of this study are to:

- evaluate the long-term safety of ustekinumab, as measured by the occurrence of malignancies, serious infections, including opportunistic infection and tuberculosis (TB), and venous thromboembolisms (VTEs) associated with hospitalization, in adult patients with CD treated with ustekinumab;
- evaluate the risk factors for malignancies, serious infection, including opportunistic infection and TB, and VTEs associated with hospitalization;
- estimate the long-term safety of adult patients with CD between users of ustekinumab and users of other CD therapies (anti-TNF agents and immunomodulators).

Hypothesis

No hypotheses are pre-specified. This study aims to describe the safety data collected for patients in a clinical practice setting.

Study Design

This is an observational, post-authorization safety study to describe the safety profile of adult patients with CD. This study will be a PASS study constituting secondary use of data from patients enrolled into the independent I-CARE study – a prospective, observational, multicenter cohort study. This study will include patients who receive ustekinumab treatment and those receiving other CD treatments within routine clinical practice, using data collected in the I-CARE study.

The source population is derived from the I-CARE study, enrolling patients with CD, ulcerative colitis or IBD at sites in 16 countries across Europe. This study will focus primarily on patients enrolled into I-CARE who are being treated for CD with ustekinumab. Patients enrolled into I-CARE will complete an electronic-diary on a monthly basis and an e-PRO questionnaire on a yearly basis. Additionally, a gastroenterologist will complete an annual summary at least once yearly. Patients enrolled in the study will

be observed for 3 years. The final patient population of the I-CARE study will be at least 10,000 IBD patients split into 6 patient groups, with approximately 2,000 patients in the ustekinumab cohort of CD patients.

Setting and Patient Population

The source population of patients will be those enrolled in the I-CARE study. Patients will be included in data collection if they meet the following eligibility criteria:

- male or female aged >18 years with a confirmed diagnosis of CD made at least 3 months before enrollment based on usual radiological, endoscopic or histological criteria.
- have received treatment with ustekinumab or other CD therapies (anti-TNF agents prescribed for CD [ie, infliximab, adalimumab, including biosimilars] and immunomodulators) per local label and clinical practice.

Because this is a non-interventional, secondary data analysis of an externally owned database of patients enrolled into the independent I-CARE study during routine clinical practice, therapy decisions will be made at the discretion of the participating physician, per routine clinical practice, prior to enrollment in the study; the sponsor will not provide guidance on any aspect of therapy, patient clinical management, or therapy dose selection.

Variables

The I-CARE protocol summarizes the frequency and timing of data collection in the I-CARE study. Data collected in the I-CARE study will be extracted from the I-CARE database to be used in this study.

Exposures

The main exposure of interest is treatment with ustekinumab prescribed for CD. The primary comparator will be anti-TNF agents prescribed for CD (ie, infliximab, adalimumab, including biosimilars). The secondary comparator group will comprise immunomodulators.

Over time, CD patients who initiate ustekinumab may have received or may later receive comparator treatments in various sequences.

Analyses will consider a conservative approach with ustekinumab which is (1) to implement a hierarchical order of exposure classification for malignant outcomes and (2) to account for malignancy lag time bias in the study analyses. For non-malignant outcomes, a 91-day at risk window will be applied for the primary analysis.

Outcomes

The outcomes of this study comprise:

- malignancies;
- serious infections (including opportunistic infections and TB);
- events of VTE recorded with/during hospitalization.

The *covariates* include (but may not be limited to):

- Age
- Gender
- Year of cohort entry
- Disease duration

- Extent of disease
- Treatments for CD that are not study exposures (eg, systemic steroids)
- Disease activity (modified Harvey-Bradshaw Index) before or at start of cohort-defining treatment, if available
- History of previous treatments with other anti-TNF agents
- History of hospitalization for CD

Other risk factors may be identified after analysis of the descriptive data.

Safety outcomes will be described using data collected from the I-CARE study. Data for malignancies, serious infections, including opportunistic infection and TB, and all hospitalizations (including those with events of VTE), related or not to CD, will be reported by the patient and validated at least yearly by gastroenterologists in the I-CARE study and will be collected for this study. All incoming hospitalization reports/charts will be reviewed for malignancies, serious infections and events of VTE; these will be adjudicated by dedicated adjudication committees, and validated and non-validated events will be summarized. Further details are available within the I-CARE protocol.

All other adverse drug reactions not actively solicited (ie, spontaneously reported) in the I-CARE study in patients who received ustekinumab will be collected and will be summarized in aggregate listings that will be included in the end of study report and where applicable in any interim reports.

Data Sources

The data source for this study will be the database for the I-CARE study.

Patient data will be handled in compliance with all applicable privacy laws.

Study Size

The I-CARE study will enroll more than 10,000 adult patients with IBD (up to 17,600 adult patients), receiving IBD treatments, including a cohort of approximately 2,000 patients with CD receiving ustekinumab at entry or during follow-up. The I-CARE study was powered to detect a lymphoma hazard ratio of at least 3.5 in the groups of patients receiving thiopurines, either alone or in combination with anti-TNF, relative to patients not receiving thiopurines (ie, receiving anti-TNF alone or no immunomodulators).

The required sample sizes to detect a hazard rate of 2.0 for different baseline incidence rates are shown in the first table below. The lowest incidence (0.0064 per patient year) is based on the malignancy incidence rate in patients treated with infliximab reported from the TREAT Crohn's registry that collected data from 6,273 North American CD patients as of 2010. Sample size requirements assuming a 1:1 and a 1:2 ratio of ustekinumab:other biologics are presented.

With a type 1 error rate of 5%, a power of 80% for a 2-sided test, 1:2 ratio comparing ustekinumab and other biologics (anti-TNF agents), a 20% of loss to follow-up, an accrual period of 1 year, and a follow-up time of 3 years, 1032 ustekinumab users would be needed to detect a hazard ratio of 2.0. Considering a 1:1 ustekinumab vs comparator treatment allocation, 1544 ustekinumab users would provide 80% power to detect a HR of 2.0. However, with the current assumptions and a 1:1 ratio comparing ustekinumab and other biologics, including 2,000 patients per treatment cohort would increase the power to 89%.

Any of the above presented sample sizes for the primary outcome of all malignancy (N=1032 to 2000) is expected to be adequate for the secondary outcome of serious infections, which occur at a higher incidence rate than malignancy.

Sample Sizes Required to Detect a Hazard Rate of 2.0 by Baseline Incidence Rate, assuming 1-year accrual and 3- year follow-up, 1:2 UST vs comparator treatment allocation

(type 1 error=0.05, type 2 error=0.2, annual loss to follow-up rate 20%, uniform accrual, exponential time to event distribution)

Baseline incidence rate (/patient year)	Ustekinumab users, N	Comparators, N	Total N needed	Total events needed, N
0.0064	1032	2064	3096	65
0.0080	828	1656	2484	65
0.0100	666	1332	1998	65
0.0120	558	1116	1674	65
0.0140	480	960	1440	65
0.0160	422	844	1266	65
0.0180	377	754	1131	65
0.0200	341	682	1023	65

Sample Sizes Required to Detect a Hazard Rate of 2.0 by Baseline Incidence Rate, assuming 1-year accrual and 3- year follow-up, 1:1 treatment allocation

(type 1 error=0.05, type 2 error=0.2, annual loss to follow-up rate 20%, uniform accrual, exponential time to event distribution)

Baseline incidence rate (/patient year)	Ustekinumab users, N	Comparators, N	Total N needed	Total events needed, N
0.0064	1544	1544	3088	65
0.0080	1240	1240	2480	65
0.0100	996	996	1992	65
0.0120	834	834	1668	65
0.0140	717	717	1434	65
0.0160	630	630	1260	65
0.0180	563	563	1126	65
0.0200	509	509	1018	65

Data Analysis

Statistical analyses will be conducted by I-CARE according to a Statistical Analysis Plan developed in close collaboration with the sponsor. The analysis set will include all patients who fall within the inclusion and exclusion criteria for this study.

Progress of the registry, including data analysis, will be included in the Development Safety Update Report/Periodic Safety Update Report (DSUR/PSUR) per the regulated timelines. These analyses will describe each cohort in terms of patient characteristics. For each of the study cohorts, annual enrollment will be described, along with the frequency of study outcomes and cumulative person-years of follow-up accrued.

Interim analyses will be performed annually from one year after completion of enrollment or from March 2020, whichever comes first, until the end of the study. The final study report is currently planned to be available in 2022. The scope of the interim analysis will be documented in the Statistical Analysis Plan.

Safety outcomes

The event rate of safety outcomes (malignancies, serious infection, including opportunistic infection and TB, and VTE associated with hospitalization) will be estimated for each cohort. Sensitivity analyses will also be performed, as described in the body of the protocol.

All other adverse drug reactions not actively solicited in the I-CARE study in patients who received ustekinumab will be collected and will be summarized in aggregate listings that will be included in the end of study report and where applicable in any interim reports. Where possible, the cumulative event rate of the outcomes will be estimated using time-to-event analyses, overall by cohorts and then in stratified analyses. Stratification factors (as measured at study entry) will be evaluated one at a time and will include gender, time since initial CD diagnosis, CD hospitalization, and previous use of systemic steroids; and for biologic cohorts, concurrent use of immunomodulators and history of previous biologic use.

For each safety outcome, risk will be compared between ustekinumab and comparators using survival analysis (Kaplan Meier plots and Cox proportional hazards regression models). Users of ustekinumab will be compared with users of anti-TNF agents and with users of immunomodulators. Study exposures will be treated as time-dependent variables. Hazard ratios will be used to estimate relative risk. Candidate variables to evaluate as potential confounders include the list of covariates under Variables, listed above.

The study is not randomized; as a result, comparisons across cohorts will be biased. When comparing the ustekinumab treatment cohort and the anti-TNF treatment cohort, to adjust for non-random treatment assignment, propensity score (PS) analysis will be performed to compare the following outcomes:

- incidence rate of malignancies
- incidence rate of serious infections
- incidence rate of venous thromboembolisms (VTEs) associated with hospitalization.

The PS calculation will be repeated for each summary report under the condition that new patients are enrolled. Outcome-specific propensity scores will be developed for each of the above outcomes, and details will be provided with the reports. Because only limited data are collected through follow-up, the PS will not be recalculated following treatment switch.

The PS will be calculated using the potential confounders listed under ‘Variables’. For the analysis of the endpoints of the present study the PS stratified by quintiles will be used.

The quality of the PS will be evaluated as follows: For each of the variables included in the PS, the difference between the treatment arms will be compared by PS stratum, using standard comparison tests to evaluate the significance of the differences. If differences are detected for a small number of variables and the number of affected strata is limited, then a sub classification will be done after which the check for difference will be repeated. As an example: if a difference in age persists only in the third quintile of the PS, then this quintile is divided, and the fifth and sixth deciles of the PS within these 2 strata will be examined. The significance of the difference for the age group will then again be assessed. If this difference persists, or if the number of variables that significantly differs, is large, then a new PS estimate will be calculated by adding one or more variables, removing variables whose significance disappears, creating interaction terms or creating new variables. These steps will be repeated until a balanced PS is obtained or one which minimizes the imbalance with the available data.

Further details of the analysis, including handling of missing data and potential non-linearity will be described in the statistical analysis plan.

Follow-up time will be evaluated according to the per protocol, as-treated, and intent-to-treat principles to account for time-varying treatment.

The verbatim terms used to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Patient demographics, medical history, disease history, current disease status and any previous IBD therapy will be collected at baseline. Ustekinumab therapy data (dose, start date and change in therapy [including change in dose]) will be collected for each patient throughout the study.

Milestones

Milestone	**Planned date**
Protocol submitted to PRAC	27 September 2017
Start of data collection	31 December 2019
End of data collection	30 September 2022
Submission of annual progress report 1	31 May 2020
Submission of annual progress report 2	31 May 2021
Submission of annual progress report 3	31 May 2022
Final report of study results	30 September 2023

5. MILESTONES

The initial planned dates for key milestones in this study are outlined below.

Milestone:	Planned Date:
Protocol submitted to PRAC	27 September 2017
Start of data collection	31 December 2019
End of data collection	30 September 2022
Submission of annual progress report 1	31 May 2020
Submission of annual progress report 2	31 May 2021
Submission of annual progress report 3	31 May 2022
Final report of study results	30 September 2023

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

CD	Crohn's disease
CRF	Case Report Form
EC	Ethics Committee
DSUR	Development Safety Update Report
ECCO	Europe Crohn's and Colitis Organisation
EFCCA	European Federation of Crohn's and Ulcerative Colitis Associations
EMA	European Medicines Agency
e-PRO	electronic-patient reported outcome
EU	European Union
GETAID	Groupe d'Etude Thérapeutique des Affections Inflammatoires Digestives
IBD	inflammatory bowel disease
ICF	informed consent form
ICH	International Conference on Harmonization
IgG1k	immunoglobulin G1 kappa
IL	interleukin
MedDRA	Medical Dictionary for Regulatory Activities
PS	propensity score
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
TB	tuberculosis
Th	T helper
TNF	tumor necrosis factor
VTE	venous thromboembolism

Definition of Term(s)

Study	The term "study" indicates the collection of data for research purposes only. The use of this term in no way implies that any interventional treatments or procedures, planned or otherwise, have been provided or performed.
Secondary use of data study	A study that has all information collected from source data or a retrospective database. Normally, there is no new collection of information from the patient, although this may be required to address specific questions. Studies/Programs/Related Research Activities with only one visit can be considered prospective or retrospective bearing in mind this definition and the source of information.
Prospective study	A study in which the outcome of interest occurs after the research begins.
Post-Authorization Safety Study (PASS)	Any study relating to an authorized medicinal product conducted with the aim of identifying, characterizing or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures.

6. BACKGROUND AND RATIONALE

6.1. Background

Ustekinumab (STELARA®) is a fully human immunoglobulin G1 kappa (IgG1k) monoclonal antibody to human interleukin (IL)-12/23p40 that binds with high affinity to the p40 subunit of human IL-12 and IL-23. By inhibiting interaction with the cell surface IL-12Rβ1 receptor protein, ustekinumab effectively neutralizes all IL-12 (T helper [Th]1) and IL-23 (Th17) mediated cellular responses. Abnormal regulation of IL-12 and IL-23 has been associated with multiple immune-mediated diseases including Crohn's disease (CD).

There is a significant medical need for new safe and effective therapies for moderate to severe, active CD. Inhibition of IL-12 and IL-23 and associated inflammatory pathways constitutes a novel mechanism of action for the treatment of CD. The therapeutic potential of this approach was demonstrated from the efficacy and safety results of a comprehensive Phase 2 and Phase 3, randomized double-blind, clinical studies for CD.

Ustekinumab (STELARA) was approved by the European Medicines Agency (EMA) for the treatment of adult patients with CD based on the results from the Phase 2 and Phase 3 clinical studies through Week 44 of maintenance treatment. A long-term extension of the patients enrolled in the Phase 3 clinical study is ongoing beyond Week 44 and is planned through Week 272. However, as part of the EMA regulatory approval for CD, the Marketing Authorization Holder committed to undertake a post-authorization safety study (PASS) in a cohort of patients with CD in the European Union (EU).

For the most comprehensive nonclinical and clinical information regarding the efficacy and safety of ustekinumab, refer to the latest version of the EU Summary of Product Characteristics for ustekinumab.[7]

6.2. I-CARE Prospective Observational Cohort Study

This protocol is a secondary data analysis of an externally owned database. The *source data* for this protocol will be the database of the *ongoing* and *independent* I-CARE cohort study. The I-CARE study is a European prospective, longitudinal, observational, multicenter cohort study, endorsed by Groupe d'Etude Thérapeutique des Affections Inflammatoires Digestives (GETAID), Europe Crohn's and Colitis Organisation (ECCO) and the European Federation of Crohn's and Ulcerative Colitis Associations (EFCCA). The objective of the independent I-CARE study is to assess the presence and extent of safety concerns (malignancies and serious infections risks) among 10,000+ patients with an established diagnosis of inflammatory bowel disease (IBD) (CD, ulcerative colitis). Patients in I-CARE are enrolled into the following groups:

- IBD patients who have never received biological agents or immunomodulators;
- IBD patients receiving thiopurines alone;
- IBD patients treated with anti-tumor necrosis factor (TNF) therapy alone (without any concomitant immunomodulators);

- IBD patients treated with anti-TNF therapy in combination with thiopurines or methotrexate;
- IBD patients treated with vedolizumab alone (without any concomitant immunomodulators);
- IBD patients treated with vedolizumab in combination with thiopurines or methotrexate;
- Crohn's disease patients treated with ustekinumab.

The primary objective of the independent I-CARE study is to describe the safety profile of anti-TNF agents alone or in combination with immunomodulators by monitoring malignancies, especially lymphoma, and opportunistic infections. For the ustekinumab cohort, we plan to observe 2000 patients for a maximum of 3 years, which will result in 6000 patients/years.

During the observational period in I-CARE, data collection is performed at least once yearly, at patient visits conducted within clinical practice. Additionally, where permitted per local regulations, patients complete an electronic-diary every month and an electronic-patient-reported outcomes (e-PRO) questionnaire on a yearly basis. The last visit is planned after 3 years of follow-up, at the end of the study, or at the time of early withdrawal from the study, if applicable.

The present study will use data collected in I-CARE to analyze the long-term safety of ustekinumab as observed in clinical practices across Europe.

6.3. Additional Pharmacovigilance Activities for Long-term Safety

The goal of this study is to address the postmarketing commitment to characterize the long-term safety profile of ustekinumab in adult patients with CD. This study will provide guidance to key stakeholders on key important risks associated with the use of ustekinumab, as described in Part III.5, 'Summary of the Pharmacovigilance Plan,' of the EU Risk Management Plan (RMP).

At the time of approval, ustekinumab had been studied beyond 52 weeks of continuous treatment in adult patients with CD in the IM-UNITI study, a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel group study, evaluating the efficacy and safety of ustekinumab maintenance therapy. At the time of approval, 2 years data was available for this study and included data from 397 patients who achieved a response to ustekinumab at Week 8 following an induction phase and were randomized to receive subcutaneous ustekinumab 90 mg every 8 weeks or every 12 weeks, or placebo during a maintenance (0 44 week) period, before entering the long-term extension (44-252 week) period. In this study, adverse events (per hundred subject years of follow-up) were similar between ustekinumab treated patients and placebo treated patients from Week 44 through to Week 96, and were similar in number to events reported in the blinded period of the maintenance period. However, the population in this study is small; therefore, there is still a need to further evaluate the long-term safety profile of ustekinumab in CD.

To address this need, a cohort of patients with CD who are receiving ustekinumab treatment, as well as cohorts of CD patients receiving anti-TNFs or immunomodulators and who are enrolled in the I-CARE study will be analyzed.

7. RESEARCH QUESTION AND OBJECTIVES

7.1. Research Question

The primary objective of this study is to evaluate the long-term safety of ustekinumab, and as compared to anti-TNF treatment in adult patients with CD.

7.2. Objectives

The objectives of this study are to:

- evaluate the long-term safety of ustekinumab, as measured by the occurrence of malignancies, serious infections, including opportunistic infection and tuberculosis (TB), and venous thromboembolisms (VTEs) associated with hospitalization in adult patients with CD treated with ustekinumab;
- evaluate the risk factors for malignancies, serious infections, including opportunistic infection and TB, and VTEs associated with hospitalization;
- estimate the long-term safety of adult patients with CD between users of ustekinumab and users of other CD therapies (anti-TNF agents and immunomodulators).

7.3. Hypothesis

No hypotheses are pre-specified. This study aims to describe the safety data collected for patients in a clinical practice setting.

8. RESEARCH METHODS

8.1. Study Design

This is an observational, post-authorization safety study to describe the safety profile of adult patients with CD. This study will be a PASS study constituting secondary use of data from patients enrolled into the independent I-CARE study a prospective, observational, multicenter cohort study. This study will include patients who receive ustekinumab treatment and those receiving other CD treatments within routine clinical practice, using data collected in the I-CARE study.

The source population is derived from the I-CARE study, enrolling patients with CD, ulcerative colitis or IBD at sites in 17 countries across Europe. This study will focus primarily on patients enrolled into I-CARE who are being treated for CD with ustekinumab. Patients enrolled into I-CARE will complete an electronic-diary on a monthly basis and an e-PRO questionnaire on a yearly basis. Additionally, a gastroenterologist will complete an annual summary at least once yearly. Patients enrolled in the study will be observed for 3 years. The final patient population of the I-CARE study will be at least 10,000 IBD patients split into 6 patient groups, with approximately 2,000 patients in the ustekinumab cohort of CD patients.

8.2. Setting and Patient Population

8.2.1. Study Setting and Duration

This study will be conducted using data collected from a cohort of patients who will be enrolled into I-CARE and who are treated with ustekinumab or other treatments for CD. The I-CARE study will be conducted in 17 countries across Europe, and patients enrolled will be observed for 3-years.

8.3. Variables

The I-CARE protocol summarizes the frequency and timing of data collection in the I-CARE study. Data collected in the I-CARE study will be extracted from the I-CARE database to be used in this study.

8.3.1. Outcomes

The outcomes of this study comprise:

- Malignancies.
- Serious infections (including opportunistic infections and TB).
- Events of VTE recorded with/during hospitalization.

The *covariates* include (but may not be limited to):

- Age
- Gender
- Year of cohort entry
- Disease duration
- Extent of disease
- Treatments for CD that are not study exposures (eg, systemic steroids)
- Disease activity (modified Harvey-Bradshaw Index; see ANNEX 3) before or at start of cohort-defining treatment, if available
- History of previous treatments with other anti-TNF agents
- History of hospitalization for CD

Other risk factors may be identified after analysis of the descriptive data.

8.3.2. Exposures

The main exposure of interest is treatment with ustekinumab prescribed for CD. The primary comparator will be anti-TNF agents prescribed for CD (ie, infliximab, adalimumab, including biosimilars). The secondary comparator group will comprise immunomodulators.

For primary data analysis, duration of therapy exposure will be calculated from informed consent date as an index date for patients starting therapy prior to enrollment or from the start of index treatment if the therapy was started after enrollment.

Additionally, a sensitivity analysis that will use exposure duration calculated from the "date starting the last continuous use" as an index date will be performed.

A separate sensitivity analysis whereby exposure is restricted to patients initiating cohort-defining medication after registry enrollment is planned.

Over time, CD patients who initiate ustekinumab may have received or may later receive comparator treatments in various sequences.

In the primary analysis for malignancy outcomes, the exposure risk window would end at the date of discontinuation from registry participation or the annual report data cutoff, whichever occurred first. Analyses will consider a conservative approach with ustekinumab which is (1) to implement a hierarchical order of exposure classification for malignant outcomes and (2) to account for malignancy lag time bias in the study analyses as described in more detail in Section 8.6.1. For non-malignant outcomes, a 91-day at risk window will be applied for the primary analysis. Additionally, sensitivity analyses of exposure classification for non-malignant outcomes are described in Section 8.6.1.

8.3.3. Selection Criteria

The source population of patients will be those enrolled in the I-CARE study. Patients will be included in data collection if they meet the following eligibility criteria:

1. Male or female aged >18 years with a confirmed diagnosis of CD made at least 3 months before enrollment based on usual radiological, endoscopic or histological criteria.

2. Have received treatment with ustekinumab or other CD therapies (anti-TNF agents prescribed for CD [ie, infliximab, adalimumab, including biosimilars] and immunomodulators) per local label and clinical practice.

Because this is a non-interventional, secondary data analysis of an externally owned database of patients enrolled into the independent I-CARE study during routine clinical practice, therapy decisions will be made at the discretion of the participating physician, per routine clinical practice, prior to enrollment in the study; the sponsor will not provide guidance on any aspect of therapy, patient clinical management, or therapy dose selection.

8.3.4. Safety Outcomes

Safety outcomes will be described using data collected from the I-CARE study.

Data for malignancies, serious infections, including opportunistic infections and TB, and hospitalizations (including those with events of VTE), related or not to CD, will be reported by the patient and validated at least yearly by gastroenterologists in the I-CARE study and will be collected for this study. All incoming hospitalization reports/charts will be reviewed for malignancies, serious infections and events of VTE; these will be adjudicated by dedicated

adjudication committees, and validated and non-validated events will be summarized. Further details are available within the I-CARE protocol.[1]

All other adverse drug reactions not actively solicited (ie, spontaneously reported) in the I-CARE study in patients who receive ustekinumab will be collected and will be summarized in aggregate listings that will be included in the end of study report and where applicable in any interim reports.

Concomitant therapies administered in conjunction with serious adverse drug reactions that are reported within the I-CARE study will be collected.

8.4. Study Size

The independent I-CARE study will enroll more than 10,000 adult patients with IBD (up to 17,600 patients), receiving IBD treatments, including a cohort of approximately 2,000 patients with CD receiving ustekinumab at entry or during follow-up. The I-CARE study was powered to detect a lymphoma hazard ratio of at least 3.5 in the groups of patients receiving thiopurines, either alone or in combination with anti-TNF, relative to patients not receiving thiopurines (ie, receiving anti-TNF alone or no immunomodulators).

The required sample sizes to detect a hazard rate of 2.0 for different baseline incidence rates are shown in Table 1. The lowest incidence (0.0064 per patient year) is based on the malignancy incidence rate in patients treated with infliximab reported from the TREAT Crohn's registry that collected data from 6,273 North American CD patients as of 2010.[3] Sample size requirements assuming a 1:1 and a 1:2 ratio of ustekinumab:other biologics are presented.

With a type 1 error rate of 5%, a power of 80% for a 2-sided test, 1:2 ratio comparing ustekinumab and other biologics (anti-TNF agents), a 20% of loss to follow-up, an accrual period of 1 year, and a follow-up time of 3 years, 1032 ustekinumab users would be needed to detect a hazard ratio of 2.0 (Table 2). Considering a 1:1 ustekinumab vs comparator treatment allocation, 1544 ustekinumab users would provide 80% power to detect a HR of 2.0. However, with the current assumptions and a 1:1 ratio comparing ustekinumab and other biologics, including 2,000 patients per treatment cohort would increase the power to 89%.

Any of the above presented sample sizes for the primary outcome of all malignancy (N 1032 to 2000) is expected to be adequate for the secondary outcome of serious infections, which occur at a higher incidence rate than malignancy.

Table 1: Sample Sizes Required to Detect a Hazard Rate of 2.0 by Baseline Incidence Rate, assuming 1-year accrual and 3- year follow-up, 1:2 UST vs comparator treatment allocation

(type 1 error=0.05, type 2 error=0.2, annual loss to follow-up rate 20%, uniform accrual, exponential time to event distribution)

Baseline incidence rate (/patient year)	Ustekinumab users, N	Comparators, N	Total N needed	Total events needed, N
0.0064	1032	2064	3096	65
0.0080	828	1656	2484	65
0.0100	666	1332	1998	65
0.0120	558	1116	1674	65
0.0140	480	960	1440	65
0.0160	422	844	1266	65
0.0180	377	754	1131	65
0.0200	341	682	1023	65

Table 2: Sample Sizes Required to Detect a Hazard Rate of 2.0 by Baseline Incidence Rate, assuming 1-year accrual and 3- year follow-up, 1:1 treatment allocation

(type 1 error=0.05, type 2 error=0.2, annual loss to follow-up rate 20%, uniform accrual, exponential time to event distribution)

Baseline incidence rate (/patient year)	Ustekinumab users, N	Comparators, N	Total N needed	Total events needed, N
0.0064	1544	1544	3088	65
0.0080	1240	1240	2480	65
0.0100	996	996	1992	65
0.0120	834	834	1668	65
0.0140	717	717	1434	65
0.0160	630	630	1260	65
0.0180	563	563	1126	65
0.0200	509	509	1018	65

8.5. Data Management

The data source for this study will be the database for the I-CARE study. GETAID will be responsible for data handling and management in I-CARE. Data for patients who meet the inclusion criteria will be extracted on an annual basis from the I-CARE database. Patient data will be handled in compliance with all applicable privacy laws.

8.6. Data Analysis

Statistical analyses will be conducted by I-CARE according to a Statistical Analysis Plan developed in close collaboration with the sponsor. The analysis set will include all patients who fall within the inclusion and exclusion criteria for this study.

Progress of the registry, including data analysis, will be included in the Development Safety Update Report/Periodic Safety Update Report (DSUR/PSUR) per the regulated timelines. These analyses will describe each cohort in terms of patient characteristics. For each of the study cohorts, annual enrollment will be described, along with the frequency of study outcomes and cumulative person-years of follow-up accrued.

8.6.1. Main Summary Measures

The verbatim terms used to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Patient demographics, medical history, disease history, current disease status and any previous IBD therapy will be collected at baseline. Ustekinumab therapy data (dose, start date and change in therapy [including change in dose]) will be collected for each patient throughout the study.

The event rate of safety outcomes (malignancies, serious infection, including opportunistic infection and TB, and VTE associated with hospitalization) will be estimated for each cohort.

For non-malignant outcomes, a 91-day at risk window will be applied for the primary analysis, where the outcome will be assigned to index drug and 91 days after last dose of index drug. If a new treatment is initiated during this period, the outcome will be assigned to both previous and current treatment.

Additionally, the following sensitivity analyses will be performed:

1. Analysis including only patients who would not initiate biologic treatment within 91 days after the last dose of index drug
2. Analysis using an "on treatment" approach, where the outcome will be assigned to index drug only during the treatment with that drug (between first and the last dose of index drug administration)
3. Analysis using a 91 days at risk window assigned to treatment where the outcome will be assigned to index drug, but not to new treatment, if that is initiated during 91 days after the last dose of index drug
4. Analysis including only patients who would not terminate treatment (including patients who did not switch) with index drug throughout the observation period

For malignancy outcomes, patients will be assigned to treatment cohorts based on a hierarchical order of exposure, as shown below:

- STELARA (ustekinumab)
- Anti-TNF biologics
- Immunomodulator therapies

Exposure to any therapy higher in the hierarchy precludes inclusion in cohorts lower in the order. For definitions of exposures, see Section 8.3.2.

Similarly, malignancies will be attributed to a treatment cohort based on exposures prior to the event and follow the same hierarchical order. For example, following exposure to ustekinumab, any subsequent malignancies would be attributed to ustekinumab, regardless of past or future exposures and duration of other therapies.

In addition to assignment of malignancy events to treatment cohorts based on a hierarchical order of exposure, lag time bias will be accounted for in the malignancy risk window. As a primary analysis, malignancies occurring within 12 months of actual treatment initiation will be excluded. Therefore, for malignancy outcomes, the exposure risk window for an individual patient will begin 12 months after the first exposure to ustekinumab, or from the time of the informed consent date if the patient was exposed to ustekinumab prior to registry enrollment and the ustekinumab treatment initiation date was not recorded. The exposure risk window would end at the date of discontinuation from registry participation or the annual report data cutoff, whichever occurred first. Furthermore, sensitivity analyses taking into account (1) no lag time and (2) a 6-month lag time period, whereby cases occurring within 6 months of actual treatment initiation are excluded, will be performed.

All other adverse drug reactions not actively solicited in the I-CARE study in patients who received ustekinumab will be collected and will be summarized in aggregate listings that will be included in the end of study report and where applicable in any interim reports. Where possible, the cumulative event rate of primary and secondary outcomes will be estimated using time-to-event analyses, overall by cohorts and then in stratified analyses. Stratification factors (as measured at study entry) will be evaluated one at a time and will include gender, time since initial CD diagnosis, CD hospitalization, and previous use of systemic steroids; and for biologic cohorts, concurrent use of immunomodulators and history of previous biologic use.

For each safety outcome, risk will be compared between ustekinumab and comparators using survival analysis (Kaplan Meier plots and Cox proportional hazards regression models). Users of ustekinumab and users of anti-TNF agents will be compared. Study exposures will be treated as time-dependent variables. Hazard ratios will be used to estimate relative risk. Candidate variables to evaluate as potential confounders include the list of covariates under Section 8.3.1, Outcomes.

The study is not randomized; as a result, comparisons across cohorts will be biased. When comparing the ustekinumab treatment cohort and the anti-TNF treatment cohort, to adjust for non-random treatment assignment, propensity score (PS) analysis will be performed to compare the following outcomes:

- incidence rate of malignancies
- incidence rate of serious infections
- incidence rate of venous thromboembolisms (VTEs) associated with hospitalization.

The PS calculation will be repeated for each summary report under the condition that new patients are enrolled. Outcome-specific propensity scores will be developed for each of the above outcomes, and details will be provided with the reports. Because only limited data are collected through follow-up, the PS will not be recalculated following treatment switch.

The PS will be collected using potential confounders listed in Section 8.3. For the analysis of the endpoints of the present study the PS stratified by quintiles will be used.

The quality of the PS will be evaluated as follows: For each of the variables included in the PS, the difference between the treatment arms will be compared by PS stratum[5,4,6] using standard comparison tests to evaluate the significance of the differences. If differences are detected for a small number of variables and the number of affected strata is limited, then a sub classification will be done after which the check for difference will be repeated. As an example: if a difference in age persists only in the third quintile of the PS, then this quintile is divided, and the fifth and sixth deciles of the PS within these 2 strata will be examined. The significance of the difference for the age group will then again be assessed.[4] If this difference persists, or if the number of variables that significantly differs, is large, then a new PS estimate will be calculated by adding one or more variables, removing variables whose significance disappears, creating interaction terms or creating new variables. These steps will be repeated until a balanced PS is obtained or one which minimizes the imbalance with the available data.

Further details of the analysis, including handling of missing data and potential non-linearity will be described in the statistical analysis plan.

Follow-up time will be evaluated according to the per protocol, as-treated, and intent-to-treat principles to account for time-varying treatment.

8.6.2. Interim Analysis

Interim analyses will be performed annually from one year after completion of enrollment or from March 2020, whichever comes first, until the end of the study. The final study report is currently planned to be available in 2022. The scope of the interim analysis will be documented in the Statistical Analysis Plan.

8.7. Quality Control

GETAID, as the sponsor of the I-CARE study, will be solely responsible for data quality and integrity.

8.8. Limitations of the Research Methods

A limitation of the research method is recognized within this study as the sample size of patients included in the study will be dependent on the number of patients enrolled in the I-CARE study and who meet the selection criteria listed in this study (see Section 8.3.3).

Because the I-CARE study is an observational study, the actual frequency of clinical follow-up will depend on practice patterns in the usual care setting. This could lead to incomplete data collection, which is not under the control of the sponsor. Additionally, limited recall of adverse events at the patient visits conducted within clinical practice may lead to incomplete information or under reporting of some adverse events or bias.

The observational nature of the I-CARE study does not exclude selection bias and the follow-up time within the study limits observation of patients to 3 years.

9. PROTECTION OF HUMAN SUBJECTS

This study will use data collected from patients in the I-CARE study; therefore, no patients will participate in this study. This study will use only de-identified data. All study reports will contain aggregate data only and will not identify individual patients or physicians.

In accordance with the laws and regulations applicable in each country, GETAID and/or National Coordinators will be responsible for obtaining approval of the protocol and its amendments, Informed Consent Form (ICF), I-CARE study recruitment procedures, and any other relevant documents in connection with the I-CARE study, from the Ethics Committee (EC) prior to commencement of the I-CARE study. In the event the EC requires changes in the protocol, ICF or GETAID intends to change the Protocol or ICF, such changes will not be implemented until Janssen is notified.

GETAID will be responsible for ensuring that the ICF is signed by or on behalf of each human subject before the first I-CARE study related procedure. This ICF shall be the document approved by each of the I-CARE study sites' related ECs, prior to the subject's participation in the study. If requested, GETAID will provide Janssen with a copy of the positive opinion letter from each EC, the approved ICF and any relevant communications with each EC, which includes but is not limited to information which may affect the conduct of the I-CARE study.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS

GETAID will provide the sponsor with an annual aggregate summary of all solicited adverse events and all other adverse drug reactions not actively solicited (expected or unexpected, deaths, transmission of an infectious agent), and pregnancies related to the I-CARE study that occurred after treatment with a Janssen medicinal product.

10.1. Definitions and Classifications

10.1.1. Adverse Event Definitions

Adverse Event

An adverse event is any untoward medical occurrence in a patient administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can be any unfavorable and unintended sign (including an abnormal finding or lack of expected pharmacological action), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition based on International Conference on Harmonization [ICH]).

This includes any occurrence that is new in onset or aggravated in severity from the baseline condition, or abnormal results of any diagnostic procedures that are conducted per clinical practice.

Adverse Drug Reaction

An adverse drug reaction (ADR) is defined as a response to a medicinal (investigational or non-investigational) product that is noxious and unintended.

An ADR, in contrast to an adverse event, is characterized by the fact that a causal relationship between the medicinal product and the occurrence is suspected. All adverse events judged by either the reporting physician or the sponsor as having a reasonable causal relationship to a medicinal product qualify as ADRs.

Serious Adverse Event

A serious adverse event, based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use, is any untoward medical occurrence that at any dose:

- Results in death
- Is life threatening
  (the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is medically important*

* Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above.

Unlisted (Unexpected) Adverse Event

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. The expectedness of an adverse event will be determined by whether or not it is listed in the applicable reference safety information.[7]

NOTE: Unlistedness of an event is only relevant for the sponsor's reporting obligations, but is not determining reporting requirements of the participating physician to the sponsor or Marketing Authorization Holder.

Product Quality Complaint

A product quality complaint (PQC) is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a product after it is released for distribution.

10.1.2. Attribution Definitions

An adverse event is considered associated with the use of the product under study if the attribution is possible, probable, or very likely according to the definitions listed below:

Not Related

An adverse event that is not related to the use of the product under study.

Doubtful

An adverse event for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), and/or the relationship in time suggests that a causal relationship is unlikely.

Possible

An adverse event that might be due to the use of the product under study. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An adverse event that might be due to the use of the product under study. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very Likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

10.1.3. Severity Criteria

Where applicable, an assessment of severity grade will be made using the following general categorical descriptors:

Mild

Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate

Sufficient discomfort is present to cause interference with normal activity.

Severe

Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The participating physician should use clinical judgment in assessing the severity of events not directly experienced by the patient (eg, laboratory abnormalities).

10.2. Special Situations

Safety events of interest for a Janssen product under study that may require expedited reporting and/or safety evaluation by Janssen include, but are not limited to:

- Drug exposure during pregnancy (maternal and paternal)
- Non-serious event malignancy in patients 30 years of age and younger, whether related to product or not
- Overdose of a product
- Exposure to a product from breastfeeding
- Suspected abuse/misuse of a product
- Inadvertent or accidental exposure to a product
- Any failure of expected pharmacological action (ie, lack of effect) of a product
- Unexpected therapeutic or clinical benefit from use of a product
- Medication error involving a product (with or without patient exposure to the Janssen product under study, eg, name confusion)
- Suspected transmission of any infectious agent via administration of a product
- Off-label use of a product (use of a product outside of its approved label)

These safety events may not meet the definition of an adverse event; however, from a policy perspective, they are treated in the same manner as adverse events.

10.3. Procedures

In this non-interventional study, ustekinumab is the Janssen product under study and other CD therapies (anti-TNF agents and immunomodulators) are the non-Janssen product(s) under study (ie, a medicinal product under study that is not marketed by Janssen).

GETAID undertakes to report any adverse event, special situation and/or PQC according to the procedures set out by Janssen in the Master Service Agreement and/or Work Order. GETAID will ensure that its employees and sub-contractors are appropriately qualified, have documented training and comply with adverse event, special situations and PQCs reporting obligations.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results of the study will be reported in a clinical study report generated by the sponsor, which will contain data collected from the I-CARE study. The sponsor will register and/or disclose the existence of and the results of clinical studies as required by law.

Patient identifiers will not be used in the publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection

(except any publication by the investigator) shall be the property of the sponsor as author and owner of copyright in such work.

Further details of publication policies and practices are provided in Annex 1.12.

12. REFERENCES

1. Clinical Protocol I-CARE. Ibd CAncer and seRious infections in Europe. Groupe d'Etude Thérapeutique des Affections Inflammatoires Digestives (GETAID). Version 6. 15 December 2017.
2. Lakatos E, Lan K. A comparison of sample size methods for the logrank statistic. Stat Med. 1992;11(2):179-191.
3. Lichtenstein G, Feagan B, Cohen R et al. Drug therapies and the risk of malignancy in Crohn's disease: results from the TREAT™ Registry. Am J Gastroenterol. 2014;109(2):212-223.
4. Rosenbaum P, Rubin D. Reducing bias in observational studies using subclassification on the propensity score. J Am Stat Assoc. 1984;79(387):516-524.
5. Rosenbaum P, Rubin D. The central role of the propensity score in observational studies for causal effects. Biometrika. 1983;70(1):41-55.
6. Rubin D. Estimating causal effects from large data sets using propensity scores. Ann Intern Med. 1997;127(8 Pt 2):757-763.
7. STELARA [Summary of Product Characteristics]. Beerse, Belgium: Janssen-Cilag International NV; 2017.

ANNEX 1: STAND-ALONE DOCUMENTS AND ADDITIONAL INFORMATION

Annex 1.1: List of Stand-alone Documents

Title	Reference No	Date
Ibd CAncer and seRious infections in Europe Protocol	EudraCT NUMBER: 2014-004728-23	15 December 2017

Annex 1.2: Regulatory Documentation

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, where applicable. A study may not be initiated until any applicable local regulatory requirements are met.

Annex 1.3: Ethics Compliance

In accordance with the laws and regulations applicable in each country, GETAID and/or National Coordinators will be responsible for obtaining approval of the I-CARE protocol and its amendments, Informed Consent Form (ICF), I-CARE study recruitment procedures, and any other relevant documents in connection with the I-CARE study, from the Ethics Committee (EC) prior to commencement of the I-CARE study. In the event the EC requires changes in the protocol, ICF or GETAID intends to change the Protocol or ICF, such changes will not be implemented until Janssen is notified.

Annex 1.4: Patient Consent

GETAID will be responsible for ensuring that the ICF is signed by or on behalf of each human subject before the first I-CARE study related procedure. This ICF shall be the document approved by each of the I-CARE study sites' related ECs, prior to the subject's participation in the study. If requested, GETAID will provide Janssen with a copy of the positive opinion letter from each EC, the approved ICF and any relevant communications with each EC, which includes but is not limited to information which may affect the conduct of the I-CARE study.

Annex 1.5: Patient Identification and Enrollment

This study will be conducted using data collected from a cohort of patients who will be enrolled into I-CARE. All patient identification and enrollment will be the responsibility of GETAID.

Annex 1.6: Patient Data Protection

GETAID, being the sponsor of the I-CARE study, will be responsible for maintenance of all records and data for the study, in compliance with all applicable legal and regulatory requirements, as well as with generally accepted conventions such as the Declaration of Helsinki and ICH-GCP.

Collection, processing and disclosure of personal data, such as patient health and medical information is subject to compliance with applicable data protection and security laws and regulations. When collecting and processing personal data, GETAID agrees to take appropriate measures to safeguard those data, maintain confidentiality of patient health and medical information, to properly inform the concerned data subjects about the collection and processing of

their personal data, to grant data subjects reasonable access to their personal data and to prevent access by unauthorized persons.

Annex 1.7: Case Report Form Completion

The data source for this study will be the database for the I-CARE study. GETAID will be responsible for data handling and management in I-CARE.

Annex 1.8: Monitoring

GETAID is solely responsible for the monitoring of the I-CARE study, in compliance with Good Clinical Practice and GETAID standard operating procedures.

Annex 1.9: On-Site Audits

The sponsor or sponsor's authorized representative and any governmental agency which regulates the sponsor may, at all reasonable time during the term of the agreement and for 3 years thereafter and upon reasonable notice, inspect, audit the books and records of GETAID with respect to the services relating to the study and for the sole purpose of evaluating GETAID's compliance with the agreement made with the sponsor and any law, regulation or policy applicable to the sponsor.

Annex 1.10: Record Retention

GETAID shall retain all applicable books and records for 3 years subsequent to the expiration or termination of the agreement with the sponsor, or for a longer period as required by applicable local and international regulatory requirements. GETAID shall respond within 1 business day of receipt of the sponsor's request for information and documentation required in relation to an FDA or other regulatory authority's request.

Annex 1.11: Study Completion/Termination

The term of the agreement between the sponsor and GETAID for this study will end in July 2020 or 3 years after the last patient is enrolled into the I-CARE study, but not later than the sponsor's receipt of a final study report or written notification that the study results have been accepted for publication in a peer reviewed journal, whichever is later.

Annex 1.12: Use of Information and Publication

All data (including without limitation, case report forms, written, printed, graphic, video and audio material, and information contained in any computer database or computer readable form) created or developed during the course of the I-CARE study will be the property of GETAID, which may utilize the data in any way it deems fit, subject to and in accordance with applicable privacy laws and the terms of this agreement.

All information concerning ustekinumab or Janssen's or its affiliates' operations, such as patent applications, formulas, manufacturing processes, basic scientific data, prior clinical data and formulation information supplied by Janssen or its affiliates to GETAID and not previously published are considered confidential and shall remain the sole property of the sponsor. GETAID agrees to maintain this information in confidence, to use this information only to accomplish this study, and not to use it for other purposes without the sponsor's prior written consent.

GETAID shall be free to publish or publicly present the results of the study and any background information provided by the sponsor that is necessary to include in any publication of study results or necessary for other scholars to verify such research results. Prior to submission for publication or presentation, GETAID will provide the sponsor with at least 60 days for review of a manuscript. The sponsor and GETAID will arrange expedited reviews for abstracts, poster presentations or other materials. Notwithstanding the foregoing, no paper that incorporates Janssen confidential information will be submitted for publication without prior written consent of the sponsor. If requested in writing, GETAID will withhold such publication for up to an additional 90 days to allow for filing a patent application. GETAID warrants the compliance of all study investigators and other personnel involved with the study, with the provisions of this paragraph. In the event that GETAID does not publish the study results within 12 months following the date that each result report is delivered to Janssen, then the sponsor shall have the right to publish such results.

GETAID grants to the sponsor and its affiliates a non-exclusive, worldwide, royalty-free, paid up license for commercial and non-commercial use of the study results contained in the results reports and the interpretation out of the study data that are owned by GETAID.

ANNEX 2: ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Section 1: Research question	Yes	No	N/A	Page Number(s)
1.1 Does the formulation of the research question clearly explain:				
1.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	16
1.1.2 The objectives of the study?	☒	☐	☐	17
1.2 Does the formulation of the research question specify:				
1.2.1 The target population? (i.e. population or subgroup to whom the study results are intended to be generalized)	☒	☐	☐	17
1.2.2 Which formal hypothesis(-es) is (are) to be tested?	☐	☒	☐	
1.2.3 if applicable, that there is no a priori hypothesis?	☒	☐	☐	17

Comments:

Section 2: Source and study populations	Yes	No	N/A	Page Number(s)
2.1 Is the source population described?	☒	☐	☐	17
2.2 Is the planned study population defined in terms of:				
2.2.1 Study time period?	☒	☐	☐	17
2.2.2 Age and sex?	☒	☐	☐	19
2.2.3 Country of origin?	☒	☐	☐	1
2.2.4 Disease/indication?	☒	☐	☐	18
2.2.5 Co-morbidity?	☐	☐	☒	
2.2.6 Seasonality?	☐	☐	☒	
2.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	19

Comments:

Section 3: Study design	Yes	No	N/A	Page Number(s)
3.1 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	18
3.2 Is the study design described? (e.g. cohort, case-control, randomized controlled trial, new or alternative design)	☒	☐	☐	17
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	20
3.4 Is sample size considered?	☒	☐	☐	19
3.5 Is statistical power calculated?	☒	☐	☐	19

Comments:

Section 4: Data sources	Yes	No	N/A	Page Number(s)
4.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
4.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc)	☒	☐	☐	17-18
4.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc)	☒	☐	☐	17-19
4.1.3 Covariates?	☒	☐	☐	18
4.2 Does the protocol describe the information available from the data source(s) on:				
4.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	19
4.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	19
4.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	19
4.3 Is the coding system described for:				
4.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☒	☐	
4.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	20
4.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☒	☐	
4.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments: WHO coding of drug therapies is described in the SAP.

Section 5: Exposure definition and measurement	Yes	No	N/A	Page Number(s)
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorizing exposure)	☒	☐	☐	18
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	SAP
5.4 Is exposure classified based on biological mechanism of action?	☒	☐	☐	18
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☒	☐	21

Comments: GETAID's I-CARE protocol specifies validity of exposure measurement.

Section 6: Endpoint definition and measurement	Yes	No	N/A	Page Number(s)
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	19
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	

Comments:

Section 7: Biases and Effect modifiers	Yes	No	N/A	Page Number(s)
7.1 Does the protocol address:				
7.1.1 Selection biases?	☒	☐	☐	22
7.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	22
7.2 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☒	☐	11
7.3 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☒	☐	
7.4 Does the protocol address other limitations?	☐	☒	☐	

Comments: Details of how confounding and modifying effect will be investigated and coped with are described in the SAP.

Section 8: Analysis plan	Yes	No	N/A	Page Number(s)
8.1 Does the plan include measurement of absolute effects?	☒	☐	☐	20
8.2 Is the choice of statistical techniques described?	☒	☐	☐	20
8.3 Are descriptive analyses included?	☒	☐	☐	20
8.4 Are stratified analyses included?	☒	☐	☐	20
8.5 Does the plan describe the methods for identifying:				
8.5.1 Confounders?	☒	☐	☐	
8.5.2 Effect modifiers?	☒	☐	☐	
8.6 Does the plan describe how the analysis will address:				
8.6.1 Confounding?	☒	☐	☐	
8.6.2 Effect modification?	☒	☐	☐	

Comments:

Section 9: Quality assurance, feasibility and reporting	Yes	No	N/A	Page Number(s)
9.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☐	☒	
9.2 Are methods of quality assurance described?	☐	☐	☒	
9.3 Does the protocol describe quality issues related to the data source(s)?	☐	☒	☐	
9.4 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	19
9.5 Does the protocol specify timelines for				
9.5.1 Start of data collection?	☒	☐	☐	21
9.5.2 Any progress report?	☒	☐	☐	21
9.5.3 End of data collection?	☒	☐	☐	21
9.5.4 Reporting? (i.e. interim reports, final study report)	☒	☐	☐	21
9.6 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	6
9.7 Are communication methods to disseminate results described?	☒	☐	☐	27
9.8 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 10: Ethical issues	Yes	No	N/A	Page Number(s)
10.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☐	☐	☒	22
10.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	22
10.3 Have data protection requirements been described?	☐	☐	☒	22

Comments:

ANNEX 3: MODIFIED HARVEY-BRADSHAW INDEX (HBI)

Harvey-Bradshaw Index (HBI): A Simple Index of Crohn's Disease Activity

The Harvey-Bradshaw Index (HBI) is considered a simple measure of Crohn's disease (CD) activity.[a,b] It consists of 5 questions, one each related to general well-being, abdominal pain, and number of liquid stools per day (all, on the prior day), and abdominal mass and CD complications. Each question is given a score based on the answer chosen, and the scores are totaled to give the overall HBI. (A score <5 is considered remission and scores >16 are considered severe disease.)

In I-CARE, patients (independently) fill out the HBI on a monthly basis. As abdominal mass is difficult to assess by patients themselves, a modified HBI, omitting the question on abdominal mass, will be used (shown below).

A simple index of Crohn's disease activity

We ask you to appreciate the degree of disease activity of your Crohn's disease

General wellbeing (yesterday)

|_|

Abdominal pain (yesterday)

|_|

Number of liquids stools per day (yesterday)

○ 0
○ 1
○ 2
○ 3
○ 4
○ 5
○ 6
○ 7
○ 8
○ 9
○ 10
○ 11
○ 12
○ 13
○ 14
○ 15
○ 16
○ 17
○ 18
○ 19
○ 20

Complication

☐ Joint pain
☐ Uveitis
☐ Erythema nodosum
☐ Oral aphtous ulcers
☐ Pyoderma gangrenosum
☐ Anal fissure
☐ Active anal fistula
☐ Anal abscess
☐ None

Scores: |_|_|

[a] Harvey RF, Bradshaw JM. A simple index of Crohn's disease activity. Lancet. 1980;315(8167):514.

[b] British Columbia Ministry of Health Services. Worksheet based on the Harvey Bradshaw Index. British Columbia Ministry of Health Services website. https://www.health.gov.bc.ca/exforms/pharmacare/5374fil.pdf. Accessed September 23, 2010.

INVESTIGATOR AGREEMENT

STELARA (ustekinumab)
Protocol RRA-20745 Amendment 1
INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen-Cilag Polska

Signature: PPD Date: PPD
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

Status: Approved 40
Protocol version: 6.0 / Version date: 18 May 2021

Signature

User	Date	Reason
Oster-Gozet Laurence PPD	13-May-2022 13:55:29 (GMT)	Document Approval