Safety of Ustekinumab in Inflammatory Bowel Disease: Pooled Safety Analysis of Results from Phase 2/3 Studies

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Background: Ustekinumab is currently approved globally in Crohn's disease (CD) and psoriatic diseases. Recent phase 3 data demonstrate safety/efficacy in ulcerative colitis (UC). Crohn's disease and UC phase 3 programs had similar study designs, facilitating integrated safety analyses.

Methods: Data from 6 ustekinumab phase 2/3 CD and UC studies were pooled, and safety was evaluated through 1 year. Patients received 1 placebo or ustekinumab (generally 130 mg or ~6 mg/kg) intravenous induction, then subcutaneous (90 mg) maintenance every 8/12 weeks. Analyses incorporated all patients who received ≥1 ustekinumab dose. Safety outcomes are presented as percentages of patients (induction) and as number

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of patients with events per 100 patient-years of follow-up (through 1 year). For key safety events, 95% confidence intervals (CIs) are provided, as appropriate. Hazard ratios with 95% CIs from time-to-event analyses for serious adverse events and serious infections were also performed.

Results: Through 1 year, 2574 patients received ustekinumab (1733 patient-years of follow-up). The number of patients with adverse events per 100 patient-years (placebo 165.99 [95% CI, 155.81–176.67] vs ustekinumab 118.32 [95% CI, 113.25–123.55]), serious AEs (27.50 [95% CI, 23.45–32.04] vs 21.23 [95% CI, 19.12–23.51]), infections (80.31 [95% CI, 73.28–87.84] vs 64.32 [95% CI, 60.60–68.21]), serious infections (5.53 [95% CI, 3.81–7.77] vs 5.02 [95% CI, 4.02–6.19]), and malignancies excluding nonmelanoma skin cancer (0.17 [95% CI, 0.00–0.93] vs 0.40 [95% CI, 0.16–0.83]) were similar between placebo and ustekinumab.

Conclusions: The safety profile of ustekinumab across the pooled inflammatory bowel disease population through 1 year was favorable and generally comparable to placebo. These data are consistent with the established safety profile of ustekinumab across indications.

ClinicalTrials.gov numbers: NCT00265122; NCT00771667; NCT01369329; NCT01369342; NCT01369355; NCT02407236.

Key Words: ustekinumab, inflammatory bowel disease, safety

INTRODUCTION

Ustekinumab is a human monoclonal antibody to interleukin (IL) 12/23p40, first approved to treat patients with moderate to severe psoriasis in 2009.[1–3] Ustekinumab has also become a well-established therapy in Crohn's disease (CD), after initial approval in 2016,[4–6] and received initial approval for ulcerative colitis (UC) in September 2019. Total postmarketing exposure and experience across all indications over 10 years is cumulatively estimated to represent 1,375,000 patient-years (PYs).

Previous publications evaluating the safety of ustekinumab in psoriasis, psoriatic arthritis, CD, and—most recently—UC have consistently demonstrated a safety profile similar to placebo.[7–11] Additionally, the Psoriasis Longitudinal Assessment and Registry (PSOLAR), focused on serious infections, malignancy, major adverse cardiovascular events (MACEs), and mortality, further supports this favorable safety profile, with 12,472 ustekinumab PYs of follow-up.[12]

Integration and analysis of the safety data for CD and UC for a combined inflammatory bowel disease (IBD) population provides more complete information for gastroenterologists, facilitating benefit/risk assessment for their IBD treatment choices. This increases the precision to detect safety signals compared with placebo for all events and increases identification of less frequent events (eg, serious adverse events [SAEs] or serious infections). Furthermore, because ustekinumab IBD indications uniquely employ intravenous (IV) induction, followed by subcutaneous (SC) maintenance dosing (90 mg every 8 or 12 weeks), these integrated safety analyses of all IBD phase 2/3 studies also provide important data examining the possibility that these higher doses or the IBD population might have a different safety profile than the psoriatic diseases.

METHODS

Trial Designs

Safety data in this analysis includes data from two phase 2 CD studies (C0379T07 [T07][13] and CERTIFI[4]), three phase 3 CD studies (two induction studies, UNITI-1 and UNITI-2, and one maintenance study, IM-UNITI[5]), and one phase 3 UC protocol (UNIFI,[11] composed of separate induction and maintenance studies). Details of patient populations and treatment regimens for studies are presented in Supplemental Table S1 and have also been previously published.[4, 5, 11, 13] All trials have been registered at Clinicaltrials.gov: NCT00265122, NCT00771667, NCT01369329, NCT01369342, NCT01369355, NCT02407236.

Randomization to study treatment was centrally performed across all studies. Stratification by investigative site was utilized across all IBD studies. Additional stratification attributes for each study are described. For CERTIFI induction, stratification included initial response to a tumor necrosis factor (TNF) antagonist (ie, response to first TNF antagonist if >1 agent was previously administered). For maintenance, stratification inclued induction dose and, for patients with an initial response to ustekinumab, remission status at 6 weeks. For UNITI, stratification included trial region and Crohn's disease activity index (CDAI) score (≤300 or >300) in both induction studies and initial response to TNF antagonist therapy (yes or no) in UNITI-1. For IM-UNITI, stratification included ustekinumab dose during UNITI and remission status at week 0 of IM-UNITI. For UNIFI, stratification included trial region and biologic failure status (yes or no) in induction and ustekinumab dose during induction, remission status at week 0 of maintenance, and oral corticosteroid use (yes or no) at week 0 of maintenance.

In all studies, patients underwent radiographic, purified protein derivative and/or interferon-γ release assay screening for *Mycobacterium tuberculosis* (TB) at screening. Patients with latent TB could be enrolled with initiation of an established concomitant treatment protocol (eg, isoniazid). Concomitant biologic use was prohibited for all IBD studies, with protocol-specified prescreening washout periods.

Safety Outcomes

Adverse events (AEs) were systematically collected in each trial throughout the study duration until the last study visit (20 weeks after last dose of study agent) and were coded and classified according to the Medical Dictionary for Regulatory Activities (MedDRA), version 21.0.

Safety outcomes assessed include AEs, SAEs, infections, serious infections, AEs leading to study agent discontinuation, injection site reactions, AEs occurring during or within 1 hour of infusion, clinical laboratory parameters, and deaths. Infections were determined based on assessment by the investigator.

Other events of interest included malignancies, serious major adverse cardiac events (MACE; cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke), thromboembolic events (deep vein thrombosis [DVT]/pulmonary embolism [PE]), anaphylactic and serum sickness-like hypersensitivity reactions, opportunistic infections (OIs) including active TB, and serious neurological disorders.

To classify other infection events, the following categories were also analyzed: *Clostridium difficile* (MedDRA preferred terms [PTs] in the MedDRA higher-level term: clostridial infections); herpes zoster (PTs in the higher-level term: herpes viral infections that also contain the words "zoster" or "varicella"); gastrointestinal (GI)-related abscesses that include the subcategories of anal, rectal, and, perirectal infections (PTs: anal abscess, rectal abscess, perirectal abscess); abdominal and intestinal infections (PTs: abdominal abscess, abscess intestinal); and other abscesses (PTs: groin, vaginal, stoma site, vulval, pelvic, perineal, and genital abscess).

In CD as previously reported,[7] all PTs possibly consistent with serious MACE were retrospectively adjudicated by an independent and blinded process performed by the Cleveland Clinic Coordinating Center for Clinical Research (http://c5research.clevelandclinic.org/Home.aspx). For UC, all PTs possibly consistent with serious MACE were adjudicated through clinical review by the sponsor. Analyses were based on adjudicated serious MACE in pooled CD and UC.

For hypersensitivity reactions, the terms anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, anaphylactoid shock, type I hypersensitivity, and serum sickness or serum sickness-like reaction were included in the analysis.

Data Analysis

All patients who received ≥1 dose of ustekinumab (IV or SC) were included in analyses. Data from induction through week 8 and maintenance through week 44 were evaluated, totaling 1 year of treatment.

Safety outcomes from induction trials are presented as percentages of patients with events, whereas safety outcomes through 1 year are presented as the number of patients per 100 PYs (95% confidence interval [CIs]) of follow-up. The latter approach was taken to adjust for potential differences in exposure between ustekinumab and placebo groups (because placebo patients crossed over to receive ustekinumab). The 95% CIs are based on an exact method assuming the observed number of events follows a Poisson distribution.

Hazard ratios (ustekinumab:placebo) with 95% CIs from time-to-event analyses for SAEs and serious infections were based on Cox proportional hazards model, with treatment as the explanatory variable adjusting for age (continuous), gender, ethnicity, duration of disease (continuous variable defined from initial disease diagnosis to induction baseline visit in years), stratified by study (UC or CD), biologic failure status (yes or no), and clinical remission status at maintenance baseline (yes or no). Initial placebo-controlled period analyses only include phase 3 CD and UC induction studies because alternate IV doses were studied in phase 2 CD. Analyses through 1 year of exposure (induction through maintenance) are presented for UC, CD, and pooled IBD and incorporate all phase 2/3 IBD studies.

Adverse events were summarized by MedDRA, system organ class and PT. Patients were classified according to actual treatment received, including in the placebo group up until the time of administration of the first ustekinumab dose or, for patients rerandomized to placebo, starting at 16 weeks after ustekinumab induction (after >5 half-lives).

Rates of malignancies were compared with the general population, with adjustment for age, sex, and race using the external National Institutes of Health Surveillance, Epidemiology, and End Results (SEER) database (2015; https://seer.cancer.gov/resources; other than nonmelanoma skin cancer [NMSC] and cervical cancer in situ, which are not included in SEER). The expected number of patients with malignancies reported is based on SEER, adjusted for age, gender, and race. Standardized incidence ratios (SIRs) were calculated by dividing observed number of patients with a malignancy in the pooled IBD population by expected number of patients from SEER with a malignancy. Confidence intervals were calculated based on an exact method assuming that the observed number of events follows a Poisson distribution.

Immunogenicity

Antibodies to ustekinumab were detected using a validated, drug-tolerant, electrochemiluminescence method (ECLIA) on the Meso Scale Discovery (MSD) platform in all phase 3 studies. In the phase 2 T07 and CERTIFI studies, an older nondrug-tolerant validated bridging enzyme immunoassay was used. Of note, though the same MSD assay was used in all phase 3 studies, a slightly more stringent cut point was employed in the UC studies, per updated regulatory guidelines. In all studies, a patient was considered positive for antibodies if treatment-emergent antibodies to ustekinumab were detected in the sample at any time, regardless of subsequent negative results.

RESULTS

Baseline Demographics

Through 1 year of follow-up across the pooled phase 2 and 3 IBD studies, a total of 2574 patients were treated with ustekinumab (825 patients in phase 3 UC studies and 1749

patients in phase 2/3 CD studies; Supplemental Figure S1), yielding a total of 1733 PYs of follow-up. In the phase 3 IBD population, median disease duration was 7.4 years. Disease duration was longer in CD (8.5 years) than UC patients (6.0 years; Table 1). The majority of CD patients had involvement of both ileum and colon (62.6%), and median baseline CDAI was 307.0. Patients with UC had a median Mayo score (range 0–12) of 9.0 at baseline. Baseline characteristics in the T07 and CERTIFI were generally similar to those in phase 3, except a slightly higher median age and weight in T07.

In the pooled IBD population at baseline, 47.1% (1388 of 2949) and 29.7% (877 of 2949) of patients were receiving concomitant corticosteroids and immunosuppressants, respectively (Supplemental Table S2). More than half (61.5%) of the pooled IBD population had a history of biological failure, 60.2% having failed at least 1 TNF antagonist, and 28.6% having failed ≥2 TNF antagonists; 30.4% of the pooled IBD population were biologic-naive. Of note, CERTIFI and UNITI-1 exclusively allowed previous TNF antagonist failures, whereas UNIFI included TNF antagonist and/or vedolizumab failures.

In the pooled IBD population, 2489 randomized patients received a single IV dose of ustekinumab; 1322 had been exposed to ustekinumab for ≥6 months and 871 for at least 1 year (Supplemental Figure S1).

Adverse Events

In induction, for the pooled phase 3 population, average duration of follow-up was similar between the placebo and ustekinumab groups (Table 2). Compared with placebo, similar proportions of ustekinumab-treated patients reported ≥1 AE (55.8% [438 of 785] vs 53.9% [853 of 1582], respectively), and these rates were not appreciably different between the two IV ustekinumab doses (Table 2). The most frequently reported AE was headache (6.5% placebo- and 6.7% ustekinumab-treated patients). Excluding IBD diseases under study, other frequently reported AEs (≥3% of patients in any treatment group) included nasopharyngitis, upper respiratory tract infection (URTI), nausea, abdominal pain, vomiting, arthralgia, pyrexia, and fatigue.

In the longitudinal analyses of the pooled IBD population (induction through maintenance up to 1 year), the average follow-up was 22.33 and 35.02 weeks for placebo- and combined ustekinumab-treated patients, respectively (Table 3). Adverse event rates through 1 year of treatment per 100 PYs of follow-up were 165.99 (95% CI, 155.81–176.67) on placebo and 118.32 (95% CI, 113.25–123.55) on ustekinumab. Of the 13 AEs occurring in at least 10 patients/100 PYs (Table 3), 3 were higher in combined ustekinumab group vs placebo (vomiting [7.21 vs 6.87], nasopharyngitis [18.11 vs 16.26], and headache [16.50 vs 16.43]), and the difference was not meaningful. In the randomized maintenance safety subset, similar trends were observed through week 44 in both dose regimens (ustekinumab 90 mg every 8 weeks and ustekinumab 90 mg every 12 weeks) compared with placebo (Table 4).

During the placebo-controlled periods, 6.2% (95% CI, 4.7–8.2) of patients in the placebo group experienced ≥1 SAE vs 4.4% (95% CI, 3.5–5.6) in the ustekinumab group. Rates were similar between ustekinumab doses (Table 2). Per 100 PYs of follow-up, SAE rates through 1 year of treatment were 27.50 (95% CI, 23.45–32.04) in the placebo and 21.23 (95% CI, 19.12–23.51) in the ustekinumab group (Table 3). The hazard ratio of time to first SAE through 1 year was 0.69 (95% CI, 0.43–1.11). Serious adverse events occurring in >3 patients in the ustekinumab group (ie, rate of ≥0.2) included CD, UC, abdominal pain, anal abscess, pneumonia, anemia, small intestinal obstruction, gastroenteritis, and nephrolithiasis; only the latter 3 occurred at numerically slightly higher rates in the combined ustekinumab vs placebo groups (small intestine obstruction (1.21 vs 0.84), gastroenteritis (0.52 vs 0.00), and nephrolithiasis (0.40 vs 0.34; Table 5).

No association between ustekinumab therapy and changes in laboratory parameters was observed (data on file).

Infections

During the placebo-controlled period, infections occurred in similar proportions of patients in placebo and combined phase 3 ustekinumab groups (19.9% [95% CI, 17.1–22.8] vs 19.3% [95% CI, 17.4–21.3], respectively; Table 2). Through 1 year of treatment in the pooled IBD population, rates of patients with any infection (per 100 PYs) was not higher in the ustekinumab (64.32 [95% CI, 60.60–68.21]) than the placebo group (80.31 [95% CI, 73.28–87.84]; Table 3). The most frequently reported infections were nasopharyngitis and URTI. Rates of other infections such as herpes zoster and *Clostridium difficile* were similar between treatment groups in both induction period (Table 2) and through 1 year (Table 3).

The number of patients with serious infections per 100 PYs was 5.53 (95% CI, 3.81–7.77) in the placebo and 5.02 (95% CI, 4.02–6.19) in the ustekinumab groups (Table 4.) The hazard ratio of time to first serious infection through 1 year was 1.03 (95% CI, 0.39–2.72). Serious infections occurring in >1 patient in the ustekinumab group (ie, a rate of ≥0.1) included pneumonia, anal abscess, gastroenteritis, viral gastroenteritis, pyelonephritis, abdominal abscess, cytomegalovirus (CMV) colitis, perirectal abscess, and cholecystitis (Table 5).

Although rates between placebo and ustekinumab are similar by indication and overall across IBD, the overall rate of serious infections in CD was numerically higher than in UC. Crohn's disease–specific manifestation of anal abscess occurred at a rate of 2.02 and 0.90 patients per 100 PYs of follow-up in placebo and ustekinumab patients, respectively (Table 5). Additionally, overall rates of GI abscesses in the induction period and through 1 year were generally similar between treatment groups, occurring in 8 (1.0%) in placebo patients and 14 (0.9%) ustekinumab patients (Table 2) and were not higher on

TABLE 1. Disease Characteristics at Baseline (Week 0 of Induction; Phase 3 Studies Only)

	Ulcerative Colitis				Crohn's Disease				Inflammatory Bowel Disease	
		Ustekinumab				Ustekinumab				
	Placebo	130 mg	6 mg/kg	Combined	Placebo	130 mg	6 mg/kg	Combined	Placebo	Ustekinumab
Patients randomized	319	320	322	642	470	467	472	939	789	1581
Age (years)										
Median	40.0	42.0	41.0	41.5	37.0	37.0	36.0	39.0	39.0	38.0
IQ range	(30.0; 51.0)	(31.0; 51.0)	(30.0; 52.0)	(30.0; 51.0)	(29.0; 47.0)	(28.0; 47.0)	(27.0; 46.0)	(27.0; 47.0)	(29.0; 49.0)	(29.0; 49.0)
Male	197 (61.8)	190 (59.4)	195 (60.6)	385 (60.0)	222 (47.2)	207 (44.3)	198 (41.9)	405 (43.1)	419 (53.1)	790 (50.0)
White	248 (77.7)	239 (74.7)	243 (75.5)	482 (75.1)	399 (84.9)	393 (84.2)	399 (84.5)	792 (84.3)	647 (82.0)	1274 (80.6)
Weight (kg) Mean (SD)	72.9 (16.8)	73.7 (16.8)	73.0 (19.3)	73.3 (18.1)	72.7 (18.7)	71.2 (19.5)	70.4 (19.3)	70.8 (19.4)	72.8 (18.5)	71.8 (18.9)
Current smokers	20 (6.3)	12 (3.8)	15 (5.0)	28 (4.4)	117 (24.9)[c]	119 (25.5)	99 (21.0)	218 (23.2)	137 (17.4)[c]	246 (15.6)
IBD disease duration (years)										
N	319	320	322	642	469	467	472	939	788	1581
Mean (SD)	8.0 (7.2)	8.1 (7.2)	8.2 (7.8)	8.2 (7.5)	11.4 (9.2)	10.5 (8.5)	10.9 (9.4)	10.7 (9.0)	10.0 (8.6)	9.66 (8.5)
Median	6.0	5.9	6.0	6.0	9.0	8.7	8.5	8.5	7.8	7.4
IQ range	(2.7; 11.3)	(2.8; 11.4)	(2.7; 11.1)	(2.8; 11.2)	(4.4; 15.6)	(3.9; 14.8)	(3.8; 15.1)	(3.8; 14.8)	(3.5; 13.7)	(3.2; 13.5)
Extent of UC disease										
N	316	318	320	638	0	0	0	0	316	638
Limited to left side of colon N (%)	167 (52.8)	183 (57.5)	168 (52.5)	351 (55.0)	-	-	-	-	167 (52.8)	351 (55.0)
Extensive	149 (47.2)	135 (42.5)	152 (47.5)	287 (45.0)	-	-	-	-	149 (47.2)	287 (45.0)
Involved GI areas										
N	0	0	0	0	468	466	472	938	468	938
Ileum only N (%)	-	-	-	-	75 (16.0)	94 (20.2)	87 (18.4)	181 (19.3)	75 (16.0)	181 (19.3)
Colon only N (%)	-	-	-	-	87 (18.6)	82 (17.6)	85 (18.0)	167 (17.8)	87 (18.6)	167 (17.8)
Ileum and colon N (%)	-	-	-	-	302 (64.5)	288 (61.8)	299 (63.3)	587 (62.6)	302 (64.5)	587 (62.6)
Mayo score (0–12)[a]										
N	319	320	321	641	0	0	0	0	319	641
Mean (SD)	8.9 (1.6)	8.9 (1.6)	8.9 (1.5)	8.9 (1.5)	-	-	-	-	8.9 (1.6)	8.9 (1.5)
Median	9.0	9.0	9.0	9.0	-	-	-	-	9.0	9.0
IQ range	(8.0; 10.0)	(8.0; 10.0)	(8.0; 10.0)	(8.0; 10.0)	-	-	-	-	(8.0; 10.0)	(8.0; 10.0)
CDAI score[b]										
N	0	0	0	0	470	467	472	939	470	939
Mean (SD)	-	-	-	-	311.7 (61.2)	313.4 (62.0)	315.6 (62.1)	314.5 (62.0)	311.7 (61.2)	314.5 (62.0)
Median	-	-	-	-	301.0	306.0	308.5	307.0	301.0	307.0
IQ range	-	-	-	-	(261.0; 351.0)	(264.0; 352.0)	(267.0; 359.0)	(265.0; 354.0)	(261.0; 351.0)	(265.0; 354.0)

Abbreviations: CDAI, Crohn's Disease Activity Index; GI, gastrointestinal; IBD, inflammatory bowel disease; IQ, interquartile; SD, standard deviation; UC, ulcerative colitis.
Data presented as N (%) unless otherwise noted.
[a]Mayo score is comprised of 4 parts: stool frequency, rectal bleeding, endoscopic findings and Physician's Global Assessment, each scored from 0–3. Moderate-to-severe UC is defined as total score of 6–12 on Mayo score (range 0–12).
[b]CDAI has a possible range of 0 to 600 (with higher scores indicating more severe disease studies.). CDAI <150 is used as a marker of remission, >450 is a marker of severe disease.
[c]Missing data for one patient.

TABLE 2. Safety During Placebo-controlled Intravenous Induction Period (Week 0-Week 8; Phase 3 Studies Only)

	Ulcerative Colitis			Crohn's Disease			Inflammatory Bowel Disease	
		Ustekinumab			Ustekinumab			Ustekinumab
	Placebo	130 mg	6 mg/kg	Placebo	130 mg	6 mg/kg	Placebo	Combined
Patients treated	319	321	320	466	471	470	785	1582
Average follow-up (weeks)	7.96	8.11	8.16	8.18	8.22	8.16	8.09	8.17
Number of Patients ≥1 N (%)								
Adverse events	156 (48.9)	133 (41.4)	160 (50.0)	282 (60.5)	275 (58.4)	285 (60.6)	438 (55.8)	853 (53.9)
95% CI	(43.3, 54.5)	(36.0, 47.0)	(44.4, 55.6)	(55.9, 65.0)	(53.8, 62.9)	(56.1, 65.1)	(52.2, 59.3)	(51.4, 56.4)
Serious adverse events	21 (6.6)	12 (3.7)	10 (3.1)	28 (6.0)	23 (4.9)	25 (5.3)	49 (6.2)	70 (4.4)
95% CI	(4.1, 9.9)	(2.0, 6.4)	(1.5, 5.7)	(4.0, 8.6)	(3.1, 7.2)	(3.5, 7.8)	(4.7, 8.2)	(3.5, 5.6)
Infections	48 (15.0)	53 (16.5)	49 (15.3)	108 (23.2)	92 (19.5)	111 (23.6)	156 (19.9)	305 (19.3)
95% CI	(11.3, 19.5)	(12.6, 21.0)	(11.6, 19.7)	(19.4, 27.3)	(16.1, 23.4)	(19.9, 27.7)	(17.1, 22.8)	(17.4, 21.3)
Serious Infections	4 (1.3)	2 (0.6)	1 (0.3)	6 (1.3)	7 (1.5)	8 (1.7)	10 (1.3)	18 (1.1)
95% CI	(0.3, 3.2)	(0.1, 2.2)	(0.0, 1.7)	(0.5, 2.8)	(0.6, 3.0)	(0.7, 3.3)	(0.6, 2.3)	(0.7, 1.8)
Number of patients with other infections of interest[a] N (%)								
Clostridium difficile[b]	2 (0.6)	1 (0.3)	0	1 (0.2)	1 (0.2)	2 (0.4)	3 (0.4)	4 (0.3)
Herpes zoster[c]	0	0	2 (0.6)	1 (0.2)	2 (0.4)	0	1 (0.1)	4 (0.3)
GI-related abscesses[d]	1 (0.3)	0	0	7 (1.5)	7 (1.5)	7 (1.5)	8 (1.0)	14 (0.9)
95% CI	(0.0, 1.7)	-	-	(0.6, 3.1)	(0.6, 3.0)	(0.6, 3.0)	(0.4, 2.0)	(0.5, 1.5)
Anal, rectal, and perirectal	1 (0.3)	0	0	6 (1.3)	3 (0.6)	3 (0.6)	7 (0.9)	6 (0.4)
95% CI	(0.0, 1.7)	-	-	(0.5, 2.8)	(0.1, 1.9)	(0.1, 1.9)	(0.4, 1.8)	(0.1, 0.8)
Abdominal and intestinal	0	0	0	0	1 (0.2)	1 (0.2)	0	2 (0.1)
95% CI	-	-	-	-	(0.0, 1.2)	(0.0, 1.2)	-	(0.0, 0.5)
Abscess, Other	0	0	0	1 (0.2)	3 (0.6)	3 (0.6)	1 (0.1)	6 (0.4)
95% CI	-	-	-	(0.0, 1.2)	(0.1, 1.9)	(0.1, 1.9)	(0.0, 0.7)	(0.1, 0.8)
Frequent adverse events (≥3% in any treatment group N (%)								
Nasopharyngitis	9 (2.8)	13 (4.0)	18 (5.6)	23 (4.9)	22 (4.7)	25 (5.3)	32 (4.1)	78 (4.9)
Upper respiratory tract infection	4 (1.3)	6 (1.9)	4 (1.3)	20 (4.3)	17 (3.6)	17 (3.6)	24 (3.1)	44 (2.8)
Nausea	7 (2.2)	8 (2.5)	7 (2.2)	22 (4.7)	27 (5.7)	25 (5.3)	29 (3.7)	67 (4.2)
Abdominal pain	8 (2.5)	8 (2.5)	6 (1.9)	20 (4.3)	14 (3.0)	24 (5.1)	28 (3.6)	52 (3.3)
Vomiting	1 (0.3)	3 (0.9)	4 (1.3)	12 (2.6)	14 (3.0)	20 (4.3)	13 (1.7)	41 (2.6)
Crohn's disease	0	0	0	35 (7.5)	22 (4.7)	14 (3.0)	35 (4.5)	36 (2.3)
Colitis Ulcerative	18 (5.6)	9 (2.8)	7 (2.2)	0	0	0	18 (2.3)	16 (1.0)
Arthralgia	3 (0.9)	3 (0.9)	6 (1.9)	22 (4.7)	36 (7.6)	24 (5.1)	25 (3.2)	69(4.4)
Pyrexia	6 (1.9)	4 (1.2)	6 (1.9)	25 (5.4)	21 (4.5)	27 (5.7)	31 (3.9)	58 (3.7)
Fatigue	5 (1.6)	6 (1.9)	8 (2.5)	16 (3.4)	9 (1.9)	15 (3.2)	21 (2.7)	38 (2.4)
Headache	14 (4.4)	22 (6.9)	13 (4.1)	37 (7.9)	40 (8.5)	31 (6.6)	51 (6.5)	106 (6.7)

Abbreviations: CI, confidence interval; GI, gastrointestinal.

[a]Infection as assessed by the investigator.

[b]*Clostridium difficile* included all preferred terms in the higher-level term of clostridial infections.

[c]Herpes zoster included preferred terms in the higher-level term of herpes viral infections that also contain the words "zoster" or "varicella."

[d]GI abscesses include all preferred terms included in the following categories: anal, rectal, and perirectal: anal abscess, rectal abscess, perirectal abscess; abdominal and intestinal: abdominal abscess, abscess intestinal; abscess, other: groin abscess, vaginal abscess, stoma site abscess, vulval abscess, pelvic abscess, perineal abscess, genital abscess.

TABLE 3. Treatment Through 1 Year: Patients with Safety Events Per 100 Patient-Years of Follow-Up[a]

	Ulcerative Colitis		Crohn's Disease		Inflammatory Bowel Disease	
	Placebo	Ustekinumab	Placebo	Ustekinumab	Placebo	Ustekinumab
Patients Treated	446	825	943	1749	1389	2574
Average follow-up (weeks)	29.14	39.53	19.11	32.89	22.33	35.02
Patient-years of follow-up	250	627	347	1106	596	1733
Key safety events, Rate (N)						
Adverse events	121.65 (304)	95.03 (596)	197.97 (686)	131.52 (1455)	165.99 (990)	118.32 (2051)
95% CI	(108.36, 136.12)	(87.55, 102.97)	(183.43, 213.36)	(124.85, 138.46)	(155.81, 176.67)	(113.25, 123.55)
Serious adverse events	18.41 (46)	12.91 (81)	34.05 (118)	25.94 (287)	27.50 (164)	21.23 (368)
95% CI	(13.48, 24.55)	(10.26, 16.05)	(28.19, 40.78)	(23.03, 29.12)	(23.45, 32.04)	(19.12, 23.51)
Infections[b]	59.23 (148)	49.75 (312)	95.52 (331)	72.59 (803)	80.31 (479)	64.32 (1115)
95% CI	(50.07, 69.57)	(44.38, 55.58)	(85.51, 106.39)	(67.65, 77.78)	(73.28, 87.84)	(60.60, 68.21)
Serious infections	4.00 (10)	3.19 (20)	6.64 (23)	6.06 (67)	5.53 (33)	5.02 (87)
95% CI	(1.92, 7.36)	(1.95, 4.92)	(4.21, 9.96)	(4.69, 7.69)	(3.81, 7.77)	(4.02, 6.19)
Serious MACE[c]	0.80 (2)	0.16 (1)	0.00 (0)	0.09 (1)	0.34 (2)	0.12 (2)
95% CI	(0.10, 2.89)	(0.00, 0.89)	(0.00, 0.86)	(0.00, 0.50)	(0.04, 1.21)	(0.01, 0.42)
Discontinuation due to adverse event	13.21 (33)	4.15 (26)	13.56 (47)	9.76 (108)	13.41 (80)	7.73 (134)
95% CI	(9.09, 18.55)	(2.71, 6.07)	(9.97, 18.04)	(8.01, 11.79)	(10.64, 16.69)	(6.48, 9.16)
Death	0.00 (0)	0.32 (2)	0.00 (0)	0.00 (0)	0.00 (0)	0.12 (2)
95% CI	(0.00, 1.20)	(0.04, 1.15)	(0.00, 0.86)	(0.00, 0.27)	(0.00, 0.50)	(0.01, 0.42)
Malignancies (excluding NMSC)	0.40 (1)	0.64 (4)	0.00 (0)	0.27 (3)	0.17 (1)	0.40 (7)
95 % CI	(0.01, 2.23)	(0.17, 1.63)	(0.00, 0.86)	(0.06, 0.79)	(0.00, 0.93)	(0.16, 0.83)
Infections of Interest, Rate (N)						
Clostridium difficile infection[d]	2.00 (5)	0.64 (4)	2.31 (8)	1.08 (12)	2.18 (13)	0.92 (16)
Herpes Zoster[e]	1.20 (3)	1.12 (7)	1.44 (5)	0.99 (11)	1.34 (8)	1.04 (18)
GI-related abscesses[f]	0.80 (2)	0.16 (1)	8.37 (29)	4.61 (51)	5.20 (31)	3.00 (52)
95% CI	(0.10, 2.89)	(0.00, 0.89)	(5.60, 12.02)	(3.43, 6.06)	(3.53, 7.38)	(2.24, 3.93)
Anal, rectal, and perirectal	0.80 (2)	0.16 (1)	7.21(25)	2.98 (33)	4.53 (27)	1.96 (34)
95% CI	(0.10, 2.89)	(0.00, 0.89)	(4.67, 10.65)	(2.05, 4.19)	(2.98, 6.59)	(1.36, 2.74)
Abdominal and intestinal	0.00 (0)	0.00 (0)	0.87 (3)	0.45 (5)	0.50 (3)	0.29 (5)
95% CI	(0.00, 1.20)	(0.00, 0.48)	(0.18, 2.53)	(0.15, 1.05)	(0.10, 1.47)	(0.09, 0.67)
Abscess, Other	0.00 (0)	0.00 (0)	0.29 (1)	1.18 (13)	0.17 (1)	0.75 (13)
95% CI	(0.00, 1.20)	(0.00, 0.48)	(0.01, 1.61)	(0.63, 2.01)	(0.00, 0.93)	(0.40, 1.28)
≥10 Adverse events occurring in any treatment group						
Nasopharyngitis	17.21	17.86	15.58	18.26	16.26	18.11
Upper respiratory tract infection	6.00	6.70	15.30	14.01	11.40	11.36
Nausea	5.60	5.74	18.76	15.46	13.25	11.94
Crohn's disease	0.00	0.00	37.81	23.59	21.96	15.06
Abdominal pain	6.00	5.10	20.78	15.19	14.59	11.54
Diarrhea	1.20	3.51	10.10	5.88	6.37	5.02

TABLE 3. Continued

	Ulcerative Colitis		Crohn's Disease		Inflammatory Bowel Disease	
	Placebo	Ustekinumab	Placebo	Ustekinumab	Placebo	Ustekinumab
≥10 Adverse events occurring in any treatment group						
Vomiting	2.40	2.55	10.10	9.85	6.87	7.21
Ulcerative Colitis	36.82	15.15	0.00	0.00	15.43	5.48
Arthralgia	9.20	8.45	22.51	21.15	16.93	16.56
Headache	9.20	11.00	21.64	19.62	16.43	16.50
Fatigue	4.80	4.46	10.10	8.23	7.88	6.86
Pyrexia	6.80	3.99	17.03	12.29	12.74	9.29
Anemia	11.20	7.81	7.21	4.07	8.89	5.42

Abbreviations: CI, confidence interval; NMSC, non-melanoma skin cancer.
[a]Ulcerative Colitis: CNTO1275UCO3001; Crohn's disease: C0379T07 (only placebo-controlled IV population), C0743T26, CNTO1275CRD3001 and CNTO1275CRD3002.
[b]Infection as assessed by the investigator.
[c]Major adverse cardiovascular events (MACE) events in Crohn's disease studies were externally adjudicated, and in ulcerative colitis, studies were identified through clinical review by the sponsor.
[d]*Clostridium difficile* included all preferred terms in the higher-level term of clostridial infections.
[e]Herpes zoster included preferred terms in the higher-level term of herpes viral infections that also contain the words zoster or varicella.
[f]GI abscesses include all preferred terms included in the following categories: anal, rectal, and perirectal: anal abscess, rectal abscess, perirectal abscess; abdominal and intestinal: abdominal abscess, abscess intestinal; abscess, other: groin abscess, vaginal abscess, stoma site abscess, vulval abscess, pelvic abscess, perineal abscess, genital abscess.

ustekinumab when adjusted for PYs (5.20 in placebo and 3.00 in ustekinumab patients; Table 3).

As previously published,[5] 1 case of active TB was reported in a 32-year-old Hungarian man in IM-UNITI who received one IV ustekinumab dose of 130 mg 10 months before onset. The patient experienced flu-like symptoms and yellowish sputum; chest radiograph and computed tomography scan results were consistent with pulmonary TB. Empiric treatment with triple anti-TB therapy resolved the symptoms. The only other active TB case through 1 year was a patient in UNIFI maintenance with pulmonary TB from Korea who received placebo (never received ustekinumab).

Through 1 year, 12 patients reported OIs in the pooled IBD population (10 ustekinumab [0.58/100PYs], 2 placebo [0.34/100 PYs]). Nine of 12 patients were receiving concomitant immunosuppressants (including corticosteroids). These events were esophageal candidiasis (all nonserious in 3 ustekinumab- and 2 placebo-treated CD patients), CMV colitis in 2 (0.32/100 PYs) ustekinumab-treated UC patients (both diagnosed ≥4 months after discontinuation of ustekinumab due to lack of efficacy/worsening UC and receiving concomitant immunosuppressants [1 receiving steroids, 1 receiving steroids/adalimumab]). Other OIs occurring in 1 patient each (ustekinumab group) were Legionella pneumonia, Listeria meningitis, disseminated histoplasmosis, cryptosporidiosis infection, and concurrent ophthalmic and oral herpes simplex.

Hypersensitivity Reactions

No serious anaphylactic reactions or serum sickness-like reactions to ustekinumab were observed. As previously reported,[7] 2 CD patients displayed signs/symptoms of hypersensitivity temporally associated with treatment (1 [0.1%] with throat tightness/shortness of breath/flushing after first and only SC ustekinumab administration and 1 [0.8%] with chest discomfort/flushing/urticaria/fever after initial IV ustekinumab dose).[14] Symptoms resolved within 1 hour after oral corticosteroid/antihistamine treatment.

Injection-site Reactions

In the phase 3 population, 26 of 7154 (0.4%) SC injections were reported to have injection-site reactions (ISRs) in the placebo group and 51 of 7055 (0.7%) in the ustekinumab group, corresponding to 1.7% of patients in the placebo and 2.6% of patients in the ustekinumab group (data not shown). The most common ISR was injection site erythema (1.6% for ustekinumab vs 0.9% for placebo), an identified adverse drug reaction for ustekinumab that has not been associated with the small (<4%) number of patients who exhibit antibodies to ustekinumab.

TABLE 4. Safety During Randomized Maintenance Period: Patients With Safety Events Per 100 Patient-Years of Follow-Up (Maintenance Week 0 Through Week 44; Phase 3 Studies Only[a])

	Ulcerative Colitis			Crohn's Disease[c]			Inflammatory Bowel Disease[c]		
		Ustekinumab			Ustekinumab			Ustekinumab	
	Placebo SC[b]	90 mg SC 12qw	90 mg SC 8qw	Placebo SC[b]	90 mg SC 12qw	90 mg SC 8qw	Placebo SC[b]	90 mg SC 12qw	90 mg SC 8qw
Patients Treated	175	172	176	133	132	131	308	304	307
Average follow-up (weeks)	42.30	41.80	42.20	31.96	36.73	35.21	37.84	39.60	39.22
Patient-years of follow-up	142	138	143	82	93	89	224	231	232
Key Safety Events, Rate (N)									
Adverse events	96.94 (138)	86.07 (119)	95.22 (136)	135.77 (111)	113.70 (106)	120.65 (107)	111.10 (249)	97.20 (225)	104.96 (243)
Serious adverse events	11.94 (17)	9.40 (13)	10.50 (15)	24.46 (20)	17.16 (16)	14.66 (13)	16.51 (37)	12.53 (29)	12.09 (28)
Infections[d]	56.90 (81)	41.95 (58)	60.21 (86)	80.73 (66)	66.50 (62)	71.03 (63)	65.59 (147)	51.84 (120)	64.36 (149)
Serious infections[d]	2.81 (4)	4.34 (6)	2.10 (3)	3.67 (3)	7.51 (7)	3.38 (3)	3.12 (7)	5.62 (13)	2.59 (6)
Discontinuation due to adverse event	14.05 (20)	6.51 (9)	3.50 (5)	12.23 (10)	10.73 (10)	4.51 (4)	13.39 (30)	8.21 (19)	3.89 (9)
Death	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)
Malignancies (excluding NMSC)	0.00 (0)	0.72 (1)	0.70 (1)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.43 (1)	0.43 (1)
≥10 Adverse events occurring in any treatment group									
Nasopharyngitis	19.67	22.42	18.20	12.23	18.23	15.79	16.96	20.74	17.28
Upper respiratory tract infection	5.62	3.62	11.20	25.69	9.65	14.66	12.94	6.05	12.53
Abdominal pain	2.81	4.34	5.60	20.79	12.87	12.40	9.37	7.78	8.21
Ulcerative Colitis	35.12	13.74	12.60	0.00	0.00	0.00	22.31	8.21	7.77
Crohn's disease	0.00	0.00	0.00	23.24	17.16	18.04	8.48	6.91	6.91
Diarrhea	1.40	3.62	4.90	8.56	11.80	5.64	4.02	6.91	5.18
Nausea	2.81	2.89	4.20	11.01	10.73	4.51	5.80	6.05	4.32
Vomiting	4.21	0.72	1.40	11.01	5.36	4.51	6.69	2.59	2.59
Arthralgia	10.54	10.85	5.60	23.24	23.60	20.30	15.17	15.98	11.23
Pyrexia	4.92	0.72	6.30	13.45	11.80	10.15	8.03	5.18	7.77
Headache	4.92	7.96	12.60	18.35	16.09	16.91	9.82	11.23	14.25

Abbreviations: SC, subcutaneous; NMSC, non-melanoma skin cancer.

[a]Ulcerative Colitis: CNTO1275UCO3001; Crohn's disease: CNTO1275CRD3003.

[b]Patients who were in clinical response to ustekinumab IV induction dosing and were randomized to placebo SC on entry into this maintenance study.

[c]Includes data up to the time of meeting loss of response criteria for patients who had a dose adjustment in Crohn's disease.

[d]Infection as assessed by the investigator.

TABLE 5. Patients With Serious Adverse Events (SAEs) and Serious Infections Per 100 Patient Years of Follow-up Through 1 Year[a]

	Ulcerative Colitis		Crohn's Disease		Inflammatory Bowel Disease	
	Placebo	Ustekinumab	Placebo	Ustekinumab	Placebo	Ustekinumab
Patients treated	446	825	943	1749	1389	2574
Average duration of follow-up (weeks)	29.14	39.53	19.11	32.89	22.33	35.02
Average duration of treatment (weeks)	20.28	28.82	9.87	18.80	13.46	22.01
Total patient-years of follow-up	250	627	347	1106	596	1733
SAEs (≥0.2 in Ustekinumab-Treatment Groups)						
Number of patients with SAEs	46	81	118	287	164	368
Number of patients with SAEs per 100 patient-years of follow-up	18.41	12.91	34.05	25.94	27.50	21.23
System-organ class/preferred term						
Crohn's disease	0.00	0.00	13.28	10.21	7.71	6.52
Ulcerative colitis	8.80	4.30	0.00	0.00	3.69	1.56
Small intestinal obstruction	0.00	0.00	1.44	1.90	0.84	1.21
Abdominal pain	0.40	0.16	0.58	0.63	0.50	0.46
Anal abscess	0.80	0.00	2.31	0.99	1.68	0.63
Pneumonia	0.00	0.48	0.87	0.36	0.50	0.40
Gastroenteritis	0.00	0.64	0.00	0.45	0.00	0.52
Nephrolithiasis	0.00	0.48	0.58	0.36	0.34	0.40
Anemia	0.40	0.32	0.58	0.18	0.50	0.23
Serious infections (≥0.1 in Ustekinumab Treatment Groups)						
Number of patients with serious infections[b]	10	20	23	67	33	87
Number of patients with serious infections[b] per 100 patient-years of follow-up	4.00	3.19	6.64	6.06	5.53	5.02
System-organ class/preferred term						
Pneumonia	0.00	0.48	0.87	0.36	0.50	0.40
Anal abscess	0.80	0.00	2.02	0.90	1.51	0.58
Gastroenteritis	0.00	0.48	0.00	0.45	0.00	0.46
Gastroenteritis viral	0.00	0.00	0.00	0.36	0.00	0.23
Pyelonephritis	0.00	0.32	0.00	0.09	0.00	0.17
Abdominal abscess	0.00	0.00	0.58	0.18	0.34	0.12
Cytomegalovirus colitis	0.00	0.32	0.00	0.00	0.00	0.12
Perirectal abscess	0.00	0.00	0.29	0.18	0.17	0.12
Cholecystitis	0.00	0.00	0.00	0.18	0.00	0.12

[a]Ulcerative Colitis: CNTO1275UCO3001; Crohn's disease: C0379T07 (only placebo-controlled IV population), C0743T26, CNTO1275CRD3001 and CNTO1275CRD3002.
[b]Infection as assessed by the investigator

Malignancies

Through 1 year of treatment in the pooled IBD population, rates of malignancies other than NMSC per 100 PYs were low and similar between placebo and ustekinumab patients (0.17 [95% CI, 0.00–0.93]; and 0.40 [95% CI, 0.16–0.83], respectively; Fig. 1A). Rates were similar for the placebo and ustekinumab groups for malignancies including NMSCs, (0.50 [95% CI, 0.10–1.47]; and 0.81 [95% CI, 0.44–1.36], respectively; Fig. 1B). Rates of patients with 1 or more NMSC were also low and comparable between treatment groups, 0.34 (95% CI, 0.04–1.21) for the placebo and 0.40 (95% CI, 0.16–0.83) for ustekinumab groups. Overall, 4 basal cell carcinomas (BCCs) and 3 squamous cell carcinomas (SCCs) were reported in the IBD population.

Across the pooled IBD population, no cases of lymphoma were reported through 1 year. Details on the reported malignancies other than NMSC are presented in Table 6. Most patients with malignancies were treated with at least 1 other biologic before ustekinumab. Only 1 patient (plasma cell myeloma) received any prior immunomodulator therapy. Additionally, half of the patients only received 2 doses of ustekinumab (one IV and one SC), and the longest exposure was 3 doses (one IV and two SC).

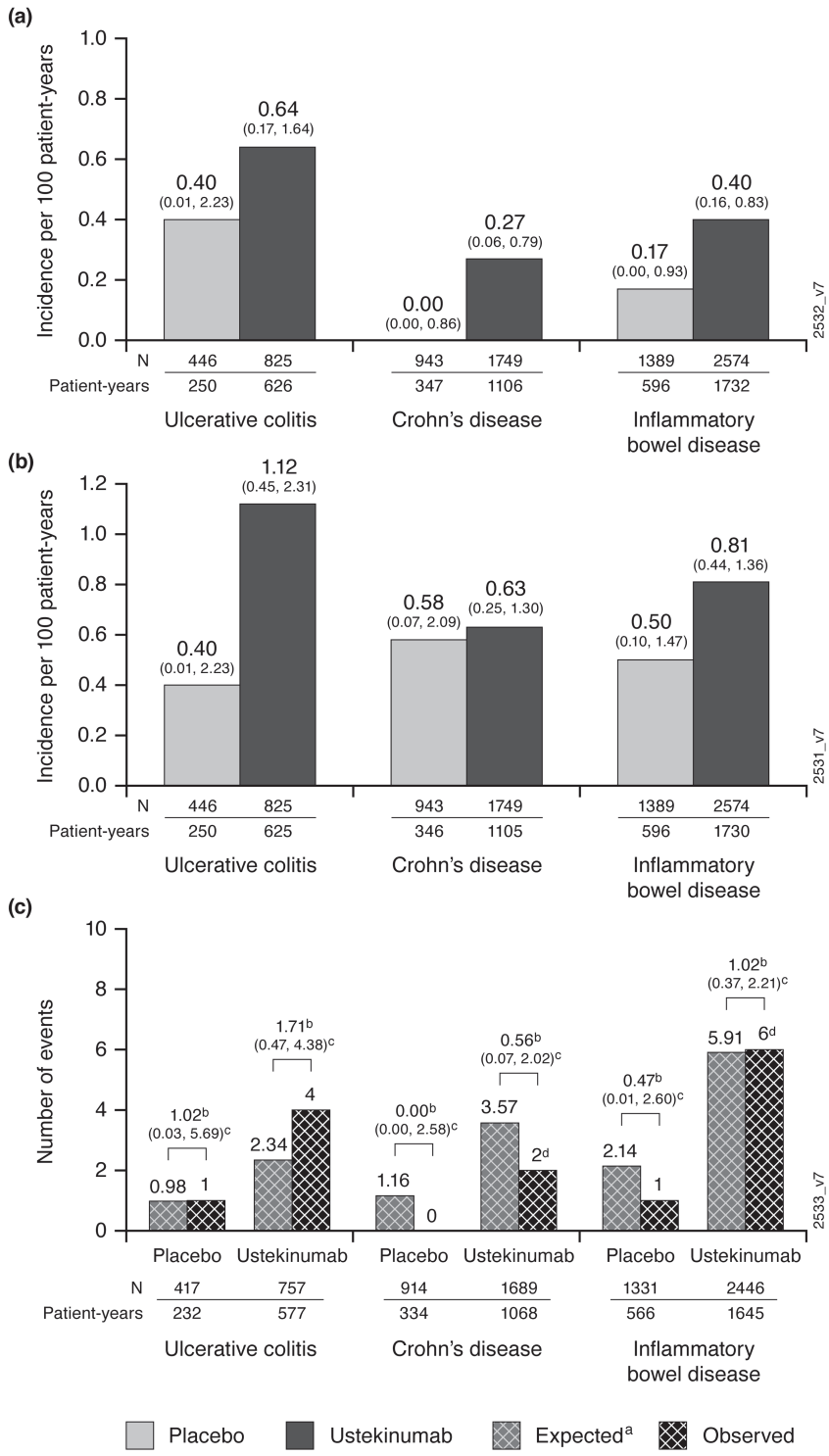

FIGURE 1. All malignances excluding NMSC (a), malignancies including NMSC (b), and malignancies compared with National Institutes of Health Surveillance, Epidemiology, and End Results (SEER) database (c). [a]One malignancy was not included as patient's race was unknown. Abbreviation: NMSC, non-melanoma skin cancer.

For CD and UC combined, SIR of the observed number of patients with malignancies in the pooled IBD population compared with the expected number from SEER was 0.47 (95% CI, 0.01–2.60) in the ustekinumab and 1.02 (95% CI, 0.37–2.21) in the placebo groups. Within UC and CD, results were generally similar (Fig. 1C). Data interpretation

TABLE 6. Reported Malignancies Through 1 Year (Excluding NMSC)

Malignacy (PT)	Age/ Sex	IBD Duration (years)	Relevant Risk Factors	Smoking Status	Study Treatment	Last Study Agent Dose (study day)	Malignancy Diagnosis (study day)	Prior IBD Therapy
Ulcerative colitis								
Prostate Cancer	61/M	1	Family history of prostate cancer	Yes-Past smoker	Ustekinumab 130 mg IV; 1 dose of 90 mg SC	56	69	Steroids, IFX, 6-MP
Rectal adenocarcinoma	32/M	6	Ulcerative colitis	No	Ustekinumab 130 mg IV; 1 dose of 90 mg SC	56	159	Steroids, ADA, IFX, GOL, 6-MP
Colon cancer	48/F	28	None	No	Ustekinumab 6 mg/kg IV; 1 dose of 90 mg SC	58	59	IFX, steroids
Papillary renal cell carcinoma	70/M	33	hypertension, diuretic use	Yes-Past smoker	Ustekinumab 130 mg IV; 1 dose of 90 mg SC	56	92	Steroids
Testis cancer	26/M	1	None	No	Placebo	285	302	Steroids
Crohn's disease								
Adenocarcinoma of small intestine & incidental carcinoid tumor	68/M	4	Family history of cancer	Yes, Past smoker	Placebo, ustekinumab 130 mg IV, 2 doses of 90 mg	196	255	IFX, steroids
Plasma cell myeloma (multiple myeloma)	57/M	34	Monoclonal IgG kappa gammopathy of undetermined significance	No	Ustekinumab 6 mg/kg IV	1	199	IFX, ADA, steroids, IMM[a]
Prostate cancer	53/M	30	Elevated prostate-specific antigen levels before randomization	Not reported	Ustekinumab induction IV 4.3 mg/kg	1	64	steroids, 5-ASA

Abbreviations: 5-ASA, 5-aminosalicylates; 6-MP, 6-mercaptopurine; ADA, adalimumab; F, female; GOL, golimumab; IFX, infliximab; IV, intravenous; NMSC, non-melanoma skin cancer; PT, preferred term Y, yes; M, male; N, no.

[a]IMM is azathioprine and/or 6-MP and/or methotrexate

is limited by small numbers of events and relatively short duration of exposure.

Major Adverse Cardiovascular Events and Deep Vein Thrombosis/Pulmonary Embolism

Incidence of adjudicated serious MACE per 100 PYs was low through 1 year, with 2 patients each in the placebo- (0.34) and ustekinumab-treated (0.12) pooled IBD population (Table 3). Adjudicated UC events were 1 nonfatal myocardial infarction (perioperative cardiac arrest) and 1 nonfatal stroke in the placebo group. Additionally, there was 1 acute myocardial infarction diagnosed in a patient who experienced respiratory failure with prolonged hypoxemia postanesthesia. This patient ultimately died from sequelae of acute respiratory distress syndrome, categorized as cardiovascular death for purpose of this analysis. In CD, there was one adjudicated nonfatal stroke in a ustekinumab-treated patient.

Through 1 year in the pooled IBD population, DVT and/or PE events were reported in 2 placebo patients (0.34 per 100 PYs, [95% CI, 0.04–1.21]) and 13 ustekinumab patients (0.75 per 100 PYs, [95% CI, 0.40–1.28]), with 16 events of DVT and/or PE. One patient with UC who was on ustekinumab therapy reported both DVT and PE events. A total of 4 IBD patients reported only PEs, 2 receiving placebo and 2 receiving ustekinumab; and 10 patients (all ustekinumab-treated) reported only DVT. In CD, 11 patients reported DVT and/or PE events, 2 in the placebo and 9 in the ustekinumab groups.

Neurologic Events

No cases of progressive multifocal leukoencephalopathy or reversible posterior leukoencephalopathy were reported. A nonserious case of progression of multiple sclerosis was reported in a UC patient (ustekinumab) with a history of relapsing-remitting multiple sclerosis. A case of possible demyelination was reported in a patient with CD (nonresponder who received 130 mg ustekinumab by IV and 90 mg SC 8 weeks later); magnetic resonance imaging findings were consistent with microvascular disease and previous small vessel insults.

Deaths

Through 1 year of follow-up, 2 deaths were reported in UC patients (1 patient who died of acute respiratory distress syndrome, described previously, and 1 due to esophageal varices hemorrhage), both previously reported in UNIFI.[11]

Immunogenicity

Through 1 year, for IBD patients who received IV and SC ustekinumab, antibodies to ustekinumab were found in 3.6% of patients. Rates were numerically lower among CD patients than UC patients (2.9% vs 4.6%), as anticipated due to the more stringent cut point used in UC studies and described previously. Overall incidence of antibodies to ustekinumab was low in CERTIFI and T07, 0.7% and 0%, respectively, as previously reported.[4, 13]

DISCUSSION

This is the first published integrated IBD safety analysis for ustekinumab, representing 2574 IBD patients (1733 PYs). Overall, ustekinumab exposure was not associated with an increase in safety events, supporting a favorable benefit-risk profile with single initial dosing up to 6 mg/kg IV followed by 90 mg SC every 8/12 weeks. These results are consistent with other integrated analyses, including cross-indications through 1 year,[7] 5-year integrated psoriasis analysis,[2] and safety data through 1 year in UC.[11] Additionally, results from this analysis further support the absence of a laboratory monitoring requirement during ustekinumab treatment.

Overall, the integrated IBD safety profile was comparable to placebo during induction and through 1 year of follow-up (including the randomized maintenance subset) in the occurrence of AEs, SAEs, and infections (including serious infections and other infections of interest) with no clinically meaningful differences between doses or dose regimens (90 mg every 8 or 12 weeks). Results of time-to-event analysis adjusted by baseline characteristics for SAEs and serious infections do not suggest any increased risks for ustekinumab and are similar to the results adjusted by 100 PYs inasmuch as baseline characteristics in these randomized studies were generally well-balanced among treatment groups.

Through 1 year, a small number of OIs were reported in placebo and ustekinumab patients. Of note, CMV colitis was diagnosed in 2 ustekinumab-treated UC patients. Although detection of CMV seems to be more common in UC compared with CD, its clinical relevance has been widely debated. Ultimately, it is unclear whether CMV in UC truly represents active infection requiring antiviral therapy[15, 16] or is simply detected by highly sensitive assays in the context of severe inflammation and often oral immunosuppressants/steroids (both of these cases). Given the low number of events, individual case descriptions, and concomitant immunosuppressant use, there is no clear increased risk of OIs with ustekinumab, which is consistent with previously published data on redundancies in the immune system.[17]

With both 5 years of follow-up in psoriasis[8] and pooled safety analysis (before UC data availability), no safety signals for malignancy were identified with ustekinumab.[2, 7, 12, 18] In this IBD population, no increased malignancy risk was identified when compared with SEER (SIR, 1.02, [95% CI, 0.37–2.21] for ustekinumab), including within individual indications of CD or UC. SEER provides a real-world evidence comparison for clinical trial data. These rates are also similar to those observed in a Swiss IBD population (SIR, 0.93, [95% CI, 0.72–1.18]).[19] A small number of NMSCs were reported in this data set and comparable between ustekinumab and placebo. A reversal of BCC:SCC ratio (4:1),[20] a marker of immunosuppression impact, was not observed. Though these and previously reported findings are reassuring, longer-term longitudinal data

and larger (eg, real-world observational) studies are ongoing to confirm current findings of no increased malignancy risk with IL-12/23 inhibition.

As reported in the literature, overall IBD patients have a two- to three-fold increased risk of venous thromboembolism,[21–23] with a reported absolute risk of 0.26 per 100 PYs.[24] This risk was higher in patients with a disease flare (0.90 per 100 PYs) vs those with chronic activity (0.54 per 100 PYs) and lower for those in remission (0.14 per 100 PYs).[24] In patients with active IBD, additional risk factors including corticosteroid use, oral contraceptive use, IBD flare, and surgery confer an even higher risk of thromboembolic events compared with the overall IBD population.[23, 24] This is relevant when evaluating risk in patients enrolled in IBD trials, as these generally require patients to have moderately to severely active disease. As presented in these analyses, the overall incidence of DVT/PE was low through 1 year, similar to placebo, and not higher than what is expected in this population.

Rates of antibodies to ustekinumab were low through 1 year, with a numerically higher rate in UC vs CD patients. Of note, a change in the ustekinumab assay specificity cut point was implemented for the UC studies to comply with updated regulatory guidelines. This change resulted in a higher false-positive rate for UC compared with CD (1.6% vs 0.8% respectively; data on file). Thus, this slight difference between rates was expected but not clinically meaningful.

There are several limitations to this study. In a lifetime disease, 1 year of treatment is relatively short; longer-term data will be needed to further support these findings. This may limit comparisons, especially for long latency events like malignancies or certain infections. Although the data contained in this article are only from clinical trials, limitations on interpretation may differ from outcomes observed in the real-world.

This integrated analysis provides additional robust safety data for the use of ustekinumab in patients with IBD. Overall, the safety profile of ustekinumab was favorable and generally comparable to placebo. These data are consistent with the established safety profile of ustekinumab across all approved indications and support a favorable benefit-risk profile of ustekinumab treatment in patients with IBD.

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