1. ABSTRACT

Name of Sponsor/Company	Janssen Cilag International NV
Name of Finished Product	STELARA®
Name of Active Ingredient(s)	CNTO1275 (ustekinumab))

* Janssen EMEA Medical Affairs is an organization that operates through different legal entities in various countries. The legal entity acting as the Sponsor for Janssen EMEA Medical Affairs studies may vary, such as, but not limited to Janssen Pharmaceutica NV or Janssen Cilag International. The term "Sponsor" is used throughout the protocol to represent these various legal entities.

Protocol No.: RRA-20745

Title of Study: 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 Party: PPD

Keywords: Non-interventional Post-authorization Safety Study

EU PAS Register Number: EUPAS21954

Marketing Authorization Holder(s): Janssen Cilag International NV

Names and Affiliations of Principal Investigator: PPD

Study Countries: United Kingdom, France, Spain, Greece, Germany, Italy, Israel, Belgium, Portugal, Ireland, Hungary, Denmark, Sweden, Netherlands and Poland.

Publication (Reference): None

Study Period: 4 March 2016 – 17 March 2023

Background and Rationale: STELARA® (ustekinumab) is a fully human immunoglobulin G1 kappa monoclonal antibody that binds with high affinity to the common p40 subunit of human interleukin (IL) 12 and IL 23 (IL 12/23p40). Ustekinumab prevents IL-12 and IL-23 bioactivity by preventing their interaction with their cell surface IL-12 receptor beta-1 (IL 12Rβ1) receptor protein. Through this mechanism of action, ustekinumab effectively neutralizes IL-12 (T helper [Th]1)- and IL-23 (Th17)-mediated cellular responses.

The clinical development program that supported the approval of ustekinumab in Crohn's disease consisted of a Phase 2a proof-of-concept study, a Phase 2b dose-ranging study, two Phase 3 intravenous induction studies, and data through Week 44 of a Phase 3 randomized withdrawal subcutaneous (SC) maintenance study.

To ensure a longer-term safety evaluation, subjects who were enrolled in the Phase 3 maintenance study and who might benefit from continued treatment, in the opinion of the investigator, could continue in the long-term extension (LTE) through Week 272 (5 total years of treatment). A total of 718 subjects continued in the LTE after Week 44. Additional data accrued through 96 weeks of treatment continued to support the overall favorable benefit-to-risk profile of ustekinumab. No new types or patterns of AEs were identified and no clear impact of ustekinumab on the safety events of serious infection, venous thromboembolism (VTE) and malignancy were seen.

In addition to the LTE, as part of the European Medicines Agency (EMA) regulatory approval for Crohn's disease, the Marketing Authorization Holder committed to undertake a post-authorization safety study (PASS) in a cohort of adult patients with Crohn's disease in the European Union (EU), RRA-20745, to analyze the long-term safety profile of ustekinumab in adult patients with Crohn's disease. RRA-20745 provides additional pharmacovigilance data to further characterize key important risks associated with the use of ustekinumab, as described in Part III.2, 'Additional Pharmacovigilance Activities,' of the EU Risk Management Plan.

This study, RRA-20745, was a secondary data analysis study in which data were analyzed for 3 cohorts of patients with Crohn's disease who received treatment with ustekinumab, anti-tumor necrosis factor (TNF) agents or non-biologic immunomodulators. The source data for RRA-20745 is the database of the independent Ibd CAncer and seRious infections in Europe (I-CARE) cohort study. The I-CARE study is a European prospective, longitudinal, observational, multicenter cohort study, sponsored by the Groupe d'Etude Thérapeutique des Affections Inflammatoires Digestives (GETAID), and endorsed by the European Crohn's and Colitis Organization (ECCO) and the European Federation of Crohn's and Ulcerative Colitis Associations (EFCCA). The objective of the observational 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) (Crohn's disease, ulcerative colitis).

Research Question and Objectives:

The primary objective of RRA-20745 was to evaluate the long-term safety of ustekinumab, and as compared to anti-TNF agents and non-biologic immunomodulators in adult patients with Crohn's disease.

The objectives of RRA-20745 were to:

- Evaluate the long-term safety of ustekinumab, as measured by the occurrence of malignancies, serious infections, including opportunistic infection and tuberculosis (TB), and VTEs associated with hospitalization in adult patients with Crohn's disease 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 Crohn's disease between users of ustekinumab and users of other Crohn's disease therapies (anti-TNF agents and immunomodulators).

Study Design: This was an observational PASS to describe the safety profile of ustekinumab in adult patients with Crohn's disease. This study, RRA-20745, is a PASS constituting secondary use of data collected from patients enrolled into the independent I-CARE study, a European prospective, observational, multicenter cohort study sponsored by GETAID.

Patients enrolled into I-CARE completed an electronic diary on a monthly basis and an electronic patient reported outcome (ePRO) questionnaire on a periodic basis. Patients also reported all hospitalizations, surgical procedures, and cancer diagnoses. Additionally, a gastroenterologist completed an annual summary at least once yearly. Patients enrolled in the I-CARE parent study were observed for at least 3 years. The final patient population of the I-CARE source study was planned to include at least 10,000 IBD patients split into 6 patient groups, with approximately 2,000 patients in the ustekinumab cohort of Crohn's disease patients. This final report for RRA-20745 includes the analysis of data entered for patients with Crohn's disease in the I-CARE database until database lock on 17 March 2023.

Setting: The I-CARE study collected data from patients in 15 countries across Europe observed for at least 3 years. This report summarizes the results of patients eligible for RRA-20745 who were followed in I-CARE between 04 March 2016 and 17 March 2023.

Patients enrolled in I-CARE started cohort-defining medication before entry (prevalent user cohorts), at entry or during follow-up in I-CARE (incident user cohorts). To maximize sample size, all eligible patients (both prevalent and incident users of treatment) were analyzed in RRA-20745. Patient demographics, medical history, disease history, current disease status and any previous IBD therapy for the RRA-20745 study were collected at baseline in I-CARE.

Patient Population and Study Size: Patients were included for data extraction if they met the following eligibility criteria:

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

In addition to the above overall eligibility criteria, the full analysis set (FAS) for this final report included all patients meeting the following additional criteria:

- those that, after entry into the I-CARE study, received at least 1 dose of any of the following treatments for Crohn's disease:
    - ustekinumab (with or without non-biologic immunomodulators [ie, thiopurines and/or methotrexate])
    - or anti-TNF (ie, infliximab, adalimumab, including biosimilars) with or without non-biologic immunomodulator (ie thiopurines and/or methotrexate)
    - or a non-biologic immunomodulator (ie, thiopurines and/or methotrexate)
- have submitted at least one ePRO during the first 6 months and two ePROs during the first year after the inclusion in I-CARE.

In addition, the safety outcome data reported by the patients had to be validated by a gastroenterologist.

In this final report, the assignment to study cohorts was determined by index treatment in the following hierarchical order:

1. Patients treated with ustekinumab (ie, received at least 1 dose of ustekinumab) prior to baseline in I-CARE, or during the study follow-up (ie, at or after baseline)
2. Patients naïve of ustekinumab, and treated with anti-TNF agents prescribed for Crohn's disease (ie, received at least 1 dose of infliximab and/or adalimumab, including biosimilars) prior to baseline in I-CARE or during the study follow-up (ie, at or after baseline)
3. Patients naïve of ustekinumab and anti-TNF agents, and treated with non-biologic immunomodulators (ie, thiopurines and/or methotrexate) prior to baseline in I-CARE or during the study follow-up (ie, at or after baseline).

Variables and Data Sources: The data source for RRA-20745 is the database for the I-CARE study.

Demographic and disease characteristics at index date when available (as recorded at baseline of I-CARE if not available at index date), Prior and concomitant therapies for Crohn's disease, extent of exposure to ustekinumab, anti-TNF and non-biologic immunomodulators were summarized for each of the 3 treatment cohorts in the following three groupings: (1) Prevalent Users, (2) Incident Users, (3) Total group (ie, Prevalent Users plus Incident Users).

Analyses utilized a conservative approach with ustekinumab which was (1) to implement a hierarchical order of exposure classification for malignant outcomes and (2) for non-malignant outcomes, a 91-day at risk window was applied for the primary analysis (31-day at risk window for non-biologics). This approach maximized the outcomes assigned to ustekinumab exposure rather than to other exposures.

Statistical Methods: Cumulative incidence of outcomes with rates per 100 PY were tabulated. Stratification of rates by the following variables were provided: gender, time since initial Crohn's disease diagnosis, Crohn's disease hospitalization, previous use of steroids and concurrent use of steroids at index date. In addition, for biologic cohorts, the following stratifications were provided: concurrent use of non-biologic immunomodulators at index date and history of previous biologic use.

For malignancy outcomes, an ITT approach was taken as the primary analysis. The ITT approach carried the index exposure forward through the end of follow-up. For the primary data analysis, a lag time bias was accounted for in the malignancy risk window such that malignancies occurring within one year of actual treatment initiation were excluded. For an individual patient, the index treatment exposure risk window for malignancy outcomes was dependent of the start date of the index treatment, the ICF date and the 12-months lag time. The primary analysis of VTE and Serious Infection outcomes used a per-protocol strategy. In the per-protocol analysis, exposure to the index treatment for an individual patient ended at the earlier of discontinuation from the study (withdrawal, data cutoff date, or death), or at the end of the 91-day period after the last index biologic treatment administration (31 days for non-biologics).

Results from descriptive analyses were presented separately for each of the three cohorts. In general, descriptive statistics, such as mean, standard deviation (SD), median, interquartile (IQ) range, minimum, and maximum for continuous variables, and counts and percentages for discrete variables were used to summarize data. Incidence rates were calculated based on the duration of treatment exposure and total number of events.

The following between-cohort comparisons were performed:

- Ustekinumab cohort versus anti-TNF cohort (primary)
- Ustekinumab cohort versus Immunomodulator cohort (secondary)

For all treatment cohort comparisons, outcome-specific propensity scores (PS) were calculated and used to control for confounding. The PS were estimated using logistic regression, and PS stratified quintiles were used to generate comparable treatment cohorts of patients receiving ustekinumab or comparator treatments. In the case of imbalance within the quintiles, attempts were made to achieve balance through sub-stratification, recategorization of variables, adding or removing variables, and creation of interaction terms.

The between-cohort relative difference in event rate was investigated using propensity score adjusted Cox proportional hazards regression models for the following safety outcomes:

- Malignancies
- Serious infections
- VTEs associated with hospitalization

The estimated Hazard Ratios (HRs) including the two-sided 95% confidence interval for the hazard ratio were presented.

Sensitivity analyses were performed for malignancy outcomes and non-malignant outcomes.

RESULTS:

PATIENT CHARACTERISTICS:

A total of 5,115 eligible unique Crohn's disease patients were included, of which 878 patients were in the ustekinumab cohort. Of the 878 patients treated with ustekinumab in the study, a higher proportion of patients were incident users (566 [64.5%]), while in the anti-TNF and non-biologics immunomodulators cohorts, a higher proportion of patients were prevalent users (3,495 [90.9%] and 972 [94.0%], respectively). In the anti-TNF cohort, 415 (10.80%) patients switched to ustekinumab treatment during follow-up. The mean (SD) duration of follow-up (FU) (the number of years of follow-up is the total time that a patient has spent in the study, irrespective of treatment switch) was comparable across cohorts (3.15 [1.10] years, 2.99 [1.28] years, and 3.07 [1.25] years), corresponding to 2,764, 11,498, and 3,170 cumulative PY of FU in the ustekinumab, anti-TNF and non-biologic immunomodulators cohorts, respectively.

The mean (SD) duration of exposure within I-CARE, calculated from index date to the date of earliest withdrawal from the study or data cut-off for all patients exposed, was numerically lower in the ustekinumab cohort than in the anti-TNF and non-biologic immunomodulators cohorts (20.07 [14.99] months, 29.01 [17.30] months and 29.82 [17.11] months, respectively).

Most patients in the ustekinumab cohort had prior exposure to at least one biologic treatment, with only 28 (3.19%) patients reporting no prior biologic treatment, 347 (39.52%) patients reporting prior exposure to one biologic and 347 (39.52%) patients reporting prior exposure to 2 biologics. Most patients within the anti-TNF cohort had not been exposed to prior biologics (2,740 [71.30%] patients), and no patients in the non-biologic immunomodulators cohort had been treated with a biologic previously, by definition.

The mean age of patients was comparable between treatment cohorts, with means (SD) ranging from 37.74 (12.31) years in the anti-TNF cohort to 39.28 (12.70) years in the ustekinumab cohort. Within the ustekinumab cohort, individual patient's age ranged from 18.12 to 78.37 years. Overall, the percentage of female patients was higher in the ustekinumab and non-biologic immunomodulators cohorts (58.88% and 56.09%, respectively) than in the anti-TNF cohort (51.47%). Reported smoking and alcohol use were similar across cohorts.

Most patients were diagnosed with Crohn's disease between 17 and 40 years of age (71.07% to 73.79% patients across cohorts). Patients in the ustekinumab cohort had a longer disease duration with mean (SD) years since Crohn's disease diagnosis of 12.13 (9.01) years, compared with 10.66 (8.99) years and 10.56 (9.37) years in the anti-TNF and non-biologic immunomodulator cohorts respectively. Most patients

had no family history of IBD (ranging from 75.05% in the non-biologic immunomodulators cohort to 77.08% in the anti-TNF cohort). The most common Crohn's disease location across cohorts was ileocolonic (ranging from 39.16% of patients in the non-biologic immunomodulators cohorts to 46.77% of patients in the ustekinumab cohort). Less than 3% of patients had a history of malignancy across all cohorts. The percentage of patients with a family history of cancer (limited to only lymphoma, colorectal cancer, melanoma, or breast cancer) ranged from 9.50% to 11.32% across cohorts.

MAIN RESULTS:

For the comparative analyses, only data coded from hospital records are used, which are considered by GETAID as the most comprehensive. Data from hospital records overlap with adjudicated events coded from ePROs.

Malignancy-Related Safety Outcomes

In the primary analysis, using an ITT approach and including all patients after at least 1 year of exposure (lag period), the number (%) of patients with at least one cancer/dysplasia coded from hospital records was 8 (1.22%) patients in the ustekinumab cohort, 56 (1.54%) patients in the anti-TNF cohort, and 24 (2.42%) patients in the non-biologic immunomodulators cohort.

Numerically lower IRs per 100 PY (95% CI) of malignancies (cancers and dysplasia) coded from hospital records were reported in the ustekinumab and anti-TNF cohorts (0.70 [0.22; 1.19] and 0.58 [0.42; 0.73] per 100 PY respectively) than in the non-biologic immunomodulators cohort (0.90 [0.54; 1.26] per 100 PY).

Stratified IRs of malignancy (cancer and dysplasia) after at least 1 year of exposure for the treatment cohorts were presented. Stratification factors included gender, time since initial Crohn's disease diagnosis, history of Crohn's disease hospitalization, previous and concurrent use at index date of systemic steroids; and for biologic cohorts, concurrent use of non-biologic immunomodulators at index date and history of previous biologic use. For all exposed patients in the ustekinumab and non-biologic immunomodulators cohorts, the confidence intervals for IRs for all sub-groups across the strata are overlapping. For all exposed patients in the anti-TNF cohort, a higher IR (95% CI) of malignancies was observed in patients with long disease duration (ie, time since diagnosis of Crohn's disease >5 years) than in patients with disease duration ≤ 5 years (0.74 [0.53; 0.94] and 0.20 [0.04; 0.37] per 100 PY, respectively).

Three sensitivity analyses were performed for the outcome of malignancies. For the sensitivity analysis using no lag period, the IR (95% CI) of cancer/dysplasia was 0.74 (0.34, 1.14), 0.59 (0.44, 0.73), and 0.95 (0.58, 1.31) for all exposed patients in the ustekinumab, anti-TNF, and non-biologic immunomodulator cohorts, respectively. For the sensitivity analysis using a 6-month lag period, the IRs were 0.90 (0.41, 1.39), 0.60 (0.44, 0.73) and 1.38 (0.83, 1.93) for all exposed patients in the ustekinumab, anti-TNF, and non-biologic immunomodulator cohorts, respectively. For the sensitivity analysis using the start date of the last continuous use period as index date, the IRs were 0.65 (0.20, 1.11), 0.34 (0.25, 0.43) and 0.41 (0.25, 0.58) for all exposed patients in the ustekinumab, anti-TNF, and non-biologic immunomodulator cohorts, respectively.

For the comparative analyses, the unadjusted HR (95% CI) and adjusted HR (95% CI) of the comparison between ustekinumab cohort and the anti-TNF cohort (primary comparator) were 1.43 (0.63, 3.21) and 2.8 (0.92, 8.30), respectively. The unadjusted HR (95% CI) and adjusted HR (95% CI) of the comparison between ustekinumab vs. non-biologic immunomodulators (secondary comparator) were 0.72 (0.30, 1.71) and 0.95 (0.31, 2.84) respectively. Similar sensitivity analyses as described for the incidence rates were

performed for the comparative analyses. The results were comparable to those obtained in the main analyses, except when using the start date of the last continuous period use as index date, in which case a statistically significant increased HR was observed in the ustekinumab cohort compared with the anti-TNF cohort (3.60 [1.18; 10.97]).

Infections (Including Serious Infections, Opportunistic Infections and Tuberculosis)

For the primary analysis of serious infections (including OI and TB), a per-protocol approach was used, applying a 91-day at-risk window for biologic treatments and a 31-day at-risk window for non-biologic treatments. Serious infections recorded from validated ePRO were reported by 7 (0.80%) patients in the ustekinumab cohort, 59 (1.54%) patients in the anti-TNF agents, and 12 (1.16%) patients in the non- biologic immunomodulators cohort. The IR per 100 PY (95% CI) of all serious infections coded from hospital records was numerically higher in the anti-TNF cohort than in the ustekinumab or non-biologic immunomodulators cohorts (1.28 [1.05; 1.51], 1.06 [0.54; 1.57] and 0.62 [0.32; 0.93], respectively). The number (%) of opportunistic infections coded from hospital records was low across the cohorts, with IRs per 100 PY (95% CI) ranging from 0.07 (0.00; 0.20) in the ustekinumab cohort to 0.14 (0.06; 0.21) in the anti-TNF cohort. Most of these infections were viral infections.

Six sensitivity analyses for the outcome of infections (including OI and TB) were performed (1) using an ITT exposure definition, (2) an analysis for patients who did not initiate biologic treatment within 91 days after the last dose of index drug, (3) using an on-treatment approach, (4) using no dual assignment, (5) including only patients who did not terminate treatment (including patients who did not switch) with index drug throughout the observation period (continuers) and (6) using the start date of the last continuous use period as index date for patients initiating treatment prior to enrollment. The IRs per 100 PY (95% CI) were similar to those from the primary analysis across treatment cohorts and sensitivity analyses, except for the sensitivity analysis (6) using the start date of the last continuous use period as index date for patients initiating treatment before enrollment; for this analysis numerically lower incidence rates were observed across cohorts vs. the primary analysis.

For the comparative analyses, the unadjusted HR (95% CI) and adjusted HR (95% CI) of the comparison between ustekinumab vs. anti-TNF (primary comparator) were 0.81 (0.47, 1.39) and 0.57 (0.28, 1.17) respectively. The unadjusted HR (95% CI) and adjusted HR (95% CI) of the comparison between ustekinumab vs. non-biologic immunomodulators (secondary comparator) were 1.33 (0.61; 2.88) and 0.57 (0.17; 1.92), respectively. Similar sensitivity analyses as described for the incidence rates were also performed for the comparative analyses. The results were similar to those obtained in the main analyses.

Venous Thromboembolism

Based on data abstracted from hospitalization reports, no events of VTEs were assigned to the ustekinumab cohort. For patients receiving anti-TNF or non-biologic immunomodulators during the study period, 2 and 1 VTEs reported during treatment and up to 91 days after treatment discontinuation were coded from hospital records, respectively.

OTHER ANALYSES:

In the ustekinumab cohort, approximately 97% of patients were bio-experienced, making it very challenging to achieve balance within the PS quintiles. For this reason, the variable for biologic experience could not be included in the PS model. Therefore, an additional comparative sensitivity analysis was performed in the sub-cohort of bio-experienced patients only.

The adjusted HR (95% CI) of malignancies for the ustekinumab vs. anti-TNF comparison was 1.68 [0.47 ; 6.10] in this population of bio-experienced patients. The adjusted HR (95% CI) of serious infections for the ustekinumab vs. anti-TNF comparison was 0.40 [0.16 ;1.00] in this same population.

ADVERSE EVENTS/ADVERSE REACTIONS:

During the reporting period (ie, prior to 17 March 2023), a total of 175 patients (160 patients with Crohn's disease, 14 patients with ulcerative colitis and 1 patient with indeterminate colitis) reported one or more SAEs after initiating treatment with ustekinumab.

The most common SAEs (PT) reported in these patients were Crohn's disease aggravated (134 events in 98 patients), lack of drug effect (36 events in 29 patients), intestinal obstruction and intestinal sub-obstruction (19 events in 17 patients) and colitis ulcerative aggravated (12 events in 10 patients). A total of 31 other patients had reported SAEs after ustekinumab initiation which were considered related to Crohn's disease or ulcerative colitis treatment by the Investigator or GETAID. Of these events, 33 events in 26 patients were disease aggravation related to IBD treatments lack of efficacy. Six patients reported other SAEs considered by the investigator or by GETAID as related to IBD treatments.

DISCUSSION AND CONCLUSION:

DISCUSSION:

A total of 878 patients treated with ustekinumab at baseline or during follow-up, 3,843 and 1,034 eligible patients treated with anti-TNF agents (with or without non-biologic immunomodulators) and non-biologic immunomodulators (never exposed to biologics), respectively were included in this PASS. Of the 878 patients treated with ustekinumab, 566 (64.5%) patients were incident users and 312 (35.5%) were prevalent users. The number of patients included in the ustekinumab cohort was lower than the initially expected number in the power calculation. At data cutoff, ustekinumab patients were on average followed for approximately 3 years, comparable to the follow-up time of comparators, with a shorter duration of exposure within the study and a relatively lower treatment discontinuation rate than comparators.

The IRs per 100 PY (95% CI) of malignancies including cancers and dysplasia coded from hospital records were generally low across cohorts, the most frequent being skin cancers reported in 3 patients in ustekinumab cohort, 18 patients in anti-TNF cohort and 11 patients in non-biologics cohort. In the primary comparative analysis using an ITT approach and a 1-year lag period, in the prespecified sensitivity analyses using no lag period and 6-months lag period, and in the additional sensitivity analysis performed in bio-experienced patients only, the adjusted HRs (95% CI) of malignancies showed an increased risk of malignancies in the ustekinumab cohort vs. anti-TNF cohort, though not statistically significant (2.8 [0.92 ; 8.30], 1.66 [0.64 ;4.31], 1.63 [0.63 ;4.25] and 1.68 [0.47 ; 6.10], respectively) . When using the start date of last continuous use period as index date, a statistically significant increased risk was observed in the ustekinumab cohort compared to anti-TNF cohort (adjusted HR [95%CI] 3.60 [1.18 ;10.97]). In the present study, the propensity score distributions for the comparator cohorts showed limited overlap, indicating there were meaningful differences between the comparator populations. Efforts to achieve balance within the propensity score quintiles were met with very limited success, resulting in residual imbalance between the cohorts. Of note, prior biologic exposure could not be included in the PS model. This impacts the causal interpretation of the results from the comparative analyses, as key confounders remained imbalanced. Patients with IBD are at increased risk of developing malignancies compared to the general population. In the present study, several known risk factors for developing malignancies in patients with IBD were

analysed and revealed that the vast majority of patients in the ustekinumab cohort were exposed to thiopurines and/or anti-TNF, and approximately 20% had been treated concomitantly with thiopurines during the study. Thiopurines have long been known to have a carcinogenic effect.

The observed IRs per 100 PY (95% CI) of serious infections coded from hospital records were numerically higher in the anti-TNF cohort compared to ustekinumab or non-biologic immunomodulators cohorts. The adjusted HRs for the primary analyses did not indicate an increased risk of serious infections associated with ustekinumab compared to anti-TNF or non-biologic immunomodulators. Overall, the number of patients reporting serious infections in the ustekinumab cohort was low, the most frequent serious infections being pneumonia in the physician-validated ePROs and GI infections in the hospital records. Similar to malignancies, the propensity score distributions calculated for serious infections as an outcome showed very limited overlap between ustekinumab and comparator cohorts, indicating there was limited comparability with respect to key confounders between the populations. There were substantial challenges in achieving balance within the propensity score quintiles, despite attempts to recategorize variables and to explore the use of interaction terms, therefore the residual imbalance is likely to impact the causal interpretation of the results from comparative analyses. Additionally, a relatively high proportion of patients in the ustekinumab cohort were concomitantly treated with corticosteroids or other non-biologic immunomodulators, known risk factors for developing serious infections. Despite the severe disease profile, the low vaccination rate and the concomitant use of immunosuppressants, the incidence rates of serious infections and opportunistic infections was low in the ustekinumab cohort, and no cases of tuberculosis were reported.

No events of VTE associated with hospitalization were assigned to the ustekinumab cohort in this study.

The available safety data from this study revealed no new safety concerns for ustekinumab, and the safety profile is generally consistent with the known safety profile of ustekinumab in this studied population.

CONCLUSIONS:

In this study of patients with Crohn's disease in Europe, the observed safety profile of ustekinumab was consistent with the established safety profile of ustekinumab from clinical trials and available postmarketing data. The imbalance between the treatment cohorts in key confounders highlights that there are important differences in the baseline characteristics of patients which are associated with treatment choices and with the outcomes of interest. The results of this study indicate that the benefit-risk profile of ustekinumab for Crohn's disease remains positive, and its risk profile in terms of malignancies, serious infections and VTEs is comparable to that of anti-TNF, and non-biologic immunomodulators in the real-world setting. Overall, the outcomes summarized in this final report are consistent with the known safety profile of ustekinumab.