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Observations and Research

Certolizumab Pegol Treatment in Patients With Crohn's Disease: Final Safety Data From the SECURE Registry

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Background: Crohn's disease (CD) treatment is associated with increased risks of infection and malignancies. Although the safety of certolizumab pegol (CZP) is well established, long-term data from community-based observational studies are lacking.

Aim: This study aimed to evaluate long-term safety outcomes of patients from the SECURE registry receiving CZP relative to other CD treatments, including corticosteroids, immunosuppressants, and biologics. The primary outcome of this observational study was the evaluation of malignancies.

Methods: Adult patients with CD were prospectively monitored for up to 8 years. Pre-specified data were collected for all enrolled patients. Adverse events of interest (AEoIs) were reported per 100 patient-years (PY) of exposure. Incidence rate ratios (IRRs) were calculated for AEoIs using multivariate regression analysis accounting for exposure to multiple treatments. Malignancies reported after any exposure to CZP were attributed to CZP. Post-hoc analyses were conducted to evaluate non-melanoma skin cancer (NMSC), lymphoma, and pregnancy outcomes.

Results: A total of 3072 patients were enrolled in the study. The risk of AEoIs was similar between patients with only CZP exposure versus comparator exposure. Among patients with any CZP exposure, there was a higher frequency of serious infections (IRR: 2.56 [95% confidence interval (CI): 2.00, 3.29]) and hypersensitivity or anaphylactic reactions (IRR: 4.11 [95% CI: 1.80, 9.38]) versus patients with comparator exposure. Malignancy rates were similar across groups; however, concomitant use of thiopurines was associated with higher odds of NMSC (odds ratio: 2.30 [95% CI: 1.09, 4.89]). Most cases of lymphoma (5/7) occurred in patients with exposure to thiopurines. Pregnancy outcomes were similar across groups.

Conclusions: No new safety signals were identified for CZP; the use of thiopurines was identified as a risk factor for NMSC.

Trial registration: NCT00844285.

Lay Summary

We report findings from SECURE, a post-approval registry study measuring safety outcomes among patients with Crohn's Disease treated with certolizumab pegol. No new safety concerns were identified; however, the use of thiopurines was a risk factor for non-melanoma skin cancer.

Key Words: certolizumab pegol, Crohn's disease, SECURE registry, malignancy, lymphoma, TNFi, non-melanoma skin cancer

Introduction

Background

Crohn's disease (CD) is a chronic inflammatory disease that affects the gastrointestinal tract, causing diarrhea, abdominal pain, fatigue, and weight loss. Crohn's disease typically requires long-term treatment with corticosteroids, immunosuppressives, such as thiopurines and methotrexate, or biologics, including tumor necrosis factor inhibitors (TNFis).[1,2] Although some studies have shown that TNFis, including infliximab, adalimumab, and certolizumab pegol (CZP), may increase the risk of serious infection, evidence of the safety of these drugs remains inconclusive.[3,4] Consistent evidence has shown that thiopurines such as azathioprine (AZA) and 6-mercaptopurine increase the risk of both non-melanoma skin cancer (NMSC) and lymphoma, likely due to their immunosuppressive effects that can compromise

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immune surveillance of cancers and facilitate replication of oncogenic viruses such as human papillomavirus (HPV) and Epstein-Barr virus (EBV).[5–9] The evidence that an analogous risk exists for TNFi therapies is less clear, potentially due to confounding effects caused by concurrent administration of TNFis and thiopurines, which are commonly taken together.[5,10] Two large-scale registries have evaluated the safety profiles of biologics used to treat CD: the TREAT registry, which evaluated infliximab, and the PYRAMID registry, which evaluated adalimumab. Both registries found no increase in the frequency of malignancies for patients taking these medications compared to other treatments.[11–13] While a large French administrative database analysis indicated that TNFi exposure was an independent risk factor for lymphoma,[14] and a United States nested case-control study showed that NMSC was increased by concomitant thiopurine use,[6] a recent meta-analysis did not support these findings.[15] Therefore, additional data regarding the potential associations between TNFi and immunosuppressive-related cancers are needed.

Certolizumab pegol is a PEGylated, humanized, Fc-free, Fab' fragment TNFi therapy that was approved by the US Food and Drug Administration (FDA) in 2008 to treat moderate-to-severe CD and is injected subcutaneously every 4 weeks following an initial dosing.[16,17] The safety and efficacy of CZP in the treatment of CD and other inflammatory diseases, including rheumatoid arthritis, axial spondyloarthritis, psoriatic arthritis, and psoriasis, have been investigated through randomized controlled trials, the results of which have shown CZP to have a similar safety profile to other TNFi therapies.[5,18] Furthermore, a study investigating CZP safety during pregnancy detected no signal for adverse pregnancy outcomes or congenital malformations.[19]

This study reports outcomes from SECURE (NCT00844285), an FDA-mandated post-approval registry study, and provides additional data regarding the safety of CZP. The study began in January 2009, with the goal of collecting prospective data on 2000 patients prescribed CZP and 2000 patients prescribed other treatments for CD, including other biological therapies. Findings are presented from an extended follow-up period, allowing for a more comprehensive evaluation of long-term safety outcomes associated with CZP.

The objective of the SECURE registry was to measure the safety outcomes among patients treated with CZP compared to those among patients exposed to other treatments. Adverse events of interest (AEoIs) included serious infections, opportunistic infections, serious cardiovascular events, congestive heart failure, demyelinating-like disorders, blood disorders and serious bleeding events, autoimmune disorders, hypersensitivity, anaphylactic reactions, or other serious skin reactions, lymphoma, and other malignancies. Lymphoma, NMSC, and pregnancy outcomes were further investigated in post-hoc analyses.

Methods

Study Design

This prospective, open-label observational registry study, conducted in the United States, was designed to monitor the long-term safety of CZP relative to other CD treatments when used in clinical practice in patients with CD. Study enrollment began in January 2009 and ended in September 2017, when the protocol was amended to reduce the patient follow-up period from 10 to 8 years and close the enrollment period following an agreement with the FDA that the study would be completed upon reaching a sufficient patient enrollment count and follow-up period cutoff. Patients were monitored from enrollment until the conclusion of the study in August 2020 (Figure 1). Selected gastroenterologists and internal medicine physicians from 196 community-based and academic practice settings across all regions of the United States participated in the registry.

Recruitment of all patients was monitored and controlled as needed to ensure balanced enrollment over time. All patients received and used their medications following their normal course of medical treatment according to

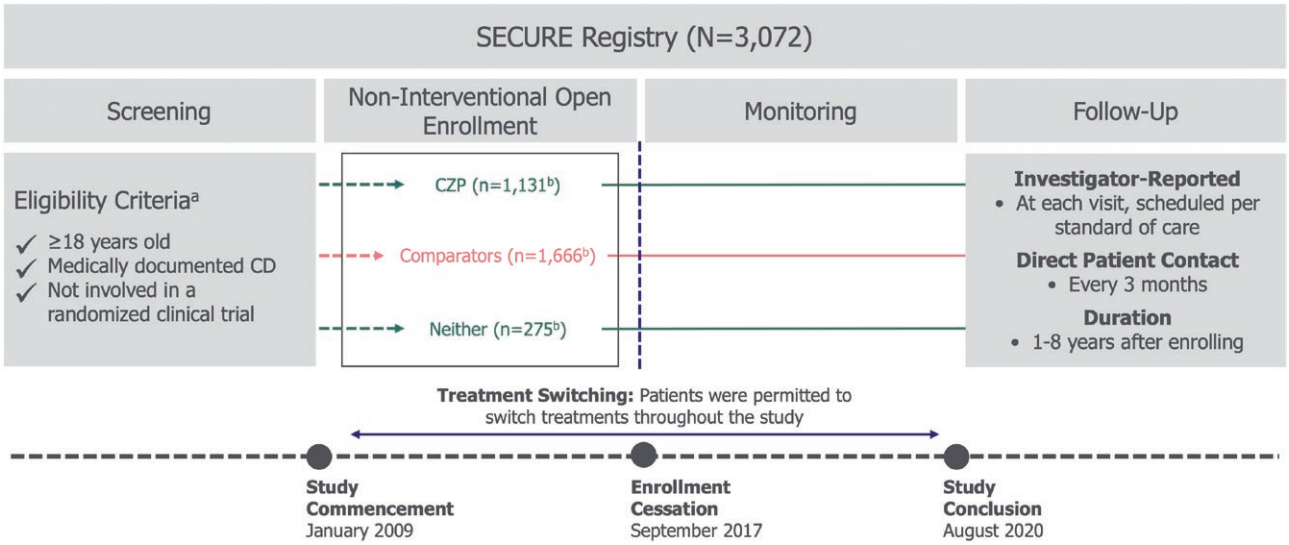

Figure 1. Study design. [a]The decision to prescribe CZP or other medications must have been made by the Investigator independently of the decision to include the patient in the study; [b]The indicated *n* numbers correspond to the number of patients in each group at baseline, but treatment switching could occur at any time. Abbreviations: CD, Crohn's disease; CZP, certolizumab pegol.

clinical judgment; no additional diagnostic or monitoring procedures were applied. Patients were permitted to add, withdraw, or switch any medication, or to be withdrawn from the study, at the discretion of their healthcare provider. Because the study was designed to follow a real-world standard of care, patients were likely to receive other treatments for CD as part of their treatment plan in the regular course of practice.

Following enrollment, no mandatory visits were required as part of this registry's protocol. Enrolled patients were followed for up to 8 years, and investigator-reported information was collected per standard of care during normal visits or via phone contact. Investigators reported all serious adverse events (SAEs) and non-serious AEoIs to the registry, which were collected and summarized in aggregate. Patient-reported data were collected every 3 months through online forms, mail surveys, or phone calls, as preferred by the patient.

All investigator-reported data were retained as source data in each patient's medical record. Data were collected for this registry study from both the physicians and patients using an electronic data capture system. Participating physicians and enrolled patients entered data into a specific electronic case report form (eCRF). Data collected from enrolled patients by mail surveys or phone calls were entered in the eCRF by an independent patient interview service.

Participants

Patients aged 18 years or older with medically documented CD were recruited by their physicians and were eligible to participate in the SECURE registry after providing written informed consent. Patients who were participating in randomized, blinded clinical trials were not eligible for inclusion; however, involvement in other registries where patients followed routine clinical practice was permitted.

The decision to prescribe CZP or other medications was made at the discretion of the healthcare provider independently of the decision to include the patient in the study. For a patient to enroll within the CZP group, they must have received treatment with CZP for the first time within 2 months following enrollment into the registry, or received treatment with CZP for ≤12 months, including a CZP dose within 2 months following enrollment (Figure 2).

Patients receiving comparator treatments were eligible to enroll within the Comparator group and participate in the registry if they were switching CD treatments or beginning CD treatment for the first time, or if they had received new CD treatment within 2 months of enrollment into the registry. Previous CZP treatment was prohibited in the Comparator group. Patients must have been receiving TNFi (or another approved biologic), immunosuppressant, or systemic corticosteroid treatment for ≤12 months at the time of enrollment and must have received the treatment within 2 months following enrollment into the registry. Approximately half of the enrolled patients had been receiving CZP for ≤12 months or were about to receive CZP at the time of enrollment.

Separately from enrollment, patients were categorized by baseline treatment status as belonging to the CZP at Baseline treatment group if they had received CZP up to 70 days prior to baseline. Patients were assigned to the Comparator at

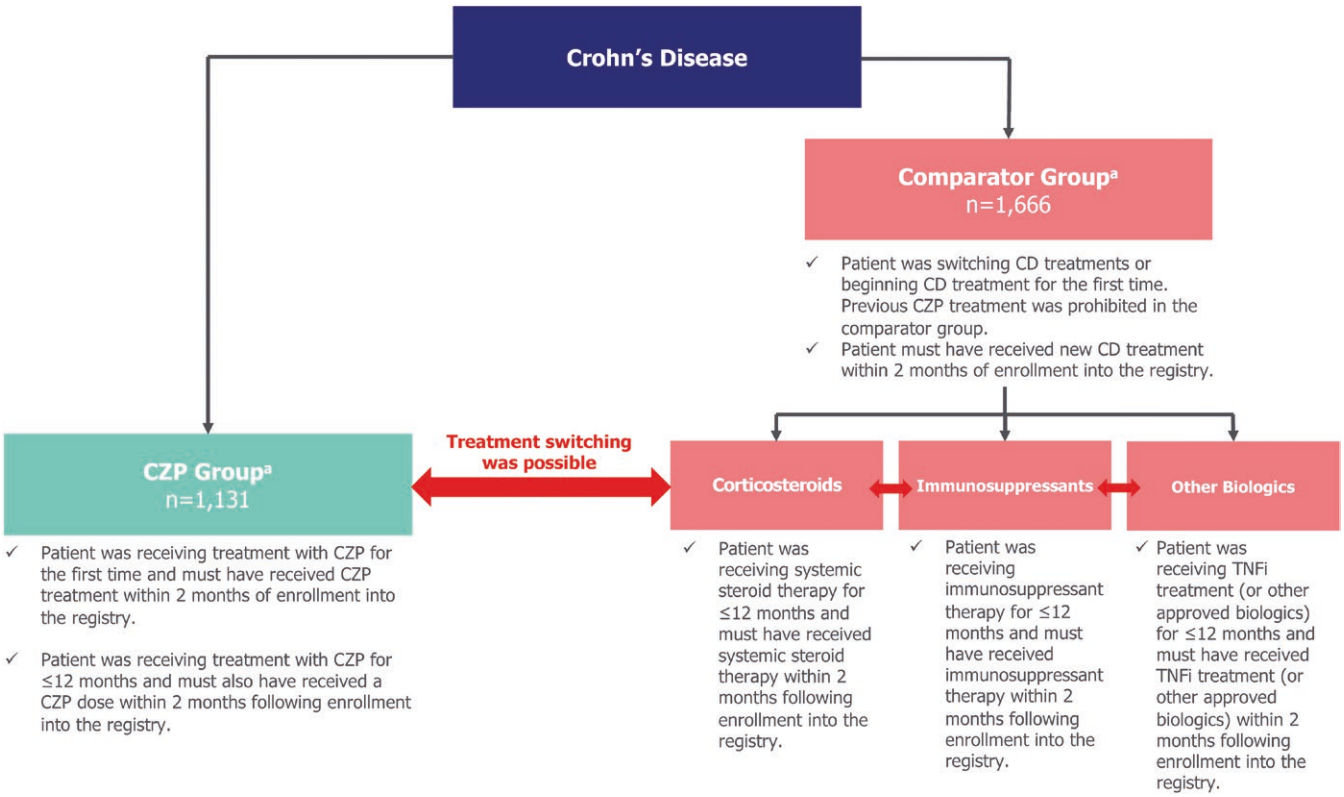

Figure 2. Enrollment group definitions. [a]Patients are categorized by treatment group at enrollment; there were 275 additional patients without exposure to CZP or a comparator at enrollment. Patients in the Comparator group received treatment with a wide variety of comparator medications, including biologics, immunosuppressants, and corticosteroids. A complete list of medications used in the Comparator group is presented in Table S3. Abbreviations: CD, Crohn's disease; CZP, certolizumab pegol; TNFi, tumor necrosis factor inhibitor.

Baseline treatment group if they had only received comparator medications or the No CZP/No Comparator at Baseline treatment group if they had received neither.

For analysis of malignancies, patient-time and events were categorized as CZP Exposure or CZP Non-Exposure, where the CZP Exposure group systematically included patient-time for patients who received CZP from their first dose until the end of the study, even after ending treatment or switching from CZP to a comparator treatment (Malignancy rules; Figure S1). As malignancies could potentially manifest after exposure, these criteria were set to allow for the latency period expected for a malignancy to be detected after exposure to a causative agent. This approach was the most conservative method to account for exposure-related malignancies. The CZP Non-Exposure group included patient-time for any patients without prior exposure to CZP up until their first exposure to CZP or the end of the reporting period.

For analysis of all nonmalignant AEoIs, patient-time and events were categorized as CZP, Comparator, Overlap, Any CZP, or Non-CZP/Non-Comparator. Patients switched groups based on treatment regimen, and AEoIs were attributed to the treatment group or groups a patient was in at the time of the event, with the rationale being that nonmalignant AEoIs, if any, would be likely to occur during treatment administration. The CZP category included patient-time with exposure only to CZP, and the Comparator category included patient-time with exposure to corticosteroids, immunosuppressants, and/or biologics other than CZP. The Overlap category included patient-time taking both CZP and a comparator or those who stopped taking one but were still within the half-life of that medication when initiating another medication. For corticosteroids, immunosuppressants, and biologics, the exposure half-lives were 7 days, 28 days, and 70 days, respectively. Any CZP included patient-time in both the CZP and Overlap groups and Non-CZP/Non-Comparator included patient-time with no exposure to CZP or any comparator, including treatments such as diet or antibiotics (Acute event rules; Figure S2).

Study Measures

The primary outcome of this observational study was the evaluation of malignancies. Other AEoIs evaluated included serious and opportunistic infections, serious cardiovascular events, congestive heart failure, demyelinating-like disorders, aplastic anemia, pancytopenia, thrombocytopenia, neutropenia, leucopenia, serious bleeding events, lupus and lupus-like illnesses, and serious skin reactions. Although not designated as AEoIs, autoimmune disorders, hypersensitivity and anaphylactic reactions, and pregnancy-related adverse events (AEs) were also summarized.

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.0. Medications were coded using the March 2018 World Health Organization Drug Reference List.

Statistical Analysis

The primary analysis of this study was descriptive and aimed to provide point estimates and 95% CIs for the rates of meaningful safety events. Adverse events rates were calculated by dividing the number of reported safety events by the patient-years (PY) at risk. Accordingly, rates are reported per 100 PY of exposure. A secondary analysis compared CZP event rates and Comparator event rates using incidence rate ratios (IRRs) and 95% CIs from conventional multivariate regression analyses. All data analyzed are for patients in the enrolled set. Missing safety data were not imputed, but if the relationship of an AE to CD treatment was missing, the event was categorized as having a reasonable probability of being caused by the treatment.

A post-hoc analysis was conducted to further evaluate any signals of association for NMSC and potential risk factors. Incidence of NMSC was assessed by exposure-adjusted incidence rates; rates are reported per 100 PY. Univariate logistic regression was used to determine the strength of association between potential risk factors and NMSC outcomes.

An additional post-hoc analysis was conducted to investigate the association between lymphoma and the use of AZA. Incidence rates of lymphoma were assessed for patients exposed to thiopurines and for those exposed to AZA using malignancy parameters; rates are reported per 100 PY.

A post-hoc analysis was also conducted to assess pregnancy outcomes. Pregnancy outcomes and related SAEs were summarized by treatment.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the current version of the applicable regulatory and International Council for Harmonisation (ICH)-Good Clinical Practice (GCP) requirements, the ethical principles that have their origin in the principles of the Declaration of Helsinki, and the local laws of the countries involved. This study was conducted in compliance with legal requirements for non-interventional studies.

Results

Patient Disposition and Baseline Characteristics

A total of 3072 patients were enrolled in the study at 196 centers in the United States. At baseline, 1131 patients were receiving CZP, 1666 patients were receiving a Comparator, and 275 patients had no exposure to CZP or a Comparator.

Eight years of follow-up data, corresponding to the full duration of the study, were collected for 107 patients (3.5%). Less than 8 years of follow-up data were collected for the remaining 2965 (96.5%). At 1 year of follow-up, while only 34 patients (3.0%) in the CZP at Baseline group had discontinued study participation, 599 (53.0%) were censored (excluded from analysis) due to treatment switching from CZP to any comparator. For patients in the Comparator at Baseline group, 129 (7.7%) had discontinued at 1 year of follow-up, and 232 (13.9%) were censored due to switching from a comparator to CZP. By the end of follow-up, 157 patients (13.9%) in the CZP at Baseline group had discontinued, and 957 (84.6%) were censored due to treatment switching. Among patients in the Comparator at Baseline group, 1010 (60.6%) had discontinued at the end of follow-up, and 481 (28.9%) were censored due to treatment switching. The most common reasons for discontinuation across the treatment groups were loss to follow-up (29.0% [n = 890]), withdrawal of consent (28.6% [n = 880]), and site closure (termination or completion of research activities

at a particular site for various reasons, such as physician relocation, their retirement, or a lack of interest in continuing the study; 24.6% [*n* = 756]).

Study retention was lower than expected due to the reasons described above. The proportion of patients followed for five or more years was 494/1131 (43.7%) among patients in the CZP at Baseline group and 781/1666 (46.9%) among patients in the Comparator at Baseline group.

The mean age of all patients at baseline was 40.0 years, and 58.5% of patients were female. Most patients were White (89.2%), and not Hispanic or Latino (95.1%). Other characteristics and disease severity at baseline are summarized in Table 1.

Medical history at baseline is summarized in Table S1. Disease severity was determined by the investigator. Patients in the CZP at Baseline group had more active disease compared with the Comparator at Baseline group. A lower proportion of patients in the CZP at Baseline group were in remission (12.3%) compared with patients in the Comparator at Baseline group (33.3%). Patients in the CZP at Baseline group had a higher percentage of moderate-to-severe (38.2%) or severe (8.4%) disease compared with patients in the Comparator at Baseline group (23.7% and 3.2%, respectively). The proportion of mild-to-moderate disease was similar for patients in the CZP at Baseline and Comparator at Baseline treatment groups (41.1% and 39.8%, respectively).

Table 1. Patient demographics and disease severity at baseline.

Characteristic	All pts (*N* = 3072)
Age (y), mean (SD)	40.0 (15.3)
Sex	
Female, *n* (%)	1796 (58.5)
Racial group	
American Indian/Alaska native, *n* (%)	7 (0.2)
Asian, *n* (%)	35 (1.1)
Black, *n* (%)	212 (6.9)
Native Hawaiian/other Pacific Islander, *n* (%)	7 (0.2)
White, *n* (%)	2740 (89.2)
Other/mixed, *n* (%)	54 (1.8)
Missing, *n* (%)	17 (0.6)
BMI (kg/m^2)	
n	3038
Mean (SD)	26.8 (7.0)
Disease severity (physician's assessment)	
Remission, *n* (%)	766 (24.9)
Mild–moderate, *n* (%)	1251 (40.7)
Moderate–severe, *n* (%)	891 (29.0)
Severe, *n* (%)	164 (5.3)
CD treatment[a]	
Corticosteroids, *n* (%)	935 (30.4)
Immunosuppressants, *n* (%)	963 (31.3)
Narcotics, *n* (%)	251 (8.2)
Other biologics, *n* (%)	1072 (34.9)

Abbreviations: BMI, body mass index; CD, Crohn's disease; pts, patients; SD, standard deviation; y, years.
Enrolled set. [a]A complete list of CD medications used in each treatment group is presented in Table S3.

Exposure to treatment is summarized by acute event and malignancy categories in Table S2. Using acute event rules, patients in the Comparator group (*n* = 2478) were primarily exposed to the biologics adalimumab (37.2%) and infliximab (34.8%), the immunosuppressants AZA (25.6%) and mercaptopurine (16.5%), and the corticosteroids prednisone (38.0%) and budesonide (24.1%; Table S3). Patients in the Any CZP group (*n* = 1428) often received treatment with other biologics in addition to CZP while within the half-life of CZP or the other biologic (40.7%); immunosuppressants (45.9%) and corticosteroids (55.6%) were received alongside CZP treatment or during the half-life of either medication. Within the Any CZP group, the most common other biologics were adalimumab (21.0%), infliximab (14.1%), and vedolizumab (6.0%). The most common immunosuppressants were AZA (21.6%), methotrexate (15.7%), and mercaptopurine (12.5%). The most common corticosteroids were prednisone (40.8%) and budesonide (23.3%).

Overall Malignancies

A total of 1463 patients initiated treatment with CZP at any point and were therefore considered exposed to CZP from initiation until the end of the reporting period for the analysis of malignancies (6720 PY; Exposure group). A total of 1887 patients initiated treatment with a comparator without prior exposure to CZP (7812 PY; Non-Exposure group). These patients were treated with a comparator until CZP exposure or the end of the reporting period. The Exposure group did not have a significantly increased risk of any malignancy compared to the Non-Exposure group (IRR: 0.72; 95% confidence interval [CI]: 0.46, 1.14; Figure 3).

Non-Melanoma Skin Cancer

Non-melanoma skin cancer had an incidence rate of 0.16 cases per 100 PY (95% CI: 0.08, 0.29) in the Exposure group, with 11 cases, and 0.22 per 100 PY (95% CI: 0.13, 0.35) in the Non-Exposure group, with 17 cases, corresponding to an IRR of 0.75 (95% CI: 0.35, 1.60; Table 2). Concomitant use of thiopurines was associated with higher odds of NMSC (odds ratio [OR]: 2.30 [95% CI: 1.09, 4.89]), with the highest risk observed for concomitant use of AZA (OR: 3.32 [95% CI: 1.58, 7.01]; Figure 4).

Lymphoma

Lymphoma had an incidence rate of 0.07 cases per 100 PY (95% CI: 0.02, 0.17) in the Exposure group, with 5 cases, and 0.03 per 100 PY (95% CI: 0.00, 0.09) in the Non-Exposure group, with 2 cases, corresponding to an IRR of 2.91 (95% CI: 0.57, 15.01; Table 2). Among the 5 patients who experienced a lymphoma event in the Exposure group, 3 had prior exposure to thiopurines, and one was diagnosed with rheumatoid arthritis. Both of the patients who experienced a lymphoma event in the Non-Exposure group had prior or concomitant exposure to AZA. Incidence rates of malignant lymphoma were not notably different between patients exposed to CZP, thiopurines (0.04 per 100 PY [95% CI: 0.00, 0.24]), and any thiopurines or AZA (0.07 per 100 PY [95% CI: 0.00, 0.39]; Table 2).

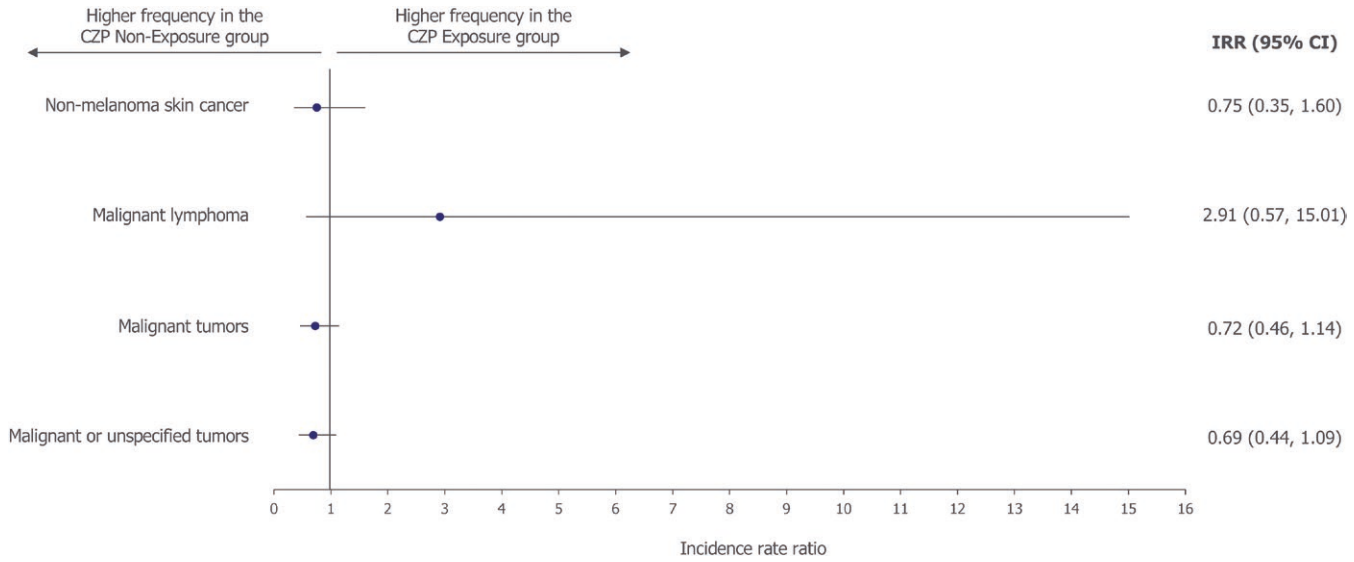

Figure 3. Incidence rate ratios (CZP Exposure/Non-Exposure) for overall malignancies. Enrolled set. Abbreviations: CI, confidence interval; CZP, certolizumab pegol; IRR, incidence rate ratio.

Table 2. Number and incidence rates of overall malignancies for patients with CZP exposure alone versus concomitant exposure to any thiopurines or azathioprine (ES).

Category *n* (%) [# of events] Incidence rate/100 PY (95% CI)	CZP Exposure *N* = 1463	CZP Non-Exposure		
		All CZP Non-Exposure[a] *N* = 1887	Thiopurines Exposure[a] *N* = 690	AZA Exposure[a] *N* = 431
Any malignancy				
Malignant or unspecified tumors	30 (2.1) [33] 0.45 (0.31, 0.65)	50 (2.6) [62] 0.65 (0.48, 0.86)	21 (3.0) [25] 0.92 (0.57, 1.40)	15 (3.5) [18] 1.08 (0.61, 1.79)
Malignant tumors	30 (2.1) [33] 0.45 (0.31, 0.65)	48 (2.5) [60] 0.63 (0.46, 0.83)	20 (2.9) [24] 0.87 (0.53, 1.35)	14 (3.2) [17] 1.01 (0.55, 1.69)
Malignant lymphoma	5 (0.3) [5] 0.07 (0.02, 0.17)	2 (0.1) [2] 0.03 (0.00, 0.09)	1 (0.1) [1] 0.04 (0.00, 0.24)	1 (0.2) [1] 0.07 (0.00, 0.39)
Non-melanoma skin cancer	11 (0.8) [12] 0.16 (0.08, 0.29)	17 (0.9) [22] 0.22 (0.13, 0.35)	10 (1.4) [13] 0.43 (0.21, 0.80)	8 (1.9) [11] 0.57 (0.25, 1.13)
Any SAE malignancy	17 (1.2) [17] 0.25 (0.15, 0.41)	30 (1.6) [33] 0.39 (0.26, 0.55)	9 (1.3) [9] 0.39 (0.18, 0.73)	6 (1.4) [6] 0.42 (0.16, 0.92)
Drug-related malignancy[b]	8 (0.5) [8] 0.12 (0.05, 0.24)	13 (0.7) [13] 0.17 (0.09, 0.29)	9 (1.3) [9] 0.39 (0.18, 0.74)	6 (1.4) [6] 0.43 (0.16, 0.93)
Drug-related SAE malignancy[b]	5 (0.3) [5] 0.07 (0.02, 0.17)	4 (0.2) [4] 0.05 (0.01, 0.13)	1 (0.1) [1] 0.04 (0.00, 0.24)	0
Malignancy resulting in death	1 (0.1) [1] 0.01 (0.00, 0.08)	7 (0.4) [7] 0.09 (0.04, 0.18)	2 (0.3) [2] 0.09 (0.01, 0.31)	1 (0.2) [1] 0.07 (0.00, 0.39)

Abbreviations: AZA, azathioprine; CI, confidence interval; CZP, certolizumab pegol; ES, enrollment set, PY, patient-years; SAE, serious adverse event.
[a]Subgroups were not mutually exclusive; patients could contribute exposure time and events to the CZP Exposure, CZP Non-Exposure, Thiopurine, and AZA groups. After exposure to CZP, all patient-time and events were attributed to the CZP Exposure group.
[b]Malignancy events were deemed drug-related by the treating physician.

Non-Malignancy Adverse Events of Interest

Adverse events other than malignancies were summarized separately to account for treatment switching, allowing patients to contribute exposure time to multiple exposure groups. A total of 824 patients had time exposed only to CZP (1436 PY; CZP group), and 2478 patients had time exposed only to a comparator (9320 PY; Comparator group). There were 1165 patients, who had time with concomitant exposure to both CZP and a comparator (1500 PY; Overlap group), 1428 patients with any time exposed to CZP both alone and with a comparator (2936 PY; Any CZP group), and 1022 patients with time not exposed to any treatment (2220 PY; Non-CZP/Non-Comparator group).

The most common AEoI observed was a serious infection, which had an incidence rate of 2.03 per 100 PY (95% CI: 1.35, 2.94) in the CZP group, 4.08 per 100 PY (3.36, 4.91) in the Any CZP group, 1.59 per 100 PY (1.34, 1.88) in the Comparator group, and 1.46 per 100 PY (0.98, 2.08) in the

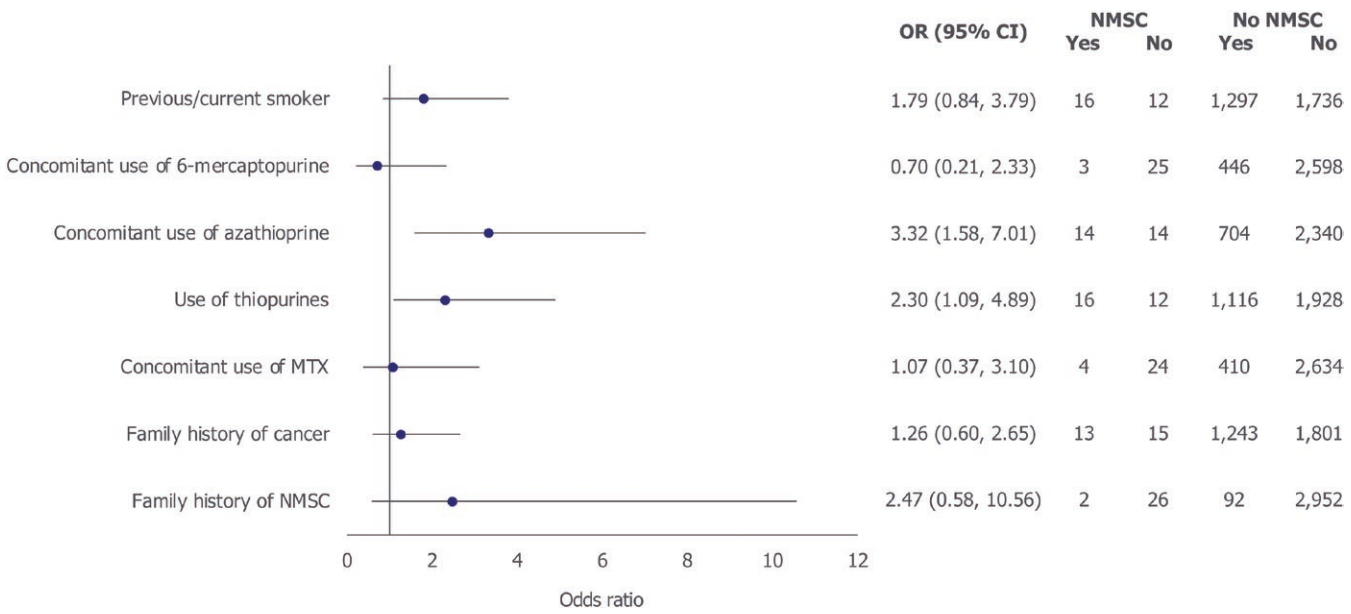

Figure 4. Odds ratios for selected potential risk factors for NMSC. Abbreviations: CI, confidence interval; MTX, methotrexate; NMSC, non-melanoma skin cancer; OR, odds ratio.

Non-CZP/Non-Comparator group (Table S4). The most common SAEs observed by the system organ class were gastrointestinal disorders, followed by infections and infestations (Table S5).

There was no evidence of increased risk of serious infection or other category of AEoIs for patients in the CZP group compared with the Comparator group (IRR: 1.28 [95% CI: 0.85, 1.92]). An increased risk of serious infections (IRR: 2.56 [95% CI: 2.00, 3.29]) and hypersensitivity or anaphylactic reactions (IRR: 4.11 [95% CI: 1.80, 9.38]) were observed for the Any CZP group compared with the Comparator group (Figure S3). Among patients without concomitant immunosuppressant or steroid exposure, those in the Any CZP group had an increased risk of serious infections compared with patients in the Comparator group (IRR: 2.85 [95% CI: 1.54, 5.26]). Similarly, the risk of hypersensitivity or anaphylactic reactions was higher among patients in the Any CZP group compared with the Comparator group (IRR: 2.69 [95% CI: 0.49, 14.71]) for patients without concomitant immunosuppressant or steroid exposure.

Pregnancies

There were 1796 female patients enrolled in the SECURE registry, 178 of whom had one or more pregnancies during follow-up. Across all treatment groups, there were 235 pregnancies with exposure to therapy in the first trimester, 209 pregnancies with exposure to therapy in the second trimester, and 197 pregnancies with exposure to therapy in the third trimester. There were 25 patients with at least one pregnancy in the CZP group (4.7% of 528 female patients in the group), 70 in the Any CZP group (7.9% of 885 female patients in the group), and 104 in the Comparator group (7.3% of 1420 female patients in the group; Table S6). The proportion of pregnancy-related SAEs was similar across groups (Table S7). The most frequent SAE was spontaneous abortion, reported for 6 (1.1%), 14 (1.6%), and 20 (1.4%) patients in the CZP, Any CZP, and Comparator groups, respectively. A premature baby was reported for 1 (0.2%), 2 (0.2%), and 5 (0.4%) patients in the CZP, Any CZP, and Comparator groups, respectively. Low birth weight was reported for 1 patient in each of the 3 groups (0.2%, 0.1%, and 0.1% for the CZP, Any CZP, and Comparator groups, respectively) and polyhydramnios was reported for 1 patient each in the CZP and Any CZP groups (0.2% and 0.1%, respectively). Polyhydramnios was not reported for any patients in the Comparator group.

Discussion

SECURE was a long-term, observational safety registry study in which patients with CD received treatment with CZP or comparator treatment and were followed for up to 8 years. Predefined AEoIs were the focus of this registry, and malignancy rates were the primary outcome measure. We found that rates of malignancies in patients receiving CZP were consistent with previous studies of CZP in CD,[5,17–19] and they were similar to those of patients using other biologics for CD treatment who participated in other long-term registries such as PYRAMID and TREAT.[11–13] For example, in the PYRAMID registry, the incidence of NMSC and lymphoma in patients exposed to adalimumab was 0.2 per 100 PY and <0.1 per 100 PY, respectively.[12] Similarly, in the TREAT registry, the incidence of NMSC and lymphoma in patients exposed to infliximab was 0.2 per 100 PY and 0.04 per 100 PY, respectively.[11] In SECURE, the incidence of NMSC and lymphoma in patients exposed to CZP was 0.16 per 100 PY and 0.07 per 100 PY, respectively. Given that NMSC is commonly associated with immunosuppressive TNFi therapy,[10] large-scale registries such as PYRAMID, TREAT, and SECURE would likely have detected any relationship between the 2. No such relationship was observed in any of the registry data.[11] These observations emphasize the lack of a causal relationship between TNFi exposure and the risk of NMSC.

In post-hoc analyses, incidence rates of NMSC were similar for patients with and without exposure to CZP (0.16 [95% CI: 0.08, 0.29] and 0.22 [95% CI: 0.13, 0.35] per 100 PY, respectively), but the risk of NMSC was higher for patients exposed to AZA or any thiopurines compared with patients who were not exposed to thiopurines (OR: 2.30 [95% CI: 1.09, 4.89]). These results are consistent with previous studies, which indicated that thiopurines were associated with an increased risk of NMSC among patients with inflammatory bowel disease.[7,20]

Evidence on the relationship between TNFi exposure and lymphoma risk is also inconclusive. While some studies have suggested a positive association between TNFi exposure and lymphoma risk, other research has failed to confirm this observation.[14,15] Similarly, in SECURE, most cases of lymphoma (5 of 7 in the study population) occurred in patients with prior or concomitant exposure to AZA or other thiopurines, or with rheumatoid arthritis (1 of 7 in the study population), both of which are known risk factors for lymphoma.[21–23] However, given that the number of patients diagnosed with lymphoma in SECURE was low, the failure to identify an association between lymphoma risk and CZP exposure should be interpreted with caution.

Analyses of AEoIs in the SECURE registry were also consistent with previous studies of CZP in CD.[18,19] No evidence for an increased risk of AEoIs was observed with CZP treatment versus Comparator treatment. An increased risk of serious infections, hypersensitivity reactions, and anaphylactic reactions was observed in the Any CZP group, which could have included comparator exposure, relative to the Comparator group. Thus, it is possible that the observed AEoIs may have been attributed to other therapies that the patients received. The increased risk of serious infections was also observed among patients without concomitant use of immunosuppressants or corticosteroids, which have individually been found to increase the risk of serious infections.[24] Serious infections, hypersensitivity reactions, and anaphylactic reactions are considered known risks of TNFi therapies.[25–27] In the TREAT registry that provided over 35 000 PY of observation, the incidence of serious infections in patients exposed to infliximab was 2.15 per 100 PY.[11] In SECURE, the incidence of serious infection was similar in patients in the CZP group at 2.03 per 100 PY. In contrast, the PYRAMID registry reported that the incidence of serious infection among patients exposed to adalimumab was 5.0 per 100 PY.[12]

Pregnancy and maternal outcomes for CZP-exposed patients in SECURE were consistent with the established safety profile of CZP and the risk summary for pregnancy in the CZP US Package Insert.[19,28] The limited number of patient pregnancies across treatment groups, variability in pregnancy follow-up for CZP-exposed versus non-CZP-exposed pregnancies, and missing/unknown pregnancy data associated with the real-world study design prevented a meaningful comparison of adverse pregnancy and maternal outcomes by treatment group.

A limitation of this study is the duration of observation for the CZP group, which was limited due to treatment switching, reflecting real-world medical practice. At 1 year into the study, more than half of the patients who received CZP at baseline were censored due to treatment switching from CZP to any comparator. Moreover, data from patients who discontinued any comparator and switched to another comparator were unavailable. Thus, direct comparisons should be interpreted cautiously, and further analyses are needed to assess whether observed trends may be influenced by intra-comparator switching. In addition, the missing or unknown pregnancy data that resulted from the real-world study design prevented a meaningful comparison of adverse pregnancy and maternal outcomes by treatment exposure group.

Despite these limitations, several factors contributed to the strength of the present findings, and the results confirm the safety profile of CZP that was observed in controlled clinical trials. The primary strengths of this study are the large sample size and duration of follow-up, including 6720 and 7812 PY of follow-up for the analysis of malignancies in the CZP Exposure and CZP Non-Exposure groups, respectively. Furthermore, the observation of real-world clinical practice and the widespread geographic coverage of sites across the United States further add to the strength of these findings. In addition, the effect of concomitant thiopurine use was examined, revealing a potential association with an increased risk of NMSC. These insights may be valuable for the management of patients on combination therapies and further inform clinical decision-making.

Conclusions

In the SECURE registry, the rates of malignancies and other AEoIs associated with CZP treatment were similar to the standard of treatment for CD and are consistent with previous long-term open-label studies of TNFis in CD, including the TREAT and PYRAMID registries.[11,13] No new safety signals were identified with respect to the well-established safety profile of CZP. Future research could explore CZP in specific subpopulations and investigate its underlying mechanisms and interactions with other therapies, helping to build on these findings and provide a more comprehensive understanding of CZP's efficacy and safety profile for therapeutic applications in clinical practice.

Supplementary Data

Supplementary data is available at *Crohn's & Colitis 360* online.

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Author Contributions

G.R.L., S.D.L., B.G.F., E.V.L., S.N., K.D., P.Q., J.C., T.R.-J., C.A., J.L.S.: substantial contributions to study conception and design, to analysis and interpretation of the data, drafting the article or revising it critically for important intellectual content, and final approval of the version of the article and author list to be published.

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Conflicts of Interest

G.R.L.: served as a speaker, consultant and/or advisory board member for AbbVie, American College of Gastroenterology (associate editor), American Regent, Business Media (editor), Celgene, Eli Lilly and Company, Endo, Ferring, Gastroenterology and Hepatology (editor), Gilead, Janssen, MSD, Morphic Therapeutics, Pfizer, Prometheus, Romark, Salix Pharma, Shire, Springer Science, Takeda, and UCB Pharma, and has received research funding from Celgene, Janssen, Pfizer, Takeda, and UCB Pharma. S.D.L.: served as a speaker, consultant and/or advisory board member for AbbVie, AMT, Bristol Myers Squibb, Eli Lilly and Company, Janssen, Pfizer, Protagonist Pharma, Takeda, and TLL Pharma, and has received research funding from AbbVie, AMT, Bristol Myers Squibb, Janssen, and Pfizer. B.G.F.: served as a speaker, consultant, and/or advisory board member for AbbVie, AbolerIS, AgomAB Therapeutics, Allianthera, Amgen, AnaptysBio, Applied Molecular Transport Inc, Arena Pharma, Avoro Capital Advisors, Atomwise, Axio Research, BioJamp, Biora Therapeutics, Boehringer Ingelheim, Boxer, Bristol Myers Squibb, Celsius Therapeutics, Celgene, Connect BioPharma, Cytoki, Disc Medicine, Duality, EcoR1, Eli Lilly and Company, Equillium, Ermium, First Wave, First Word Group, Galapagos, Galen Atlantica, Genentech, Gilead, Gossamer Pharma, GSK, Hinge Bio, Hot Spot Therapeutics, Index Pharma, Imhotex, Immunic Therapeutics, JAK Academy, Janssen, Japan Tobacco Inc., Kaleido Biosciences, Landos Biopharma, Leadiant, L.E.K. Consulting, Lenczner Slaght, LifeSci Capital, Lument AB, Millennium, MiroBio, Morgan Lewis, Morphic Therapeutics, Mylan, OM Pharma, Origo BioPharma, Orphagen, Pandion Therapeutics, Pendopharm, Pfizer, Prometheus Therapeutics and Diagnostics, Play to Know AG, Progenity, Protagonist, PTM Therapeutics, Q32 Bio, Rebiotix, REDX Pharma, Roche, Sandoz, Sanofi, Seres Therapeutics, Silverback Therapeutics, Surrozen Inc., Takeda, Teva, Thelium, Tigenix, Tillotts Pharma, Ventyx Biosciences, VHSquared Ltd., Viatris, Ysios, Ysopia, and Zealand Pharma; employee of Alimentiv Inc.; shareholder of Gossamer Pharma. E.V.L.: served as a speaker, consultant, and/or advisory board member for AbbVie, Allergan, Alvotech, Amgen, Arena, Avalo Therapeutics, Boehringer Ingelheim, Bristol Myers Squibb, Calibr, Celgene, Celltrion Healthcare, Eli Lilly and Company, Fresenius Kabi, Genentech, Gilead, GSK, Gossamer Bio, Iota Biosciences, Iterative Scopes, KSL Diagnostics, Janssen, Morphic, Ono Pharma, Pfizer, Protagonist, Scipher Medicine, Sun Pharma, Surrozen, Takeda, and UCB Pharma, and has received research funding from AbbVie, Amgen, AstraZeneca, Bristol Myers Squibb, Celgene, Genentech, Gilead, Janssen, Pfizer, Receptos, Robarts Clinical Trials, Takeda, Theravance, and UCB Pharma; shareholder of Exact Sciences. S.N.: employee of Ferring Pharmaceuticals. K.D.: employee of Ferring Pharmaceuticals. P.Q.: served as a consultant for UCB Pharma and is an employee and owner of PQ Clinical Consulting Ltd. J.C.: employee and shareholder of UCB Pharma. T.R.-J.: employee and shareholder of UCB Pharma. C.A.: consultant for and shareholder of UCB Pharma. J.L.S.: employee and shareholder of UCB Pharma.

Consent for Publication

All the results presented in this article are in aggregate form, and no personally identifiable information was used for this study.

Data Availability

Underlying data from this manuscript may be requested by qualified researchers 6 months after product approval in the United States and/or Europe, or global development is discontinued, and 18 months after trial completion. Investigators may request access to anonymized individual patient-level data and redacted trial documents which may include: analysis-ready datasets, study protocol, annotated case report forms, statistical analysis plans, dataset specifications, and clinical study reports. Prior to the use of the data, proposals need to be approved by an independent review panel at www.Vivli.org, and a signed data-sharing agreement will need to be executed. All documents are available in English only, for a pre-specified time, typically 12 months, on a password-protected portal.

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