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Alimentary Tract

Long-term safety of ustekinumab in Crohn's disease: Descriptive analysis from an observational post-authorisation safety study using I-CARE cohort data

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ABSTRACT

Background: Limited data are available from large, prospective cohort studies evaluating the long-term safety of ustekinumab in patients with Crohn's disease.
Aims: To evaluate the long-term safety profile of ustekinumab in adult patients with Crohn's disease.
Methods: RRA-20745 was an observational post-authorisation safety study. Data were derived from the I-CARE study (NCT02377258), a European prospective, observational, multi-centre cohort study. Malignancies, serious infections (including opportunistic infections and tuberculosis), and venous thromboembolism associated with hospitalisations were evaluated.
Results: Data for 878 patients with Crohn's disease who received ustekinumab (mean follow-up 37.8 months), were included (median age 37.4 years, 58.9 % female, 64.5 % incident ustekinumab users and 35.5 % prevalent users). There were 7 malignancies reported in 7 patients (by organ affected: skin, 3 patients [0.4 %], blood, lymph nodes, rectum, breast, 1 patient [0.1 %] each). Serious infections were reported by 16 (1.8 %) patients (6 prevalent users, 10 incident users). The most common serious infections were gastrointestinal (7 patients, 0.8 %), followed by pulmonary infections (3 patients, 0.3 %). 1 patient (0.1 %; prevalent cohort) reported a bacterial opportunistic infection. No patients reported tuberculosis or venous thromboembolism.
Conclusions: In the RRA-20745 observational cohort, ustekinumab had a safety profile consistent with that observed in clinical trials and available post-marketing data.
Trial registration number: NCT02377258.

1. Introduction

Crohn's disease is a chronic, progressive inflammatory disease of the gastrointestinal tract [1]. It has traditionally been thought to be mediated by a T helper cell (Th) 1 and Th17 immune response [2–4]. Interleukin (IL)-12 and IL-23 have been implicated in the differentiation and signalling of Th1 cells [5].

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Ustekinumab, a fully human immunoglobulin G1 kappa monoclonal antibody that binds to the shared p40 subunit of IL-12 and IL-23, is approved in the USA and the European Union for, among other indications, patients with moderately to severely active Crohn's disease [6,7]. While real-world studies have confirmed the benefit–risk profile of ustekinumab in patients with Crohn's disease [8–13], large prospective cohort studies evaluating the long-term safety of ustekinumab in Crohn's disease beyond 2 years are limited.

This study aimed to evaluate the long-term safety of ustekinumab in adult patients with Crohn's disease, with a follow-up period of up to 3 years.

2. Materials and methods

2.1. Study design

RRA-20745 was an observational post-authorisation safety study (PASS) aiming to describe the long-term safety profile of ustekinumab in adult patients with Crohn's disease, as measured by the occurrence of malignancies, serious infections, and venous thromboembolic events associated with hospitalisation. It constituted secondary use of data collected from patients enrolled in the independent I-CARE study (NCT02377258), a European prospective, observational, multicentre cohort study sponsored by the Groupe d'Étude Thérapeutique des Affections Inflammatoires du Tube Digestif (GETAID) [14].

In the I-CARE study, around 500 investigators collected safety and effectiveness data at sites in 15 countries across Europe from more than 10,000 patients with a diagnosis of Crohn's disease, ulcerative colitis, or inflammatory bowel disease, who were instructed to remain under close monitoring for at least 3 years [15,16]. Here we summarise the long-term safety data for adult patients with Crohn's disease who were treated with ustekinumab, were followed in I-CARE between 4 March 2016 and 17 March 2023 (the data cutoff date), and were eligible for RRA-20745.

Patients' baseline demographics and disease characteristics were collected by investigators and entered in an electronic case report form (eCRF). During the observational period, patients completed an electronic diary (e-diary) on a monthly basis, including any change (type and dose) in all medications recorded at inclusion, details of disease activity, and details of whether they had been diagnosed with a dysplasia or malignancy, had experienced any infection, or had been hospitalised for their condition and/or a related complication. If a patient reported a hospitalisation, or a malignancy or high-grade dysplasia, the investigators were instructed to provide the related hospitalisation report or diagnostic pathology report, respectively. The investigators reviewed the patient data on an annual basis and checked, supplemented, or corrected it if necessary. In addition, the safety outcome data reported by the patients had to be validated by a gastroenterologist. If complete, the data collected during the preceding year were approved and collated in an annual summary.

I-CARE was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice guidelines, and applicable regulatory requirements. Local institutional review boards or ethics committees reviewed and approved the study protocol and oversaw trial conduct and documentation. Written informed consent was obtained from all participants.

2.2. Eligibility criteria

The full eligibility criteria for the I-CARE study have been previously reported [14]. Patients were included in the I-CARE Crohn's disease cohort 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 enrolment based on usual radiological, endoscopic, or histological criteria, and were receiving treatment with ustekinumab or other Crohn's disease therapies (anti-tumour necrosis factor [TNF] agents [i.e., infliximab, adalimumab, and biosimilars] and non-biologic immunomodulators) per local label and clinical practice. In this paper we present a descriptive analysis of ustekinumab-treated patients as per the primary objective of the study.

In addition to the overall I-CARE eligibility criteria, the full analysis set (FAS) for the currently presented analysis of RRA-20745 included all patients meeting the following additional criteria; they had, after entering the I-CARE study, received at least 1 dose of ustekinumab (with or without non-biologic immunomodulators [i.e., thiopurines and/or methotrexate]), and had submitted at least one e-diary during the first 6 months and two electronic patient-reported outcomes (ePROs) during the first year after inclusion in I-CARE.

Patients who received their first dose of ustekinumab after entry into the study were considered incident users; patients who had ongoing treatment with ustekinumab at study entry were considered prevalent users.

2.3. Assessments and outcomes

The objective of this analysis was to describe the long-term safety of ustekinumab in adult patients with Crohn's disease: the occurrence of malignancies, serious infections (defined as infections requiring hospitalisation) including opportunistic infections and tuberculosis (TB), and venous thromboembolism (VTE) associated with hospitalisation were evaluated.

Patients' demographics and disease characteristics were collected on the index date where available (or at the baseline of I-CARE if not available on the RRA-20745 index date), together with prior and concomitant therapies for Crohn's disease, and extent of exposure to ustekinumab in the following three groupings: (1) prevalent users, (2) incident users, (3) total group (i.e., prevalent users plus incident users).

2.4. Statistical analysis

For malignant outcomes, an intent-to-treat (ITT) approach was taken for the primary analysis. The ITT approach carried the index exposure forward through the end of follow-up. In this analysis, a 6-month latency period from the reported start date of ustekinumab was applied for the risk window, as well as a 1-year latency period, to account for the long latency of malignancies.

For the primary analysis of the non-malignant outcomes of infection and VTE, a per-protocol approach using a 91-day at-risk window was applied. The ongoing exposure risk after stopping therapy due to the half-life of ustekinumab was accounted for by considering an additional 90 days of exposure time [17,18]. In the per-protocol analysis, exposure to the index treatment for an individual patient ended at discontinuation from the study (i.e., withdrawal, data cutoff date, or death), or at the end of the 91-day period after the last ustekinumab treatment administration, whichever was earlier.

Results from descriptive analyses are presented. Descriptive statistics, such as mean, standard deviation (SD), median, interquartile range (IQR), minimum, and maximum for continuous variables, and counts and percentages for discrete variables were used to summarise data. Incidence rates were calculated based on the duration of treatment exposure and total number of events. Cumulative incidence of outcomes with rates per 1,000 patient-years (PY) were tabulated. Stratification of rates by the following

variables are provided: sex, time since initial Crohn's disease diagnosis, Crohn's disease hospitalisation, previous use of steroids, and concurrent use of steroids on the index date.

Sensitivity analyses were performed for malignant outcomes and non-malignant outcomes. For malignant outcomes, the following sensitivity analysis was performed: 'no latency period' (i.e., removing the 6-month or 1-year latency period after starting ustekinumab treatment from time at risk at the start of ustekinumab or at the time of informed consent date if the patient was exposed to ustekinumab prior to registry enrolment and the ustekinumab treatment initiation date was not known). For non-malignant outcomes, the following sensitivity analyses were performed: 'ITT exposure', 'no biologic within 91 days' (i.e., including only patients who did not start biologic treatment within 91 days after the last dose of ustekinumab), 'on treatment' (i.e., the outcome was assigned to ustekinumab only during the treatment with that drug). All analyses were performed using SAS® 9.4 software (SAS Institute, Cary, NC, USA).

3. Results

3.1. Patient disposition, demographics, and baseline characteristics

A total of 878 unique patients Crohn's disease who received ustekinumab in the I-CARE study were eligible for inclusion in this analysis. Among these patients, 566 patients (64.5 %) were incident users and 312 (35.5 %) were prevalent users (Table 1). The mean (SD) duration of follow-up was 3.2 (1.1) years, corresponding to 2,764 cumulative PY of follow-up (Table 1).

Demographics and baseline characteristics are shown in Table 2. The median age at enrolment was 37.4 years (range 18.1–78.4) for all patients, 37.1 years (range 18.1–78.4) for prevalent users, and 37.5 years (range 18.2–72.3) for incident users. A total of 517 patients (58.9 %) were female: 199 were prevalent users (63.8 %) and 318 were incident users (56.2 %). Patients had a median time since diagnosis of 10.3 years (range 0.2–47.2).

A summary of prior and concomitant Crohn's disease therapies other than ustekinumab can be seen in Table S1. Most patients had prior exposure to at least one biologic treatment, with only 28 patients (3.2 %) reporting no prior exposure to biologics. A total of 347 patients (39.5 %) reported prior exposure to one biologic, and 433 patients (49.3 %) reported prior exposure to two or more biologics. The most common concomitant medications were systemic corticosteroids (263 patients [30.0 %]) and azathioprine (156 patients [17.8 %]).

3.2. Treatment exposure

The extent of exposure to ustekinumab within the I-CARE study was calculated from date of informed consent for prevalent users and start of ustekinumab treatment for incident users to either withdrawal from study, or death, or data cutoff, whichever was earlier. Among all patients, total exposure to ustekinumab was 17,623 patient-months (median 17.0 months; range 0–67; Table S2). Among prevalent and incident users, total exposure was 8,676 patient-months (median 37.0 months; range 0–52), and 8,947 patient-months (median 13.0 months; range 0–67), respectively.

3.3. Malignancies and dysplasias

Using a 6-month and a 12-month latency period, a total of 7 (0.9 %) and 5 (0.8 %) patients, respectively, reported a malignancy when coded from hospital records (Table 3). Most malignancies were reported by prevalent users (4 patients) for both latency periods. Using a 6-month latency period, the incidence rate of malignancies was 4.8 per 1,000 PY (95 % CI 1.3–8.4) for all exposed patients, and using a 12-month latency period, it was 4.4 per 1,000 PY (95 % CI 0.5–8.2) for all exposed patients. The most common malignancy was skin cancer, occurring in 3 patients (0.5 %; 2 cases of melanoma and 1 case of basal cell carcinoma); all 3 patients were prevalent users. Breast cancer was reported in 1 (0.2 %) patient (prevalent user). Cancer of the lymph nodes (Hodgkin lymphoma), blood (myeloid leukaemia), and rectum were reported in 1 (0.2 %) patient each (all incident users). The patient with Hodgkin lymphoma had a family history of malignancy (mother with lymphoma) but no personal history of prior malignancy. No other patients with incident malignancy had a family or personal history of malignancy. When stratified by baseline characteristics after at least 1 year of exposure, the CIs of incidence rates for all subgroups were overlapping (Table S3).

Using a 6-month latency period, there were a total of 6 (0.8 %) dysplasias, corresponding to an incidence rate of 4.1 per 1,000 PY (95 % CI 0.8–7.5); 3 were reported in prevalent users (anus, colon, rectum; 1 [0.1 %] patient each), and 3 in incident users (cervix uteri, 1 [0.1 %] patient, and colon, 2 [0.3 %] patients) (Table 4). Using a 12-month latency period, there were a total of 3 (0.5 %) dysplasias (anus, colon, rectum), corresponding to an incidence rate of

Table 1
Patient disposition ($N = 878$ unique patients).

Index treatment	Ustekinumab		
	Prevalent users ($n = 312$)	Incident users ($n = 566$)	All exposed patients ($N = 878$)
Baseline treatment, n (%)			
Ustekinumab	312 (100)	0	312 (35.5)
Anti-TNF	0	383 (67.7)	383 (43.6)
Infliximab	0	160 (28.3)	160 (18.2)
Adalimumab	0	223 (39.4)	223 (25.4)
Azathioprine	36 (11.5)	149 (26.3)	185 (21.1)
6-mercatopurine	6 (1.9)	25 (4.4)	31 (3.5)
Methotrexate	25 (8.0)	41 (7.2)	66 (7.5)
Patients who discontinued (stopped or switched) treatment, n (%)	74 (23.7)	96 (17.0)	170 (19.4)
End of follow-up by reason, n (%)			
Withdrawal of consent (patient choice)	62 (19.9)	45 (8.0)	107 (12.2)
Death	1 (0.3)	2 (0.4)	3 (0.3)
Lost to follow-up	3 (1.0)	6 (1.1)	9 (1.0)
Other	10 (3.2)	14 (2.5)	24 (2.7)
Follow-up (duration on ustekinumab)[a], years, mean (SD)	2.7 (1.1)	3.9 (1.0)	3.2 (1.1)
Patient-years, n	847	1,916	2,764

TNF, tumour necrosis factor; SD, standard deviation.
[a] Number of years of follow-up is the total time that a patient has spent in the study, irrespective of treatment switch.

Table 2
Demographics and baseline characteristics at enrolment date[a].

Characteristic	Ustekinumab		
	Prevalent users (n = 312)	Incident users (n = 566)	All exposed patients (N = 878)
Age, years			
n	312	566	878
Mean (SD)	39.3 (12.8)	39.3 (12.6)	39.3 (12.7)
Median	37.1	37.5	37.4
Range	18.1–78.4	18.2–72.3	18.1–78.4
(IQR)	(29.1–47.8)	(29.0–48.5)	(29.0– 48.1)
Missing	0	0	0
Weight, kg			
n	284	530	814
Mean (SD)	70.2 (16.2)	70.5 (15.6)	70.4 (15.8)
Median	68.0	68.0	68.0
Range	39.0–128.0	40.0–130.0	39.0–130.0
(IQR)	(58.0–82.0)	(59.0–80.0)	(59.0–80.0)
Missing	28	36	64
Body mass index, kg/m^2			
n	281	527	808
Mean (SD)	24.6 (5.1)	24.4 (5.0)	24.5 (5.0)
Median	23.8	23.4	23.5
Range	14.3–53.3	15.0–53.3	14.3–53.3
(IQR)	(21.2–27.4)	(20.9–27.0)	(21.1–27.2)
Missing	31	39	70
Years since CD diagnosis[b]			
N	312	566	878
Mean (SD)	13.0 (8.6)	11.6 (9.2)	12.1 (9.0)
Median	11.4	9.6	10.3
Range	0.4–44.9	0.2–47.2	0.2–47.2
(IQR)	(6.6–17.8)	(4.4–16.3)	(5.1–16.9)
Missing	0	0	0
Sex, n (%)			
Female	199 (63.8)	318 (56.2)	517 (58.9)
Male	113 (36.2)	248 (43.8)	361 (41.1)
Smoking status, n (%)			
Current	63 (20.2)	110 (19.4)	173 (19.7)
Former	94 (30.1)	147 (26.0)	241 (27.5)
Never	126 (40.4)	271 (47.9)	397 (45.2)
Missing/ND	29 (9.3)	38 (6.7)	67 (7.6)
Alcohol use			
Yes	43 (13.8)	80 (14.1)	123 (14.0)
No	239 (76.6)	450 (79.5)	689 (78.5)
Missing/NA/ND	30 (9.6)	36 (6.4)	66 (7.5)
History of IBD surgery			
No history	1 (0.3)	3 (0.5)	4 (0.5)
1 surgery	123 (39.4)	179 (31.6)	302 (34.4)
2 or more surgeries	45 (14.4)	87 (15.4)	132 (15.0)
Missing/NA/ND	143 (45.8)	297 (52.5)	440 (50.1)
Montreal classification at worst stage			
Age of diagnosis			
A1 below 16 years	60 (19.2)	76 (13.4)	136 (15.5)
A2 between 17 and 40 years	215 (68.9)	409 (72.3)	624 (71.1)
A3 41 years and above	37 (11.9)	81 (14.3)	118 (13.4)
Location			
N	283	523	806
L1 ileal	99 (35.0)	192 (36.7)	291 (36.1)
L2 colonic	47 (16.6)	91 (17.4)	138 (17.1)
L3 ileocolonic	137 (48.4)	240 (45.9)	377 (46.8)
L4[c] isolated upper disease	27 (9.5)	56 (10.7)	83 (10.3)
Behaviour			
N	281	524	805
B1 non-stricturing, non-penetrating	118 (42.0)	230 (43.9)	348 (43.2)
B2 stricturing	101 (35.9)	191 (36.5)	292 (36.3)
B3 penetrating	62 (22.1)	103 (19.7)	165 (20.5)
Perianal disease			
Yes	90 (28.9)	166 (29.3)	256 (29.2)
No	194 (62.2)	360 (63.6)	554 (63.1)
Missing/NA/ND	28 (9.0)	40 (7.1)	68 (7.7)
Family history of IBD			
Yes	36 (11.5)	61 (10.8)	97 (11.1)
No	231 (74.0)	430 (76.0)	661 (75.3)
Unknown	18 (5.8)	43 (7.6)	61 (7.0)
Missing	27 (8.7)	32 (5.7)	59 (6.7)

(*continued on next page*)

Table 2 (*continued*)

Characteristic	Ustekinumab		
	Prevalent users (n = 312)	Incident users (n = 566)	All exposed patients (N = 878)
History of malignancies			
Yes	8 (2.6)	18 (3.2)	26 (3.0)
No	276 (88.5)	514 (90.8)	790 (90.0)
Missing/NA/ND	28 (9.0)	34 (6.0)	62 (7.1)
Family history of malignancies [d]			
Yes	35 (11.2)	57 (10.1)	92 (10.5)
No	210 (67.3)	416 (73.5)	626 (71.3)
Unknown	39 (12.5)	61 (10.8)	100 (11.4)
Missing/NA/ND	28 (9.0)	32 (5.7)	60 (6.8)

CD, Crohn's disease; IBD, inflammatory bowel disease; IC, informed consent; IQR, interquartile range; NA, not applicable; ND, not available; SD, standard deviation; TNF, tumour necrosis factor; yr, year.
[a] For all exposed patients, patient baseline characteristics were collected at study baseline rather than index therapy start.
[b] Years since CD diagnosis = (IC date − diagnosis date + 1)/365.25.
[c] L4 is a modifier that can be added to L1–L3 when concomitant upper gastrointestinal disease is present.[33]
[d] Only lymphoma, colorectal cancer, melanoma, breast cancer.

Table 3
Malignancies[a] (all cases after 6 months and 1 year of exposure)[b].

	Ustekinumab		
	Prevalent users (n = 312)	Incident users (n = 566)	All exposed patients (N = 878)
6-month latency period			
Eligible patients, n (%)	300 (96.2)	463 (81.8)	763 (86.9)
Exposure risk window for malignant outcomes, PY	793	655	1,448
Patients with at least one malignancy coded from hospital records, n (%)	**4 (1.3)**	**3 (0.6)**	**7 (0.9)**
By organ affected			
Blood	0	1 (0.2)	1 (0.1)
Breast	1 (0.3)	0	1 (0.1)
Lymph nodes	0	1 (0.2)	1 (0.1)
Rectum	0	1 (0.2)	1 (0.1)
Skin	3 (1.0)	0	3 (0.4)
Incidence rate of malignancies coded from hospital records· per 1,000 PY [95 % CI]	5.0 [0.1–10.0]	4.6 [0–9.8]	4.8 [1.3–8.4]
Patients with personal history of HGD, n (%)	5 (1.7)	4 (0.9)	9 (1.2)
12-month latency period			
Eligible patients, n (%)	285 (91.3)	372 (65.7)	657 (74.8)
Exposure risk window for malignant outcomes, PY	695	446	1,141
Patients with at least one malignancy coded from hospital records, n (%)	**4 (1.4)**	**1 (0.3)**	**5 (0.8)**
By organ affected			
Breast	1 (0.4)	0	1 (0.2)
Lymph nodes	0	1 (0.3)	1 (0.2)
Skin	3 (1.1)	0	3 (0.5)
Incidence rate of malignancies coded from hospital records per 1,000 PY [95 % CI]	5.8 [0.1–11.4]	2.2 [0–6.6]	4.4 [0.5–8.2]
Patients with personal history of HGD, n (%)	5 (1.8)	3 (0.8)	8 (1.2)

CI, confidence interval; e-diary, electronic diary; ePRO, electronic patient-reported outcomes; HGD, high-grade dysplasia; I-CARE, Ibd CAncer and seRious infections in Europe; PY, patient-years.
[a] Data in this table are derived from hospitalisation reports or e-diaries. Data from hospitalisation reports were extracted and coded into the clinical database of I-CARE.
[b] Any malignancies occurring after date of informed consent for prevalent users with no initiation date recorded, or ≥ 6 months or ≥ 1 years after ustekinumab index date for incident users and prevalent users with known initiation date, per the protocol.

2.6 per 1,000 PY (95 % CI 0.0–5.6); each dysplasia was reported by 1 (0.2 %) patient (all prevalent users) (Table 4).

A sensitivity analysis was performed for the outcome of malignancies (Table S4). Using no latency period, the incidence rate of malignancies was 4.0 per 1,000 PY (95 % CI 1.0–6.9) for all exposed patients.

3.4. Serious infections, opportunistic infections, and tuberculosis

Serious infections coded from hospital records were reported by 16 (1.8 %) patients (Table 5). A total of 6 prevalent users (1.9 %) and 10 incident users (1.8 %) reported serious infections coded from hospital records. The most common serious infections were gastrointestinal infections (7 patients, 0.8 %), followed by pulmonary infections (3 patients, 0.3 %). The incidence rate of all serious infections (including serious opportunistic infections) coded from hospital records was 10.6 per 1,000 PY (95 % CI 5.4–15.7).

The incidence of opportunistic infections (serious and non-serious) was very low, with only one patient in the prevalent cohort reporting a bacterial opportunistic infection (salmonella enteritis). No patients reported tuberculosis infections.

Sensitivity analyses ('ITT exposure for non-malignant outcomes', 'no biologic within 91 days', and 'on treatment') for the outcome of infections reported similar incidence rates per 1,000 PY when compared with the primary analysis (Tables S5, S6, and S7).

3.5. VTE associated with hospitalisation

No patients included in the RRA-20745 study reported VTE events during treatment with ustekinumab or up to 91 days after treatment discontinuation (Table 6).

Table 4
Dysplasias[a] (all cases after 6 months and 1 year of exposure)[b].

	Ustekinumab		
	Prevalent users (n = 312)	Incident users (n = 566)	All exposed patients (N = 878)
6-month latency period			
Eligible patients, n (%)	300 (96.2)	463 (81.8)	763 (86.9)
Exposure risk window for dysplasia outcomes, PY	793	655	1,448
Patients with at least one dysplasia coded from hospital records, n (%)	**3 (1.0)**	**3 (0.6)**	**6 (0.8)**
By organ affected			
Anus	1 (0.3)	0	1 (0.1)
Cervix uteri	0	1 (0.2)	1 (0.1)
Colon	1 (0.3)	2 (0.4)	3 (0.4)
Rectum	1 (0.3)	0	1 (0.1)
Incidence rate of dysplasias coded from hospital records per 1,000 PY [95% CI]	3.8 [0–8.1]	4.6 [0– 9.8]	4.1 [0.8–7.5]
Patients with personal history of HGD, n (%)	5 (1.7)	4 (0.9)	9 (1.2)
12-month latency period			
Eligible patients, n (%)	285 (91.3)	372 (65.7)	657 (74.8)
Exposure risk window for dysplasia outcomes, PY	695	446	1,141
Patients with at least one dysplasia coded from hospital records, n (%)	3 (1.1)	0	3 (0.5)
By organ affected			
Anus	1 (0.4)	–	1 (0.2)
Colon	1 (0.4)	–	1 (0.2)
Rectum	1 (0.4)	–	1 (0.2)
Incidence rate of dysplasias coded from hospital records per 1,000 PY [95 % CI]	4.3 [0.0–9.2]	–	2.6 [0.0–5.6]
Patients with personal history of HGD, n (%)	5 (1.8)	3 (0.8)	8 (1.2)

CI, confidence interval; ePRO, electronic patient-reported outcomes; HGD, high-grade dysplasia; I-CARE, Ibd CAncer and seRious infections in Europe; PY, patient-years.
[a] Data in this table are derived from hospitalisation reports or e-diaries. Data from hospitalisation reports were extracted and coded into the clinical database of I-CARE.
[b] Any dysplasias occurring after date of informed consent for prevalent users with no initiation date recorded, or ≥ 6 months or ≥ 1 years after ustekinumab index date for incident users and prevalent users with known initiation date, per the protocol.

Table 5
Infections (including serious infections, opportunistic infections and tuberculosis)[a,b].

	Ustekinumab		
	Prevalent users (n = 312)	Incident users (n = 566)	All exposed patients (N = 878)
Eligible patients, n (%)	312 (100)	566 (100)	878 (100)
Cumulative exposure for non-malignant outcome, PY	734	780	1,514
Patients with serious infections coded from hospital records, n (%)	**6 (1.9)**	**10 (1.8)**	**16 (1.8)**
GI infections Pulmonary infections Skin and subcutaneous tissue infection Other infections	4 (1.3)1 (0.3)01 (0.3)	3 (0.5)2 (0.4)1 (0.2)4 (0.7)	7 (0.8)3 (0.3)1 (0.1)5 (0.6)
Incidence rate of all serious infections coded from hospital records per 1,000 PY [95 % CI]	**8.2 [1.6–14.7]**	**12.8 [4.9–20.8]**	**10.6 [5.4–15.7]**
Patients with opportunistic infections coded from hospital records, n (%)	**1 (0.3)**	**0**	**1 (0.1)**
Incidence rate of all opportunistic infections coded from hospital records per 1,000 PY [95 % CI] (including all serious or non-serious opportunistic infections following hospitalisation)	**1.4 [0–4.0]**	**0 [NA]**	**0.7 [0–2.0]**

CI, confidence interval; GI, gastrointestinal; I-CARE, Ibd CAncer and seRious infections in Europe; NA, not applicable; PY, patient-years.
[a] Data in this table come from hospitalisation reports. Data from hospitalisation reports were extracted and coded into the clinical database of I-CARE.
[b] Patients reporting infections during treatment exposure and up to 91 days after treatment discontinuation, per protocol.

4. Discussion

The I-CARE study collected data from adult patients with Crohn's disease in 15 countries across Europe, who were observed for at least 3 years. In this observational PASS to describe the long-term safety profile of ustekinumab in adult patients with Crohn's disease who had been included in I-CARE, ustekinumab had a safety profile that was consistent with that observed in clinical trials [19]. The overall safety profile of ustekinumab was favourable in this real-world population, with a median time since diagnosis of 10 years.

Patients with inflammatory bowel disease (including Crohn's disease) are at increased risk of certain malignancies compared with the general population; these include haematologic malignancies, invasive malignancies, basal-cell carcinoma, and malignancies of the small intestine, anus, and biliary tract [20,21]. Age, disease duration, and smoking status are independent predictors of an increased risk of malignancy among patients with Crohn's disease [22]. The most frequent malignancy reported in the primary analysis was skin cancer (reported in 3 patients; 2 cases of melanoma and 1 case of basal cell carcinoma). No clinically meaningful pattern in the types of malignancies reported was observed. The results of sensitivity analyses for malignancies were similar to the primary analysis, supporting the robustness of the primary analysis.

Moderate-to-severe disease activity is independently associated with increased risk of serious infection among patients with Crohn's disease [23,24]. Rates of serious infections were similar to previously published rates for ustekinumab and other biologic therapies [25–27]. Results of sensitivity analyses for infections were also similar to the primary analysis; however, the incidences of malignancies and serious infections in this study were

Table 6
Venous thromboembolism events reported during treatment and up to 91 days after treatment discontinuation[a,b].

	Ustekinumab		
	Prevalent users (n = 312)	Incident users (n = 566)	All exposed patients (N = 878)
Eligible patients, n (%)	312 (100)	566 (100)	878 (100)
Cumulative exposure for non-malignant outcomes using ITT population, PY	734	780	1,514
Patients with VTE coded from hospital records, n (%)	0	0	0
Incidence rate of all VTEs coded from hospital records per 1,000 PY [95 % CI]	0 [NA]	0 [NA]	0 [NA]

I-CARE, Ibd CAncer and seRious infections in Europe; ITT, intent-to-treat; NA, not applicable; PY, patient-year; VTE, venous thromboembolism event.
[a] Data in this table come from hospitalisation reports. Data from hospitalisation reports were extracted and coded into the clinical database of I-CARE.
[b] Patients reporting VTEs during treatment exposure and up to 91 days after treatment discontinuation, per protocol.

low. These findings compare favourably with other treatments [28–30]. After more than 5 years of follow-up, the large observational TREAT registry of more than 6,000 patients with Crohn's disease showed that treatment with narcotic analgesics, prednisone, or infliximab was associated with an increased risk of serious infection [24].

Patients with certain Crohn's disease subtypes are also at increased risk of VTE events and TB [31,32]; however, no cases of VTE or TB were reported in this analysis.

Strengths of this study include the fact that it reflects patients treated in routine clinical care, making it more generalisable than the highly selected populations in clinical trials. The capture of outcomes reported by patients and confirmed by physicians also strengthens the data. Inclusion of data on disease severity, lifestyle factors, and family history provide extra depth to the description of the patient population beyond what may be routinely available in real-world data. Inclusion of a variety of sensitivity analyses also contributes to the robustness of the conclusions. The results could be assumed to be generalisable to similar settings and patient populations in Europe with Crohn's disease treated with the drugs of interest in real-world clinical practice.

This study was limited by the fact that the sample size was dependent on the number of patients enrolled in the I-CARE study who met the selection criteria for this analysis. The actual frequency of clinical follow-up in the I-CARE study was dependent on the patients, who were responsible for their own follow-up through e-diaries, and who could have failed to provide comprehensive accounts of their state of health, which was not under the control of GETAID. This could have led to incomplete data collection. Furthermore, the observational nature of the I-CARE study did not exclude selection bias, and the follow-up time within the study limits observation of patients to approximately 3 years. The high proportion of prevalent users in the analysis increases the chances of bias, such as immortal time bias, potential adjustment for intermediates, and depletion of susceptibles; however, this does not apply to the incident population. Finally, as the patients included in this analysis were treatment-experienced, with a median of 10 years since diagnosis of Crohn's disease and a number of lines of previous therapies prior to ustekinumab, it is difficult to attribute an event to a specific drug.

5. Conclusions

In conclusion, in this study of adult patients with Crohn's disease in Europe the observed long-term safety profile of ustekinumab was consistent with the established safety profile of ustekinumab from clinical trials and available post-marketing data.

Author contributions

Laurent-Peyrin Biroulet: formal analysis, writing – review and editing. Maciej Nazar: conceptualization, methodology, writing – review and editing. Anna Sheahan: writing – review and editing. Anja Geldhof: conceptualization, methodology, supervision, writing – review and editing. Ahlem Azzabi: writing – review and editing. Filip Baert: formal analysis, writing – review and editing. Charlotte Mailhat: writing – review and editing. Hélène Rousseau: data curation, formal analysis, writing – review and editing. Jean-François Rahier: formal analysis, writing – review and editing. Laurent Beaugerie: conceptualization, methodology, formal analysis, writing – review and editing.

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Data availability statement

The data underlying this article will be shared upon reasonable request to the corresponding author.

Declaration of competing interest

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M.N. is an employee of Johnson&Johnson.

A.S. is an employee and shareholder of Johnson&Johnson.

A.G. is an employee of J&J and holds company stock/stock options.

A.A. is an employee of Johnson&Johnson and holds company stock/stock options.

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H.R. has no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2025.09.026.

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