Janssen Research & Development

Clinical Overview

Treatment of Adult Patients with Moderately to Severely Active Crohn's Disease (272-Week Submission) and Adult Patients with Moderately to Severely Active Ulcerative Colitis (96-Week Submission)

STELARA® (ustekinumab)

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Prepared by: Janssen Research & Development, LLC;
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
6-MP	6-mercaptopurine
ADR	adverse drug reaction
AE	adverse event
AZA	azathioprine
CDAI	Crohn's Disease Activity Index
CMV	cytomegalovirus
CRP	C-reactive protein
DVT	deep vein thrombosis
ECLIA	electrochemiluminescent immunoassay
eCRF	electronic case report form
EUPI	European Union Product Information
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
IL	interleukin
ITT	intention-to-treat
IV	intravenous
LOR	loss of response
LTE	long-term extension
MACE	major adverse cardiovascular event
MAH	Marketing Authorisation Holder
MCS	Mental Component Summary
MS	multiple sclerosis
MSD	Meso Scale Discovery
MTX	methotrexate
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NMSC	nonmelanoma skin cancer
PCS	Physical Component Summary
PK	pharmacokinetic(s)
PsA	psoriatic arthritis
PSOLAR	Psoriasis Longitudinal Assessment and Registry
q8w	every 8 weeks
q12w	every 12 weeks
SAE	serious adverse event
SC	subcutaneous
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
SF-36	36-item Short Form Health Survey
SIR	standardized incidence ratio
SOC	system-organ class
TB	tuberculosis
TNF	tumor necrosis factor
UC	ulcerative colitis
VTE	venous thromboembolism

1. PRODUCT DEVELOPMENT RATIONALE

1.1. Pharmacologic Class

Ustekinumab (STELARA®) is classified according to the Anatomical Therapeutic Chemical (ATC) Classification System as an Interleukin Inhibitor (ATC code L04AC05). Ustekinumab is a human immunoglobulin G1 kappa monoclonal antibody that binds with high affinity and specificity to the p40 subunit common to both human interleukin (IL)-12 and human IL-23.

1.2. Targeted Indication

Ustekinumab was approved in 2016 for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumor necrosis factor (TNF) antagonist or have medical contraindications to such therapies. Ustekinumab was approved in 2019 for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic or have medical contraindications to such therapies.

Ustekinumab is also approved for the treatment of adults and pediatric patients aged 6 years and older with psoriasis and adults with active psoriatic arthritis (PsA).

The data provided in this document are not intended to change the approved indications but rather to supplement the data for the approved Crohn's disease and UC indications.

1.3. Background Information

1.3.1. Crohn's Disease Studies

The standard of medical care for Crohn's disease, the unmet medical need, and the scientific background supporting the use of ustekinumab in the treatment of Crohn's disease were summarized in the initial submission (CRD/Mod2.5/Sec1.3, 1.4).

The initial dossier provided data through 1 year of treatment. The data supporting the maintenance of efficacy and the continued safety of ustekinumab through 2 years of treatment in subjects with moderately to severely active Crohn's disease was subsequently provided (CRD W96/Mod2.5/Sec1.3).

This update provides relevant data on the maintenance of efficacy and the continued safety of ustekinumab through 5 years of treatment in subjects with moderately to severely active Crohn's disease.

The Marketing Authorisation Holder (MAH) therefore proposes to update the European Union Product Information (EUPI) with relevant data on the maintenance of efficacy and the continued safety of ustekinumab through 5 years of treatment in subjects with moderately to severely active Crohn's (CRD_UC/Mod1.3.1).

1.3.2. Ulcerative Colitis Studies

The standard of medical care for UC, the unmet medical need, and the scientific background supporting the use of ustekinumab in the treatment of UC were summarized in the initial submission (UC/Mod2.5/Sec1.3, 1.4).

The initial dossier provided data through 1 year of treatment. This update provides relevant data on the maintenance of efficacy and the continued safety of ustekinumab through 2 years of treatment in subjects with moderately to severely active UC.

The MAH therefore also proposes to update the EUPI with relevant data on the maintenance of efficacy and the continued safety of ustekinumab through 2 years of treatment in subjects with moderately to severely active UC (CRD_UC/Mod1.3.1).

1.4. Clinical Development Program

All studies included in this submission were conducted and reported in accordance with the ethical principles originating in the Declaration of Helsinki and in accordance with the International Council for Harmonisation Good Clinical Practice guidelines, applicable regulatory requirements, and in compliance with the respective protocols.

1.4.1. Crohn's Disease Studies

The clinical development program for ustekinumab in Crohn's disease was described in the initial submission (CRD/Mod2.5/Sec1.5) and updated for the long-term extension (LTE) in the 2-year submission (CRD W96/Mod2.5/Sec1.4).

The Phase 3 studies which supported the submissions included 2 induction studies and 1 maintenance study (Figure 1). The induction studies were as follows:

- CNTO1275CRD3001 (hereafter referred to as CRD3001) included subjects who failed at least 1 TNF antagonist, and
- CNTO1275CRD3002 (hereafter referred to as CRD3002) included subjects who failed conventional therapy (including subjects who were naïve to TNF antagonists and those with TNF antagonist experience but without documented failure).

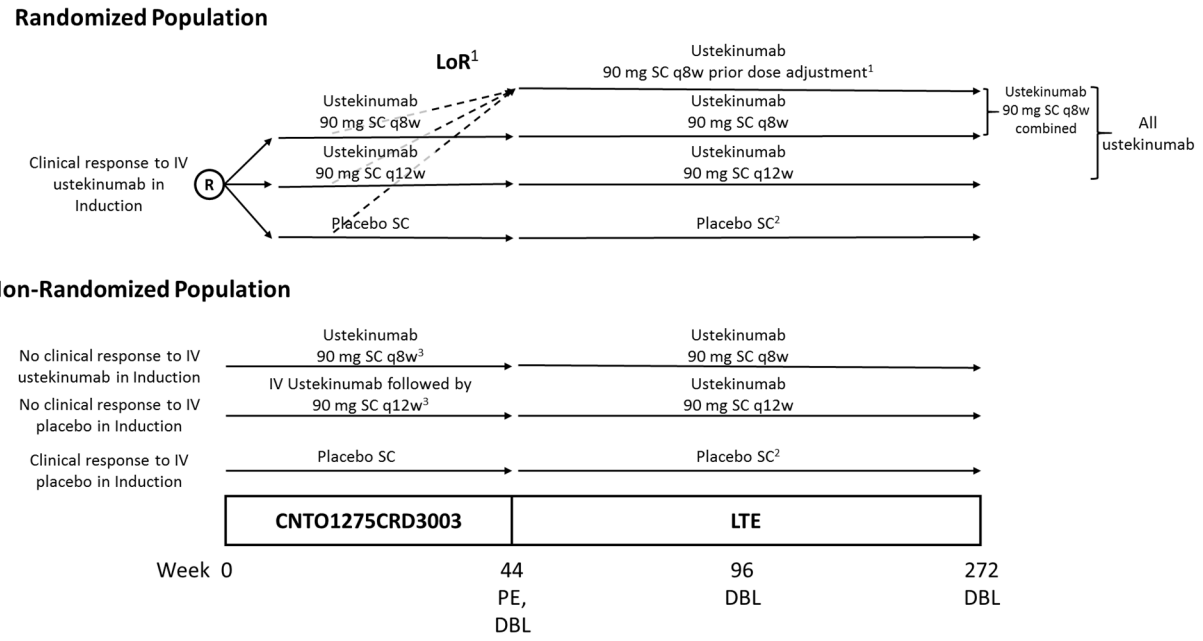
The maintenance study CNTO1275CRD3003 (hereafter referred to as CRD3003) targeted subjects who were in clinical response to intravenous (IV) ustekinumab at Week 8 of the CRD3001 or CRD3002 induction studies. Subjects in clinical response to IV ustekinumab in an induction study were randomized at Week 0 of CRD3003 to receive subcutaneous (SC) placebo, ustekinumab 90 mg SC every 12 weeks (q12w; hereafter referred to as the q12w group), or ustekinumab 90 mg SC every 8 weeks (q8w; hereafter referred to as the q8w group) and comprised the primary population of the maintenance study.

Subjects who subsequently met loss of response (LOR) criteria at any time between Week 8 and Week 32 were eligible to have a single dose adjustment to ustekinumab 90 mg q8w. These subjects were evaluated 16 weeks after dose adjustment and were discontinued from ustekinumab if not clinically improved.

Subjects not in clinical response to ustekinumab induction, subjects not in clinical response to placebo induction, and subjects in clinical response to placebo induction were also eligible to enter CRD3003 and comprised the nonrandomized population, who were also treated with ustekinumab or placebo.

All subjects who were enrolled in CRD3003 and who might benefit from continued treatment, in the opinion of the investigator, were eligible to continue treatment in the CRD3003 LTE through Week 272 (5 total years of treatment). Subjects who entered the LTE continued to receive the same treatment regimen that they were receiving at the end of the main study (placebo, ustekinumab 90 mg SC q8w, or ustekinumab 90 mg SC q12w), with the first dose in the LTE occurring at Week 44. There was no dose adjustment in the LTE. Of note, subjects receiving placebo were discontinued from CRD3003 after treatment assignments were unblinded to the investigative sites after the Week 44 analyses were completed.

Figure 1: Study Populations and Treatment Groups in CNTO1275CRD3003 (Maintenance Study and Long-term Extension)



[1] Subjects dose adjusted after meeting LOR criteria. Note that dose adjustment was only allowed between Week 8 and Week 32 of the CNTO1275CRD3003 main study, and no dose adjustment occurred in the LTE.
[2] All subjects receiving placebo were discontinued upon unblinding of the study.
[3] Subjects not in clinical response at Week 8 were discontinued from treatment.
Note: The last dose will be at Week 252, and the last safety data will be at Week 272.

Abbreviations: DBL=database lock; IV=intravenous; LOR=loss of response; LTE=long-term extension; PE=primary endpoint; q8w=every 8 weeks; q12w=every 12 weeks; R=randomization; SC=subcutaneous; Wk=week.

The focus of this submission for Crohn's disease is on the pharmacokinetics (PK), immunogenicity, efficacy, and safety data collected from Week 44 through Week 272 of the CRD3003 LTE. These data demonstrate the continued effect of ustekinumab on key efficacy

parameters in subjects with moderately to severely active Crohn's disease, as well as a stable safety profile, through 5 years of treatment.

1.4.2. Ulcerative Colitis Studies

The clinical development program for ustekinumab in UC was described in the initial submission (UC/Mod2.5/Sec1.5). The studies which supported the submission consisted of 2 Phase 3 studies, an IV induction study and a SC maintenance study, which were conducted under a single protocol CNTO1275UCO3001 (hereafter referred to as UCO3001) but were designed and analyzed as 2 separate studies (UCO3001 induction and UCO3001 maintenance) with separate endpoints and Type I error control.

The UCO3001 induction study included subjects with moderately to severely active UC who had an inadequate response or failure to tolerate conventional or biologic therapy (ie, a TNF antagonist and/or the integrin antagonist, vedolizumab). Subjects who were in clinical response at Week 8 were eligible to enter the maintenance study. Subjects who were not in clinical response at Week 8 received SC ustekinumab at Week 8. Those who subsequently responded at Week 16 were eligible to enter the maintenance study; those who were not in clinical response at Week 16 were discontinued from study agent and did not enter the maintenance study (Figure 2).

The UCO3001 maintenance study targeted subjects who demonstrated a clinical response to induction treatment with IV ustekinumab. Subjects who were in clinical response to a single IV ustekinumab dose during induction comprised the primary population in the maintenance study and were randomized at Week 0 of UCO3001 maintenance to receive SC placebo, ustekinumab 90 mg SC q12w or ustekinumab 90 mg SC q8w. The following subjects from the induction study were included in the primary population of the maintenance study:

- Subjects who were randomized to receive IV ustekinumab at Week 0 of the induction study and were in clinical response at Week 8 of the induction study.
- Subjects who were randomized to receive IV placebo at Week 0 of the induction study and were not in clinical response at Week 8 but were in clinical response at Week 16 of the induction study after receiving an induction dose of IV ustekinumab (~6 mg/kg) at Week 8.

Other subjects who were responders to study agent in the induction study also entered the maintenance study but were not randomized and were not included in the key efficacy analyses. These subjects from the induction study comprise the nonrandomized population of the maintenance study:

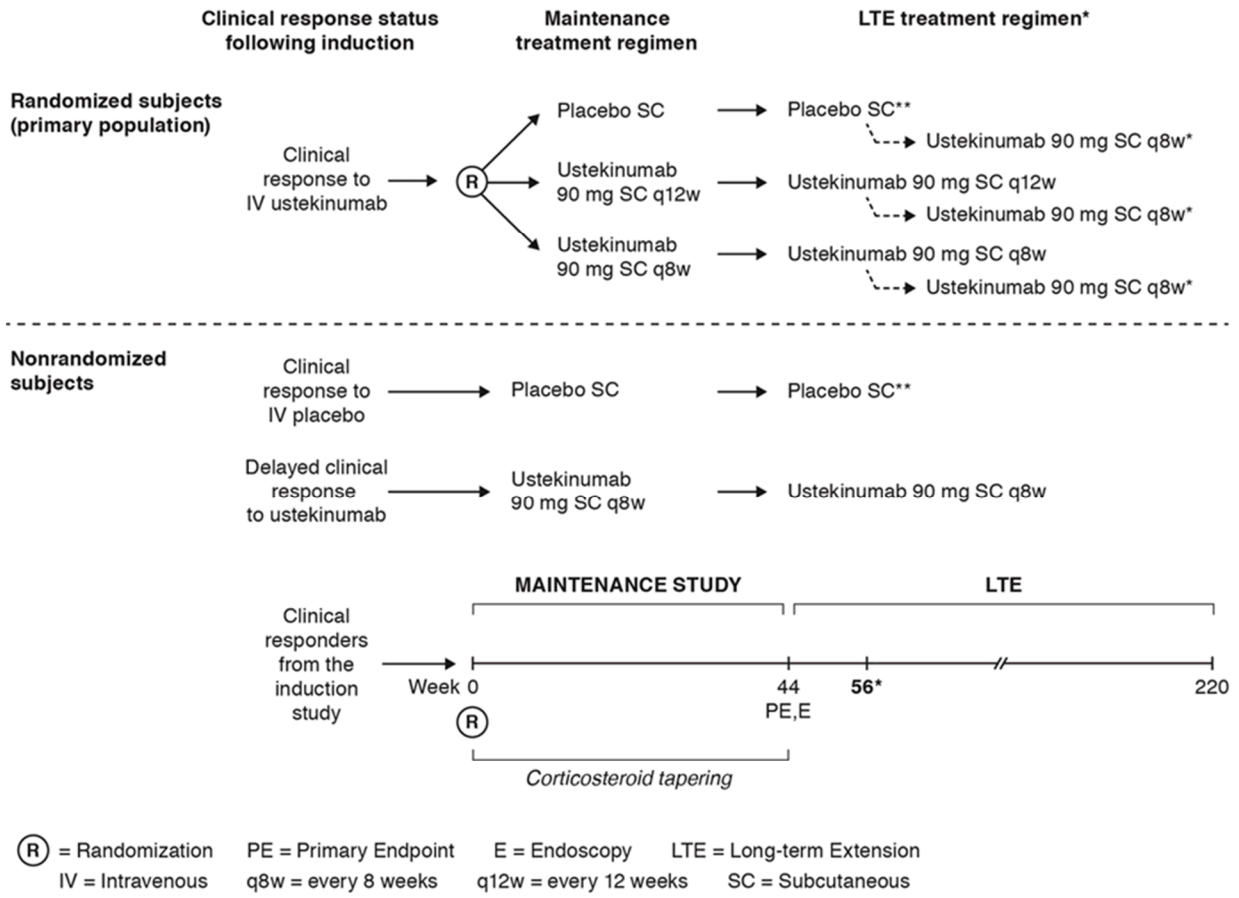
- Placebo-only subjects: Subjects who were randomized to receive IV placebo at Week 0 of the induction study and were in clinical response at Week 8 of the induction study.
- Delayed responders: Subjects who were randomized to receive IV ustekinumab at Week 0 of the induction study and were not in clinical response at Week 8 but were in clinical response at Week 16 of the induction study after receiving an additional dose of ustekinumab (90 mg SC) at Week 8.

Subjects in the nonrandomized population were assigned to treatment as shown in Figure 2.

Subjects who completed the safety and efficacy evaluations at Week 44 and who, in the opinion of the investigator, might benefit from continued treatment had the opportunity to participate in the LTE. Subjects were to continue to receive the same treatment regimen during the LTE that they were receiving at the end of the maintenance study (either placebo, ustekinumab 90 mg SC q12w [hereafter referred to as the q12w group], or ustekinumab 90 mg SC q8w [hereafter referred to as the q8w group]), with the first dose in the LTE being administered at Week 48.

During the LTE, all subjects were to be assessed for worsening of UC disease activity based on the clinical judgment of the investigator. Subjects in the primary population (ie, those who were randomized at maintenance Week 0) whose UC disease activity worsened were eligible for a single dose adjustment to ustekinumab 90 mg q8w beginning at Week 56. Subjects who were not in the primary population (ie, placebo induction responders, ustekinumab induction delayed responders) were not eligible for a dose adjustment during the LTE. The LTE phase of the study began at Week 44 and will continue through Week 220.

Figure 2: Schema for the CNTO1275UCO3001 Maintenance Study and Long-term Extension



R = Randomization PE = Primary Endpoint E = Endoscopy LTE = Long-term Extension
IV = Intravenous q8w = every 8 weeks q12w = every 12 weeks SC = Subcutaneous

* Subjects in the primary analysis population (ie, those who were randomized at maintenance Week 0) whose UC disease activity worsened, based on the clinical judgement of the investigator, were eligible for a single dose adjustment during the LTE, as early as Week 56.
** Subjects discontinued after study was unblinded to investigative sites.

The focus of this submission for UC is on the PK, immunogenicity, efficacy, and safety data collected from Week 44 through Week 96 of the UCO3001 maintenance study LTE. These data demonstrate the continued effect of ustekinumab on key efficacy parameters in subjects with moderately to severely active UC, as well as a stable safety profile, through 2 years of treatment.

2. OVERVIEW OF BIOPHARMACEUTICS

2.1. Formulation Used in Crohn's Disease and Ulcerative Colitis Clinical Studies

The IV and SC formulations used in the Crohn's disease studies were previously reported in the original submission (CRD/Mod2.5/Tab1), and the single-use prefilled syringe for SC administration used in the LTE was presented in the Week 96 update (CRD W96/Mod2.5/Sec2.1).

The same IV formulation and the single-use prefilled syringe for SC administration as were used in the Crohn's disease studies were also used in the UC studies and were previously reported in the original submission (UC/Mod2.5/Sec2.1).

2.2. Bioanalytical Methods

Serum ustekinumab concentrations in blood samples collected in the LTEs in the CRD3003 and UCO3001 studies were measured using a validated electrochemiluminescent immunoassay (ECLIA) method on the Meso Scale Discovery (MSD®) platform (CRD_UC/Mod2.7.2/Sec1.1.1).

Analyses of antibodies to ustekinumab in the CRD3003 and UCO3001 studies were performed using a validated, sensitive, and drug-tolerant ECLIA method on the MSD platform (CRD_UC/Mod2.7.2/Sec1.2.1).

3. OVERVIEW OF CLINICAL PHARMACOLOGY

For Crohn's disease, comprehensive information on the PK and immunogenicity from the Crohn's disease clinical studies through Week 44 was provided in the initial submission (CRD/Mod2.7.2), and data from the CRD3003 LTE (ie, from Week 44 to Week 92 for PK and from Week 0 of induction through Week 96 for immunogenicity) were provided in the 2-year submission (CRD W96/Mod2.7.2). In this submission, the primary focus is the summary of ustekinumab concentration data collected from Week 44 through Week 252 in the Crohn's disease LTE (Section 3.1.1) and immunogenicity data based on samples collected through Week 272 (the final safety visit) of the LTE (Section 3.2.1). Additional details are provided in the Summary of Clinical Pharmacology (SCP; CRD_UC/Mod2.7.2).

For UC, comprehensive information on PK and immunogenicity from the UCO3001 induction and maintenance clinical studies through Week 44 was provided in the initial submission (UC/Mod2.7.2). In this submission, the primary focus is the summary of ustekinumab concentration data collected from Week 44 through Week 92 for subjects who continued into the UC LTE (Section 3.1.2) and immunogenicity data based on samples collected through Week 96 of the LTE (Section 3.2.2). Additional details are provided in the SCP (CRD_UC/Mod2.7.2).

Comparisons of results across the Crohn's disease and UC studies include ustekinumab PK (Section 3.1.3) and immunogenicity (Section 3.2.3).

3.1. Pharmacokinetics

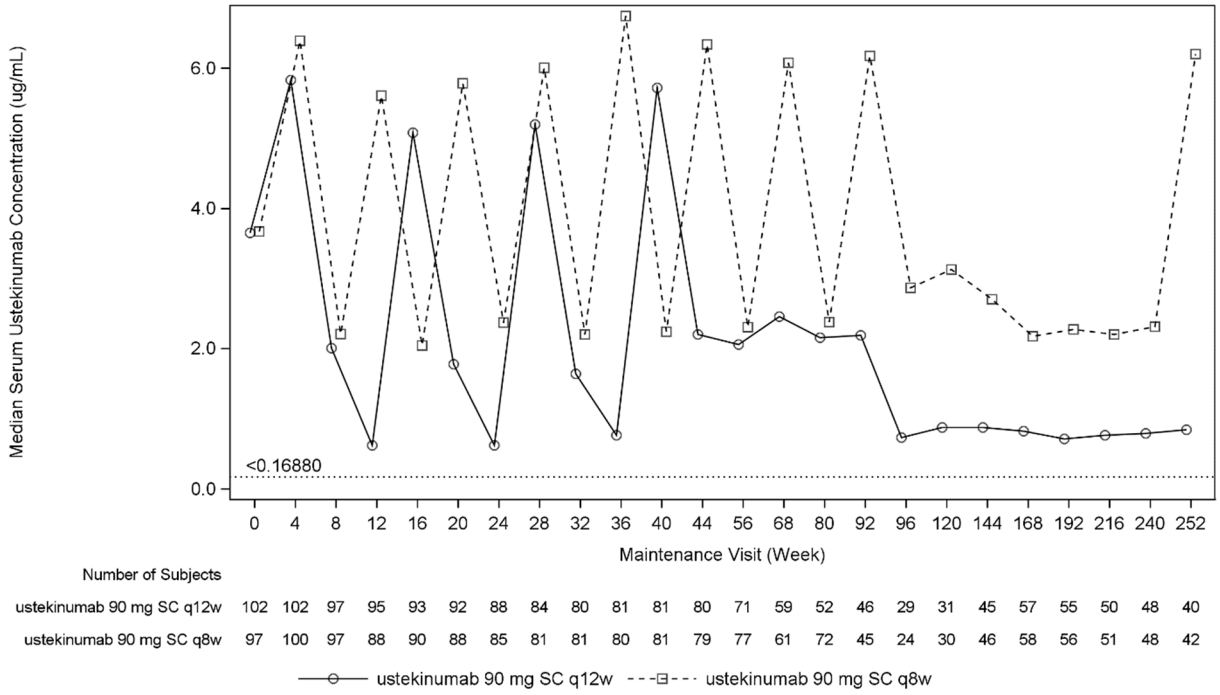
3.1.1. Crohn's Disease Studies

3.1.1.1. Randomized Subjects

Based on the CRD3003 study visit schedule, ustekinumab concentrations were evaluated q12w from Week 44 up to the time of study unblinding (eg, at Weeks 44, 56, 68, 80, 92, etc). Randomized subjects received study agent at all monthly visits until study unblinding. After the study was unblinded to the investigative sites, subjects receiving placebo were terminated from study participation, and subjects receiving ustekinumab continued to receive ustekinumab and had study visits scheduled to coincide with their dose regimen (either q8w or q12w). For most subjects, study unblinding occurred after the Week 92 visit. Accordingly, for randomized subjects, concentration data summaries after Week 92 focus on the common dose administration visits for the 2 ustekinumab dose regimens (ie, Weeks 96, 120, 144, 168, 192, 216, and 240) to allow comparison of trough concentrations between both ustekinumab regimens and at Week 252, the last planned study visit to assess efficacy in the LTE (CRD_UC/Mod2.7.2/Sec2.1.1).

Subjects who received ustekinumab 90 mg q12w or q8w during the LTE had sustained ustekinumab concentrations through Week 252 (Figure 3). In the LTE, median trough concentrations in the q8w group were ~3-fold greater than those in the q12w group (CRD_UC/Mod2.7.2/Tab2). In addition, median ustekinumab concentrations during the LTE were consistent with those observed during the main portion of the maintenance study for the respective treatment groups (CRD_UC/Mod2.7.2/Tab2). At Week 252 (which was at trough [12 weeks post-dose] for subjects receiving ustekinumab q12w, and 4 weeks post-dose for those receiving ustekinumab q8w), median serum ustekinumab concentrations were 0.84 µg/mL in the q12w group and 6.20 µg/mL in the q8w group.

Figure 3: Median Serum Ustekinumab Concentration (micrograms/mL) Over Time from Maintenance Week 0 through 252; Subjects Who Were Randomized and Received Ustekinumab in the Maintenance Study who Entered the Long-term Extension and Did Not Have a Dose Adjustment (CNTO1275CRD3003)



Abbreviations:q8w=every 8 weeks; q12w=every 12 weeks; SC=subcutaneous.

3.1.1.2. Nonrandomized Subjects

Among nonrandomized subjects, concentration data summaries after Week 92 also focus on the common dose administration visits for the q12w and q8w dose regimens (ie, Weeks 104, 128, 152, 176, 200, 224, and 248) to allow comparison of trough concentrations between both ustekinumab regimens and at Week 252, the last planned study visit to assess efficacy in the LTE (CRD_UC/Mod2.7.2/Sec2.1.2). Nonrandomized subjects who received ustekinumab 90 mg SC q12w or q8w during the LTE had sustained ustekinumab concentrations through Week 252. Based on the common dose administration visits from Week 96 through Week 240 of the LTE, median trough ustekinumab concentrations in nonrandomized subjects ranged from 0.79 µg/mL to 0.96 µg/mL in the q12w group compared with 1.83 µg/mL to 2.33 µg/mL in the q8w group. At Week 252 (ie, which was not a trough concentration but 4 weeks post-dose for both the q12w and q8w groups), median serum ustekinumab concentrations in nonrandomized subjects were 5.01 µg/mL in the q12w group and 5.77 µg/mL in the q8w group.

These results indicate that nonrandomized subjects had sustained levels of ustekinumab throughout the LTE similar to those observed for randomized subjects.

3.1.1.3. Serum Ustekinumab Concentration by Concomitant Immunomodulator Use

The impact of the use of immunomodulators (6-mercaptopurine [6-MP], azathioprine [AZA], or methotrexate [MTX]) at induction baseline on serum ustekinumab concentrations during the CRD3003 LTE was assessed (CRD_UC/Mod2.7.2/Sec2.1.3). In their respective treatment groups, median serum ustekinumab concentrations were generally comparable between subjects who were receiving immunomodulators as compared with those who were not receiving immunomodulators.

3.1.2. Ulcerative Colitis Studies

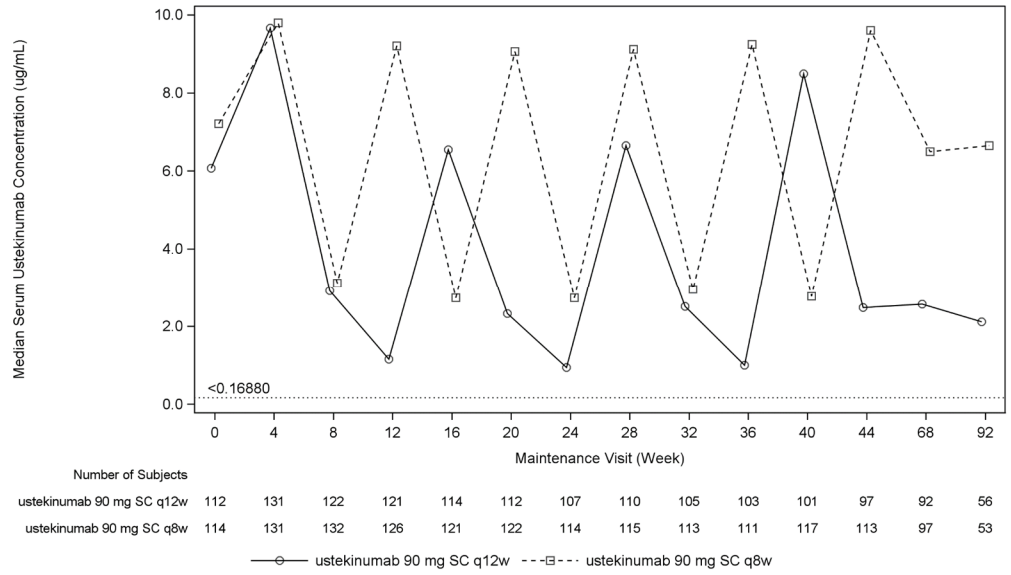
3.1.2.1. Randomized Subjects

To evaluate the consistency of systemic ustekinumab exposure in subjects receiving ustekinumab, serum ustekinumab concentrations were summarized over time in randomized subjects who continued to receive ustekinumab q12w or q8w during the UCO3001 LTE (CRD_UC/Mod2.7.2/Sec2.2.1).

Based on the UCO3001 LTE visit schedule, blood samples for the measurement of serum ustekinumab concentrations were collected every 24 weeks from Week 44 (ie, at Week 44, Week 68, and Week 92). Accordingly, concentration data for subjects receiving ustekinumab q12w up to the time of dose adjustment were available 8 weeks after the respective ustekinumab dose administrations at Week 36, Week 60, and Week 84, but not at trough. Concentration data for subjects receiving ustekinumab q8w were available 4 weeks after the respective ustekinumab dose administrations at Week 40, Week 64, and Week 88, but not at trough.

Randomized subjects who received ustekinumab during the LTE had sustained levels of ustekinumab throughout the LTE (Figure 4). Subjects randomized to ustekinumab q12w in maintenance who continued to receive ustekinumab 90 mg in the LTE (ie, at Week 48, Week 60, Week 72, Week 84, and Week 96) had median ustekinumab concentrations ranging from 2.11 µg/mL to 2.56 µg/mL 8 weeks after ustekinumab dosing over the time period from Week 68 to Week 92 (CRD_UC/Mod2.7.2/Tab3). Subjects randomized to ustekinumab q8w in maintenance who continued to receive ustekinumab 90 mg q8w in the LTE (ie, at Week 48, Week 56, Week 64, Week 72, Week 80, Week 88, and Week 96) had median ustekinumab concentrations ranging from 6.49 µg/mL to 6.66 µg/mL 4 weeks after ustekinumab dosing over the time period from Week 68 to Week 92.

Figure 4: Median Serum Ustekinumab Concentration (micrograms/mL) Over Time from Maintenance Week 0 through 92; Subjects Who Were Randomized and Received Ustekinumab in the Long-term Extension and Did Not Have a Dose Adjustment (CNTO1275UCO3001)



Abbreviations:q8w=every 8 weeks; q12w=every 12 weeks; SC=subcutaneous.

Dose Adjustment

Randomized subjects in the maintenance study whose UC disease activity worsened during the LTE were eligible, beginning at Week 56, for a single dose adjustment. Because the subjects who had a dose adjustment initiated ustekinumab q8w at different visits, concentration data summaries for these subjects are not representative of the expected concentrations over time for subjects who continued receiving ustekinumab q8w.

Among subjects randomized to ustekinumab q12w, serum ustekinumab concentrations at Week 44 were similar between subjects who underwent a dose adjustment compared with those who did not (2.51 µg/mL and 2.50 µg/mL, respectively; CRD_UC/Mod2.7.2/Sec2.2.1.1). After dose adjustment from ustekinumab q12w to ustekinumab q8w, median serum ustekinumab concentrations were 2.97 µg/mL and 3.83 µg/mL at Week 68 and Week 92, respectively.

Among subjects randomized to the ustekinumab q8w group, median ustekinumab concentrations at Week 44 through Week 92 were generally comparable between subjects who underwent a sham dose adjustment compared with those who did not need dose adjustment.

3.1.2.2. Nonrandomized Subjects (Ustekinumab Induction Delayed Responders)

At Week 44, the median serum ustekinumab concentration among subjects in the ustekinumab induction delayed-responder group (7.83 µg/mL) was slightly lower than that of subjects who responded to the single ustekinumab IV induction dose, were randomized to ustekinumab q8w, and did not have a dose adjustment (9.67 µg/mL; CRD_UC/Mod2.7.2/Sec2.2.2). This difference in ustekinumab concentration was no longer apparent at Week 68 and Week 92, where the median concentrations in delayed responders (6.21 µg/mL and 5.94 µg/mL, respectively) were comparable to those in subjects randomized to ustekinumab q8w who did not have a dose adjustment (6.49 µg/mL and 6.66 µg/mL, respectively).

Median ustekinumab concentrations in ustekinumab induction delayed responders during the LTE were generally comparable with those observed during the main portion of the maintenance study. Specifically, median ustekinumab concentration at 4 weeks after ustekinumab administration during the LTE ranged from 5.94 µg/mL to 6.21 µg/mL compared with 5.75 µg/mL to 8.70 µg/mL in the main portion of the study.

3.1.2.3. Serum Ustekinumab Concentration by Concomitant Immunomodulator Use

The impact of the use of immunomodulators (6-MP, AZA, or MTX) at the start of induction on serum ustekinumab concentrations during the UCO3001 LTE was assessed (CRD_UC/Mod2.7.2/Sec2.2.3). In their respective treatment groups, median serum ustekinumab concentrations were generally comparable between subjects who were receiving immunomodulators as compared with those who were not receiving immunomodulators.

3.1.3. Comparison of Ustekinumab Pharmacokinetics in the Crohn's Disease and Ulcerative Colitis Studies

Week 68 and Week 92 were the only concurrent timepoints in both the CRD3003 and UCO3001 LTEs through Week 92 (CRD_UC/Mod2.7.2/Sec3.1). Comparison of serum ustekinumab concentrations in the main portions of the CRD3003 and UCO3001 maintenance studies through Week 44 were presented in the Week 44 UC SCP (UC/Mod2.7.2).

Following the same SC maintenance dose regimens, ustekinumab concentrations were similar between subjects with Crohn's disease and UC. Median serum ustekinumab concentrations at Week 68 were as follows in the q12w and q8w groups, respectively (CRD_UC/Mod2.7.2/Tab4):

- Crohn's disease: 2.46 µg/mL and 6.08 µg/mL
- UC: 2.56 µg/mL and 6.49 µg/mL

A similar pattern was observed at Week 92.

3.2. Immunogenicity

3.2.1. Crohn's Disease Studies

The incidence of antibodies to ustekinumab remained low among subjects in the CRD3003 LTE. Of the 532 subjects who were treated with IV ustekinumab, received maintenance SC ustekinumab, and entered the LTE, 5.8% were positive for antibodies to ustekinumab from induction Week 0 through the final safety visit (CRD_UC/Mod2.7.2/Sec4.1).

3.2.2. Ulcerative Colitis Studies

The incidence of antibodies to ustekinumab remained low among subjects in the UCO3001 LTE through Week 96. Among 400 subjects who received ustekinumab in induction, maintenance, and the LTE, 5.5% were positive for antibodies to ustekinumab from induction Week 0 through Week 96 (CRD_UC/Mod2.7.2/Sec4.2).

3.2.3. Comparison of Immunogenicity in the Crohn's Disease and Ulcerative Colitis Studies through Week 96

The immunogenicity profile of ustekinumab in subjects with Crohn's disease and with UC were generally comparable.

To compare the immunogenicity of ustekinumab in subjects with Crohn's disease versus subjects with UC, the incidence of antibodies to ustekinumab through Week 96 was compared for subjects receiving continuous ustekinumab for both diseases (CRD_UC/Mod2.7.2/Sec4.3). Among subjects with inflammatory bowel disease (IBD; Crohn's disease or UC) who received ustekinumab after induction and entered the LTE, the incidence of antibodies to ustekinumab through Week 96 was comparable in subjects with Crohn's disease and subjects with UC (4.7% [25/532] and 5.5% [22/400], respectively).

4. OVERVIEW OF EFFICACY

4.1. Population Studied

4.1.1. Crohn's Disease Studies

The Phase 3 Crohn's disease program encompassed a broad range of subjects with moderately to severely active Crohn's disease, including those who failed 1 or more TNF antagonists or failed conventional therapy (corticosteroids and/or immunomodulators). The majority of subjects who failed conventional therapy were naïve to TNF antagonists.

The main efficacy analyses were based on subjects who were randomized at Week 0 of the maintenance study, entered the LTE, and received study agent in the LTE (ie, randomized subjects). Efficacy analyses were also performed based on all subjects who entered the LTE and received study agent, which includes both randomized and nonrandomized subjects in CRD3003 (ie, all treated subjects). In addition, analyses of clinical remission and clinical response were performed based on all subjects randomized at Week 0 of the maintenance study, regardless of whether subjects entered the LTE or not, by the original randomized treatment group.

Of 1,281 subjects who completed the ustekinumab induction studies CRD3001 and CRD3002 and were enrolled in CRD3003, a total of 718 subjects continued into the LTE. Of the 397 randomized subjects in CRD3003, 298 subjects continued into the LTE (CRD_UC/Mod2.7.3/CRD/Sec2.1.1).

4.1.2. Ulcerative Colitis Studies

This Phase 3 UC program encompassed a broad range of subjects with moderately to severely active UC who had an inadequate response to, or failed to tolerate either conventional therapy (corticosteroids and/or immunomodulators) or biologic therapy (TNF antagonists and/or the integrin antagonist, vedolizumab). The majority of subjects who had an inadequate response to or failed to tolerate conventional therapy were naïve to biologic therapy.

A total of 588 subjects completed the safety and efficacy evaluation at Week 44 in the UCO3001 maintenance study and, in the opinion of the investigator, would benefit from continued treatment and were treated in the LTE (CRD_UC/Mod2.7.3/UC/Sec2.1.1). Among these, 399 subjects were from the primary population for the maintenance study (ie, were in clinical response to ustekinumab IV induction and were randomized at maintenance Week 0) and 189 subjects were not part of the primary population for the maintenance study (ie, placebo induction responders and ustekinumab induction delayed responders [nonrandomized subjects]).

Of the 399 subjects randomized at maintenance baseline who were treated during the LTE, 141 subjects in the q12w group and 143 subjects in the q8w group are the primary focus for evaluating efficacy endpoints. Among the 189 nonrandomized subjects who were treated during the LTE, 116 subjects were ustekinumab induction delayed responders and continued to receive ustekinumab 90 mg SC q8w throughout maintenance and into the LTE, and 73 subjects who were in clinical response to placebo IV induction (responders to placebo IV induction) continued to receive placebo SC throughout maintenance and during the LTE until study unblinding, when they were discontinued from the study.

4.2. Demographics and Baseline Disease Characteristics

4.2.1. Crohn's Disease Studies

Among randomized subjects treated in the LTE, 56.4% were female, 85.2% were white, the median age was 36.5 years, and the median weight was 69.90 kg (CRD_UC/Mod2.7.3/CRD/Sec2.1.2). The induction and maintenance baseline disease characteristics of the randomized subjects treated in the LTE were consistent with those of the overall randomized population in the maintenance study and were representative of a population with moderately to severely active Crohn's disease.

At Week 44, the clinical disease characteristics for randomized subjects who were treated in the LTE were generally similar for the ustekinumab treatment groups and numerically higher (eg, Crohn's Disease Activity Index [CDAI] scores) or lower (eg, Inflammatory Bowel Disease Questionnaire [IBDQ] scores, clinical remission rates) for subjects with prior dose adjustment, indicating higher disease activity for subjects with prior dose adjustment. Among subjects in the q12w and q8w groups, the proportions in clinical remission (defined as a CDAI score of <150

points) were 77.4% and 84.1%, respectively, and the median CDAI scores were 95.5 and 70.5, respectively, at Week 44. Among subjects with prior dose adjustment, 63.4% were in clinical remission and the median CDAI score was 130.0.

4.2.2. Ulcerative Colitis Studies

Among randomized subjects treated in the LTE, 58.1% were male, 74.4% were white, the median age was 40.0 years, and the median weight was 71.60 kg (CRD_UC/Mod2.7.3/UC/Sec2.1.2). The induction and maintenance baseline disease characteristics of the randomized subjects treated in the LTE were consistent with those of the overall randomized population in the maintenance study and were representative of a population with moderately to severely active UC.

At Week 44, the clinical disease characteristics for randomized subjects who were treated in the LTE were generally similar for the ustekinumab treatment groups. Among subjects in the q12w and q8w groups, the proportions in clinical remission (defined as a Mayo score ≤2 points, with no individual subscore >1) were 46.1% and 52.4%, respectively, and the proportions with endoscopic healing were 56.7% and 61.5%, respectively.

The clinical disease characteristics at Week 44 among subjects in the ustekinumab induction delayed-responder group (who received ustekinumab q8w during maintenance and the LTE) compared with the clinical disease characteristics of randomized subjects from the ustekinumab q8w group were indicative of higher disease activity in the ustekinumab induction delayed-responder group. The proportions of subjects in clinical remission and the proportions of subjects with endoscopic healing (38.8% and 47.4%, respectively) at Week 44 in the ustekinumab induction delayed-responder group were lower compared with the randomized ustekinumab q8w group (52.4% and 61.5%, respectively).

4.3. Statistical Methods

4.3.1. Crohn's Disease Studies

A summary of statistical methods for the Crohn's disease LTE is provided in the Crohn's disease Summary of Clinical Efficacy (SCE; CRD_UC/Mod2.7.3/CRD/Sec1.3). The main efficacy analyses were based on subjects who were randomized at Week 0 of the maintenance study, entered the LTE, and received study agent (ie, randomized subjects).

The primary focus for efficacy endpoints through Week 252 were subjects randomized to ustekinumab who continued to receive ustekinumab 90 mg SC q12w and 90 mg SC q8w (ie, the groups of subjects who did not meet LOR criteria in the main study). The MAH believes this approach offers the best means to assess the durability of effect of prolonged maintenance treatment with ustekinumab and avoids potential confounding of interpretation introduced by subjects meeting LOR criteria.

Because subjects receiving placebo were discontinued from the study after treatment assignments were unblinded to the investigative sites after completion of the Week 44 analyses, a direct comparison of findings between placebo and ustekinumab treatment groups was not warranted and, in general, no statistical comparisons were performed for the efficacy endpoints in the LTE.

Furthermore, the main intent of presenting data for the ustekinumab 90 mg q12w and q8w treatment groups is to show that with both treatment regimens, clinical remission and clinical response are maintained over time. It is important to note that subjects were selected to participate in the LTE because, in the opinion of the investigator, they had responded to treatment in the main study, so treatment group assignments were no longer random. For this reason, a direct comparison between ustekinumab treatment groups should be interpreted with caution.

4.3.1.1. Efficacy Evaluations in the Long-term Extension

The main efficacy analyses through Week 252 were based on an as-observed analysis approach with treatment failure rules applied. In the as-observed analysis approach, at each analysis timepoint, only those subjects who had data available or who had a treatment failure (ie, had a Crohn's disease-related surgery or discontinued study agent due to lack of efficacy or due to an adverse event [AE] indicated to be worsening of Crohn's disease) prior to that time point were included in the analysis. Subjects who had a treatment failure were considered not to have met binary endpoints and had their induction baseline values carried forward from time of the treatment failure onwards for continuous endpoints. This approach was considered reasonable as only those subjects with missing data not related to treatment failure (presumably missing at random) were excluded from the analysis. Results for the more conservative intention-to-treat (ITT) analyses are available in the Week 272 CRD3003 clinical study report (Mod5.3.5.1/CNTO1275CRD3003/W272/Sec6.2).

To reflect clinical practice where treatments are optimized either through increases in dose or dosing frequency, the key efficacy endpoints of clinical remission and clinical response were also evaluated based on an analytical approach that treats dose adjustment as a treatment strategy, where subjects who had a dose adjustment were not considered to be treatment failures.

4.3.2. Ulcerative Colitis Studies

A summary of statistical methods for the UC LTE is provided in the UC SCE (CRD_UC/Mod2.7.3/UC/Sec1.3). The main efficacy analyses for the LTE were based on subjects who were randomized at Week 0 of the maintenance study, entered the LTE, and received study agent during the LTE, with the primary focus being subjects randomized to ustekinumab 90 mg SC q12w or 90 mg SC q8w. The main intent is to show that efficacy was maintained over time with ustekinumab maintenance treatment. Because subjects receiving placebo were to terminate from study participation after study unblinding, a direct comparison of findings between placebo and ustekinumab treatment groups was considered to be confounded; therefore, no statistical comparisons were performed.

Furthermore, the main intent of presenting data for the ustekinumab 90 mg q12w and q8w treatment groups is to show that with both treatment regimens, symptomatic remission and improvements in partial Mayo score are maintained over time. It is important to note that subjects were selected to participate in the LTE because, in the opinion of the investigator, they had responded to treatment in the main study, so treatment group assignments were no longer random. For this reason, a direct comparison between ustekinumab treatment groups should be interpreted with caution.

4.3.2.1. Efficacy Evaluations in the Long-term Extension

Analyses of key efficacy endpoints such as symptomatic remission and the change from maintenance baseline in partial Mayo score were based on an as-observed analysis approach with treatment failure rules applied. In the as-observed analysis approach, at each analysis time point, only those subjects who had data available or who had a treatment failure (ie, had an ostomy or colectomy, discontinued study agent due to lack of therapeutic effect or due to an AE of worsening of UC or had a dose adjustment) prior to that time point were included in the analysis. Subjects who had a treatment failure were considered not to be in symptomatic remission and had their induction baseline values carried forward from the time of the treatment failure onwards for partial Mayo score. This analysis approach was considered reasonable as only those patients with missing data not related to treatment failure (presumably missing at random) were excluded from the analysis.

Analyses of other endpoints (for eg, corticosteroid-free symptomatic remission, inflammatory biomarkers [C-reactive protein (CRP), fecal calprotectin], general health-related quality of life [IBDQ, 36-item Short Form Health Survey (SF-36)]) were based on the ITT analysis approach, in which the subjects with treatment failure and insufficient data were considered not to have met binary endpoints. In this analysis approach, the number of subjects included in the analysis was fixed over time. As it was expected that more subjects would undergo dose adjustment (a treatment failure criterion) or discontinue study agent over time, the proportion of subjects who achieved binary endpoints was expected to decrease over time. As such, the ITT analysis approach was considered conservative.

To reflect clinical practice where treatments are optimized either through increases in dose or dosing frequency, the key efficacy endpoint of symptomatic remission was also analyzed based on an analytic approach that treats dose adjustment as a treatment strategy, where subjects who had a dose adjustment were not considered to be treatment failures.

Further, selected endpoints were summarized for randomized subjects who had a dose adjustment in the LTE and for the ustekinumab induction delayed responders in the nonrandomized population.

4.4. Key Efficacy Findings

4.4.1. Crohn's Disease Studies

The main efficacy analyses were based on subjects who were randomized at Week 0 of the maintenance study, entered the LTE, and received study agent (ie, randomized subjects; Section 4.4.1.1). Health economics outcomes (Section 4.4.1.3), efficacy and PK (Section 4.4.1.4), and efficacy and immunogenicity (Section 4.4.1.5) were also evaluated for the randomized population. Selected efficacy summaries are also provided for subjects who had a dose adjustment between Week 8 and Week 36 (due to LOR) as part of their treatment experience (ie, subjects who had a dose adjustment were not considered to be treatment failures; Section 4.4.1.2).

Efficacy analyses based on all subjects who entered the LTE and received study agent (ie, all treated subjects) were also performed and are considered supportive. Results are presented in the Crohn's disease SCE (CRD_UC/Mod2.7.3/CRD/Sec2.2).

A summary of endpoints at Week 252 for CRD3003 in randomized subjects who did not meet LOR criteria and entered the LTE is presented in Table 1. Unless noted otherwise, the data presented are based on the as-observed analysis approach.

Table 1: Maintenance of Key Efficacy Endpoints at Week 252 in CNTO1275CRD3003; Randomized Subjects Who Did Not Meet LOR Criteria in Maintenance and Entered the LTE

	Ustekinumab 90 mg q12w	Ustekinumab 90 mg q8w
Randomized subjects who did not meet LOR criteria in maintenance and entered the LTE [a, b]	84	82
Clinical remission [c]		
Subjects in clinical remission	61.3% (38 /62)	76.3% (45/59)
TNF antagonist failures (CRD3001)	54.2% (13/24)	63.2% (12/19)
Conventional therapy failures (CRD3002)	65.8% (25/38)	82.5% (33/40)
TNF antagonist naïve	57.7% (15/26)	79.3% (23/29)
Clinical response [d]		
Subjects in clinical response	72.6% (45/62)	79.7% (47/59)
TNF antagonist failures (CRD3001)	62.5% (15/24)	68.4% (13/19)
Conventional therapy failures (CRD3002)	78.9% (30/38)	85.0% (34/40)
TNF antagonist naïve	76.9% (20/26)	82.8% (24/29)
Corticosteroid-related outcomes [e]		
Corticosteroid-free clinical remission	54.8% (34/62)	71.2% (42/59)
Corticosteroid-free clinical response	66.1% (41/62)	72.9% (43/59)
CRP		
Subjects with normalization (≤3 mg/L) among those with abnormal CRP (>3 mg/L) at induction baseline	37.0% (17/46)	35.0% (14/40)
IBDQ score		
Subjects with a ≥16-point improvement from induction baseline	58.7% (37/63)	80.4% (45/56)
SF-36: Subjects with a ≥5-point improvement from induction baseline in:		
PCS	55.6% (30/54)	63.3% (31/49)
MCS	50.0% (27/54)	61.2% (30/49)

Abbreviations: CDAI=Crohn's Disease Activity Index; CRP=C-reactive protein; IBDQ=Inflammatory Bowel Disease Questionnaire; LOR=loss of response; LTE=long-term extension; MCS=Mental Component Summary (score); PCS=Physical Component Summary (score); q8w=every 8 weeks; q12w=every 12 weeks; SF-36=36-item Short Form Health Survey.

a. Subjects who were in clinical response to ustekinumab IV induction dosing, were randomized to receive study agent on entry into the maintenance study, and did not meet loss of response criteria from Week 8 through Week 32.
b. Subjects who completed the safety and efficacy evaluation at Week 44 and, in the opinion of the investigator, would benefit from continued treatment were treated in the LTE.
c. Clinical remission is defined as a CDAI score <150.
d. Clinical response is defined as a reduction in CDAI of at least 100 points or being in clinical remission.
e. In clinical remission or clinical response and not receiving corticosteroids at Week 252.

Adapted from: TEFCREM11A; TEFCREM09AA; TEFCREM05AA; TEFCREM07AA; TEFCRES11A; TEFCRES09AA; TEFCRES05AA; TEFCRES07AA TEFCRP03AA; TEFIBDQ03AA; TEFSF03AA; Mod5.3.5.1/CNTO1275CRD3003/W272.

4.4.1.1. Maintenance of Clinical Improvement

4.4.1.1.1. Clinical Remission from Week 44 Through Week 252

Efficacy as measured by clinical remission (defined as a CDAI score of <150 points) was generally maintained in the LTE. From Week 44 through Week 252, the proportions of randomized subjects in clinical remission ranged from 61.3% to 86.1% in the q12w group and 76.3% to 87.1% in the q8w group (Figure 5).

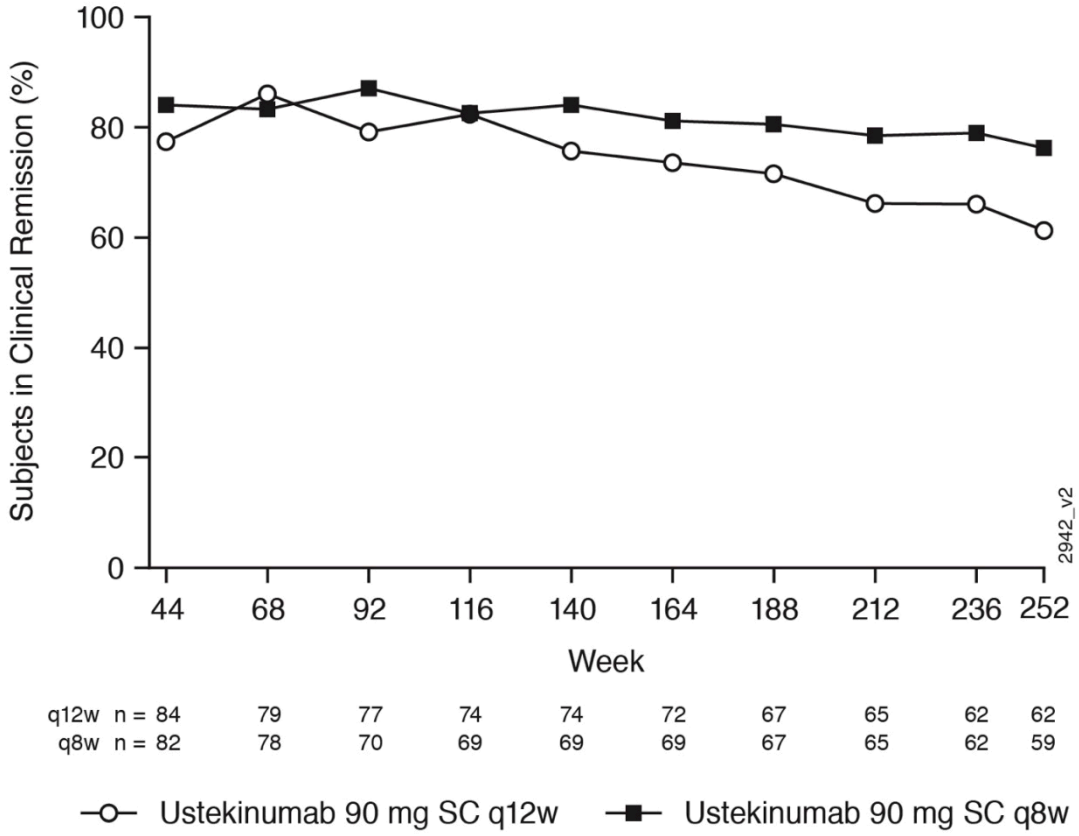
At Week 252, the proportions of randomized subjects in clinical remission were numerically higher in the q8w group (76.3%) compared with the q12w group (61.3%). The proportion of randomized subjects in clinical remission at Week 252 with prior dose adjustment in the main study was 63.3% (CRD_UC/Mod2.7.3/CRD/Sec2.2.1.1).

The proportions of randomized subjects in clinical remission were generally maintained from Week 44 through Week 252 for subjects who failed at least 1 TNF antagonist (CRD3001) and those with conventional therapy failures only (ie, TNF antagonist nonfailures, the majority of whom were naïve to TNF antagonists [CRD3002]). Of note, the proportions of TNF antagonist nonfailure subjects in clinical remission were generally higher than for subjects who were TNF antagonist failures.

The results at Week 252 were as follows:

- CRD3001 (TNF antagonist failures): The proportions of randomized subjects in clinical remission were 54.2% and 63.2% for subjects in the q12w and q8w groups, respectively.
- CRD3002 (conventional therapy failures, including subjects who were naïve to TNF antagonists and those with TNF antagonist experience but without documented failure): The proportions of randomized subjects in clinical remission were 82.5% and 65.8% for subjects in the q12w and q8w groups, respectively.
  - The proportions of randomized subjects in clinical remission in the subgroup who were TNF antagonist naïve were 57.7% in the q12w group and 79.3% in the q8w group.

Figure 5: Proportion of Subjects in Clinical Remission (Observed Case After Treatment Failure Rules Applied) From Week 44 Through Week 252; Randomized Subjects Who Entered The Long-Term Extension



Abbreviations: n=sample number; q8w=every 8 weeks; q12w=every 12 weeks; SC=subcutaneous.

4.4.1.1.2. Clinical Response from Week 44 Through Week 252

Clinical response was defined as a reduction from Week 0 of an induction study in the CDAI score of ≥100 points. Subjects with a CDAI score of ≥220 to ≤248 points at Week 0 of induction study CRD3001 or CRD3002 were considered to be in clinical response if a CDAI score of <150 was attained (ie, they were in remission).

Efficacy as measured by clinical response was generally maintained in the LTE. From Week 44 through Week 252, the proportions of randomized subjects in clinical response over time ranged from 69.4% to 91.7% in the q12w group and 79.7% to 94.3% in the q8w group (Figure 6).

At Week 252, the proportions of randomized subjects in clinical response were 72.6% and 79.7% for subjects in the q12w and q8w groups, respectively (CRD_UC/Mod2.7.3/CRD/Sec2.2.2.1).

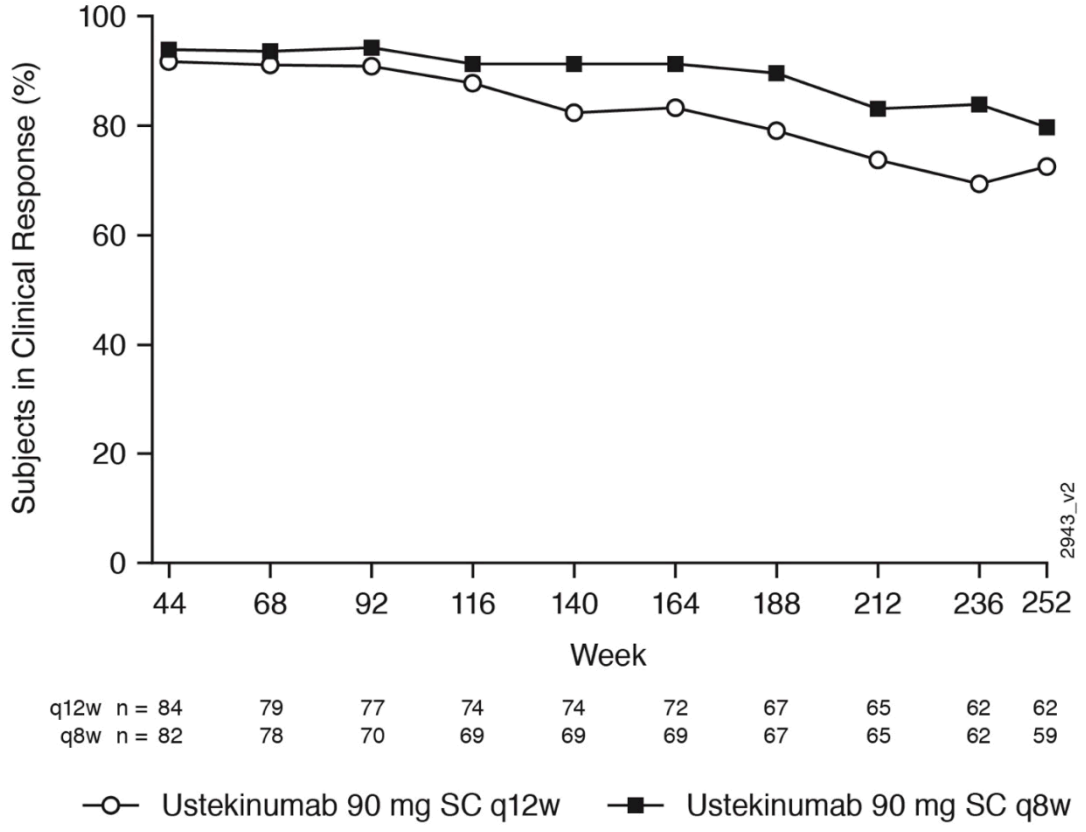
The proportions of randomized subjects in clinical response were generally maintained from Week 44 through Week 252 for subjects who failed at least 1 TNF antagonist (CRD3001) and

those with conventional therapy failures only (ie, TNF antagonist nonfailures [CRD3002]). In addition, the proportions of TNF antagonist nonfailure subjects in clinical response were generally higher than for subjects who were TNF antagonist failures.

The results at Week 252 were as follows:

- CRD3001 (TNF antagonist failures): The proportions of randomized subjects in clinical response were 62.5% and 68.4% for subjects in the q12w and q8w groups, respectively.
- CRD3002 (conventional therapy failures, including subjects who were naïve to TNF antagonists and those with TNF antagonist experience but without documented failure): The proportions of randomized subjects in clinical response were 78.9% and 85.0% for subjects in the q12w and q8w groups, respectively.
  - The proportions of randomized subjects in clinical response in the subgroup who were TNF antagonist naïve were 76.9% in the q12w group and 82.8% in the q8w group.

Figure 6: Proportions of Subjects in Clinical Response (Observed Case After Treatment Failure Rules Applied) From Week 44 Through Week 92; Randomized Subjects Who Entered The Long-Term Extension



Abbreviations:n=sample number; q8w=every 8 weeks; q12w=every 12 weeks; SC=subcutaneous.

4.4.1.1.3. Change in Crohn's Disease Activity Index Over Time

The median change from maintenance baseline in CDAI scores for randomized subjects from Week 44 through Week 252 ranged from -54.0 to -12.5 in the q12w group and from -50.0 to -31.0 in the q8w group (CRD_UC/Mod2.7.3/CRD/Sec2.2.3).

4.4.1.1.4. Corticosteroid-Related Outcomes

Overall, a majority of subjects were in corticosteroid-free clinical remission, corticosteroid-free clinical response, and were able to eliminate corticosteroids after 5 years of ustekinumab exposure (CRD_UC/Mod2.7.3/CRD/Sec2.2.5).

4.4.1.1.4.1. Corticosteroid-free Clinical Remission

The proportions of randomized subjects in clinical remission at Week 252 and not receiving corticosteroids at Week 252 were 54.8% and 71.2% for subjects in the q12w and q8w groups, respectively.

4.4.1.1.4.2. Corticosteroid-free Clinical Response

The proportions of randomized subjects in clinical response at Week 252 and not receiving corticosteroids at Week 252 were 66.1% and 72.9% for subjects in the q12w and q8w groups, respectively.

4.4.1.1.4.3. Elimination of Corticosteroids

The proportions of randomized subjects who were receiving oral corticosteroids at maintenance baseline, entered the LTE, and were able to eliminate oral corticosteroids by Week 252 were 66.7% and 65.4% in the q12w and q8w groups, respectively.

4.4.1.1.5. Fistula Response

A fistula response was defined as a ≥50% reduction in the number of draining fistulas. At Week 252, 3 of 4 randomized subjects with fistulas at induction baseline were in fistula response in the q12w group, and 2 of 4 randomized subjects with fistulas at induction baseline were in fistula response in the q8w group (CRD_UC/Mod2.7.3/CRD/Sec2.2.6).

At Week 252, the proportions of all treated subjects with fistulas at induction baseline who were in fistula response were numerically higher for subjects in the q8w group (83.3% [15/18]) compared with subjects in the q12w group (69.2% [9/13]).

4.4.1.1.6. Biomarkers of Inflammation

Overall, improvements in the inflammatory biomarker CRP were generally maintained from Week 44 to Week 252 (CRD_UC/Mod2.7.3/CRD/Sec2.2.7.1).

4.4.1.1.6.1. C-reactive Protein

Subjects with Normalized CRP

From Week 44 to Week 252, the proportions of randomized subjects with normalized CRP among subjects with an abnormal CRP at induction baseline ranged from 29.8% to 40.0% in the q12w group and 26.1% to 42.9% in the q8w group. The proportions of randomized subjects with normalized CRP levels were generally maintained in both ustekinumab groups, with 36.1% at Week 44 and 37.0% at Week 252 in the q12w group and 30.4% at Week 44 and 35.0% at Week 252 in the q8w group.

Change in CRP Over Time from Maintenance Baseline

Among randomized subjects, from Week 44 through Week 252, the median change from maintenance baseline in CRP levels (mg/L) ranged from -0.26 to 0.17 and -0.62 to 0.06 in the q12w and q8w groups, respectively. At Week 252, the median changes from maintenance baseline in CRP levels (mg/L) were 0.10 and 0.01 for randomized subjects in the q12w and q8w groups, respectively.

4.4.1.1.7. Health-Related Quality of Life

Overall, improvements in measure of health-related quality of life were generally maintained from Week 44 through Week 252 for randomized subjects in the q12w and q8w groups (CRD_UC/Mod2.7.3/CRD/Sec2.2.8).

4.4.1.1.7.1. IBDQ

Overall, improvements in IBDQ were generally maintained from Week 44 through Week 252 for randomized subjects in the q12w and q8w groups. At Week 252, the proportions of subjects with at least a 16-point improvement in IBDQ score from baseline of the induction study were numerically higher for subjects in the q8w group (80.4%) compared with subjects in the q12w group (58.7%).

4.4.1.1.7.2. SF-36

Overall, improvements in SF-36 scores were generally maintained from Week 44 through Week 252 for randomized subjects in the q12w and q8w groups. At Week 252:

- The proportions of randomized subjects with at least a 5-point improvement from baseline of the induction study in SF-36 Physical Component Summary (PCS) scores were 55.6% and 63.3% for subjects in the q12w and q8w groups, respectively.
- The proportions of randomized subjects with at least a 5-point improvement from baseline of the induction study in SF-36 Mental Component Summary (MCS) scores were 50.0% and 61.2% for subjects in the q12w and q8w groups, respectively.

4.4.1.2. Dose Adjustment as a Treatment Strategy for Subjects Who Were Randomized at Week 0 of Maintenance

To reflect clinical practice where treatments are optimized either through increases in dose or dosing frequency, the data presented here focus on an analytic approach that treats dose adjustment as a treatment strategy, where subjects who were randomized at Week 0 and had a dose adjustment during the maintenance study were not considered to be treatment failures (CRD_UC/Mod2.7.3/CRD/Sec2.2.4). For subjects randomized to the q12w and q8w groups at Week 0 of maintenance, efficacy was generally sustained through Week 252.

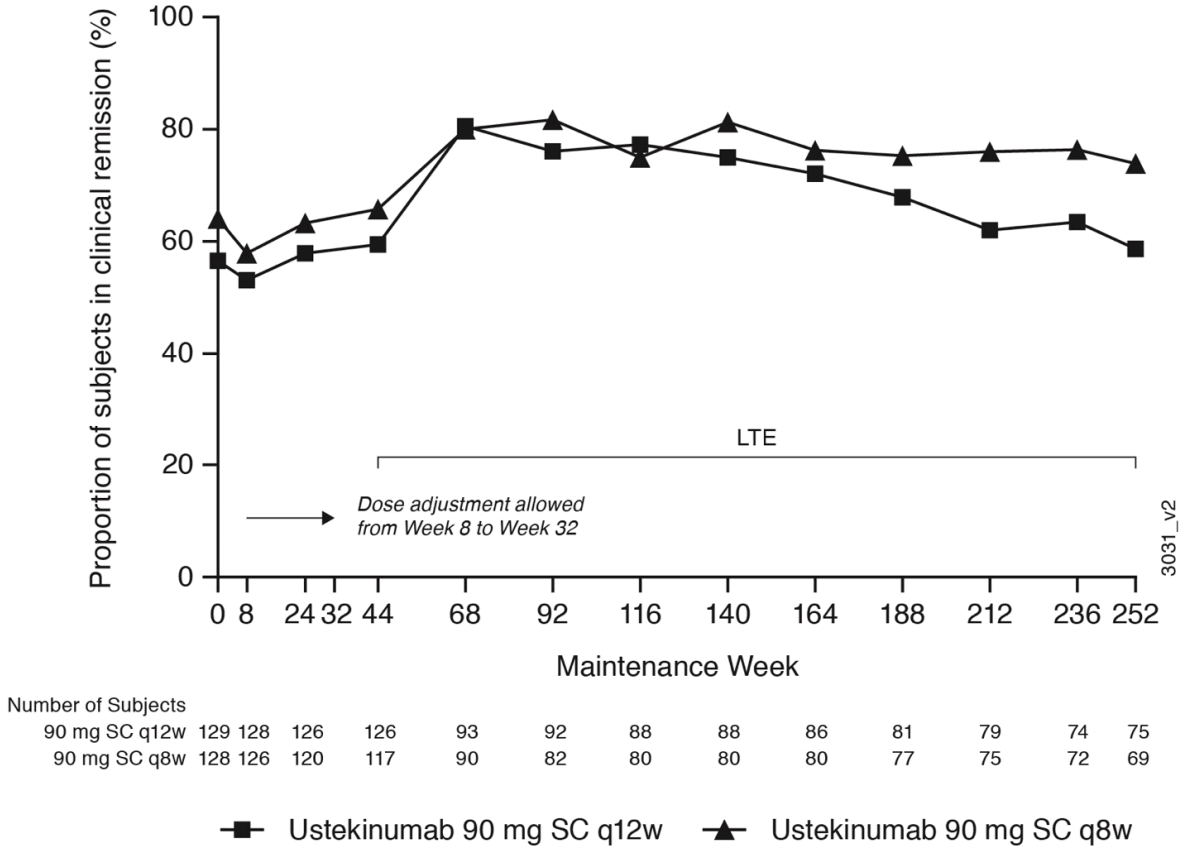
Clinical Remission

From Week 0 through Week 252, the proportions of randomized subjects in clinical remission ranged from 53.1% to 80.6% in the q12w group and 57.9% to 81.7% in the q8w group (Figure 7). At Week 252, the proportions of randomized subjects in clinical remission were numerically higher in the q8w group (73.9%) compared with the q12w group (58.7%).

Clinical Response

From Week 0 through Week 252, the proportions of randomized subjects in clinical response ranged from 68.9% to 99.2% in the q12w group and 75.2% to 97.7% in the q8w group. At Week 252, the proportions of randomized subjects in clinical response were 69.3% and 78.3% for subjects in the q12w and q8w groups, respectively.

Figure 7: Number of Subjects in Clinical Remission Over Time Through Week 252 (Dose Adjustment Is Not Considered As Treatment Failure); Subjects Randomized at Week 0 of Maintenance (CNTO1275CRD3003)



Abbreviations: q8w=every 8 weeks; q12w=every 12 weeks; SC=subcutaneous.

Data source: Attachment TEFCREM24AA; [TEFCREM24AA.RTF] [CNTO1275\CRD3003\DBR_W272\RE_W272\PROD\TEFCREM24AA.SAS] 29MAR2020, 22:00

4.4.1.3. Health Economics

From Week 44 through the final safety visit (Week 272), rates of Crohn's disease-related hospitalizations and surgeries for the randomized population were low in both ustekinumab groups (11.9% and 4.8%, respectively, in the q12w group; and 9.8% and 1.2%, respectively, in the q8w group). Most notably, very low rates were observed for these events overall despite the disease severity of the original subject population (CRD_UC/Mod2.7.3/CRD/Sec2.2.9).

The randomized-withdrawal study design, in which all randomized subjects began maintenance as responders to ustekinumab induction (with 60% of these subjects also in remission) likely explains the low overall rates of these events. A comparison to placebo was not considered relevant as subjects receiving placebo were discontinued after study unblinding.

4.4.1.4. Efficacy and Pharmacokinetics

The populations for the analyses of efficacy and PK were subjects randomized to ustekinumab who entered the maintenance study and the LTE. The relationships between average serum trough ustekinumab concentrations from Week 44 through Week 252 and efficacy measures at Week 252 were assessed (CRD_UC/Mod2.7.3/CRD/Sec2.2.10).

In general, no clear trends for exposure-response were observed for the proportions of subjects in clinical remission or clinical response, which suggests that ustekinumab exposure during the LTE was sufficient to maintain efficacy. In the combined ustekinumab treatment group, median CRP at Week 252 decreased with increasing serum ustekinumab concentration quartiles. Among subjects with abnormal CRP (>3 mg/L) at induction baseline, the proportions of subjects with normalized CRP at Week 252 tended to increase with increasing serum ustekinumab concentration quartile.

4.4.1.5. Efficacy and Immunogenicity

Among subjects who were treated with IV ustekinumab, received maintenance SC ustekinumab, and entered the CRD3003 LTE, the incidence of antibodies to ustekinumab was low (5.8%) through the final safety visit (Section 3.2.1).

In subjects randomized to ustekinumab, the proportions of subjects in the all ustekinumab group who were in clinical remission at Week 252 were comparable between those who were positive and those who were negative for antibodies to ustekinumab (CRD_UC/Mod2.7.3/CRD/Sec2.2.11). A similar pattern was observed for subjects in clinical response. However, these data should be interpreted with caution due to the small number of subjects who were positive for antibodies to ustekinumab.

4.4.2. Ulcerative Colitis Studies

The main efficacy analyses were based on subjects who were randomized at Week 0 of the maintenance study, and received study agent in the LTE (ie, randomized subjects; Section 4.4.2.1). Health economics outcomes (Section 4.4.2.6), efficacy and PK (Section 4.4.2.7), and efficacy and immunogenicity (Section 4.4.2.8) were also evaluated for subjects randomized at Week 0 of maintenance and who received study agent in the LTE.

Selected efficacy summaries are also provided for subjects who had a dose adjustment during the LTE (Section 4.4.2.2), subjects who had a dose adjustment as part of their treatment experience (ie, subjects who had a dose adjustment were not considered to be treatment failures; Section 4.4.2.3), subjects who resumed treatment after treatment interruption (Section 4.4.2.4) and for ustekinumab induction delayed responders who were treated in the LTE (Section 4.4.2.5).

A summary of endpoints at Week 92 for UCO3001 maintenance in randomized subjects who were treated in the LTE is presented in Table 2. To be more reasonably reflective of efficacy in the LTE, the key efficacy endpoint of symptomatic remission was analyzed based on an as-observed analysis approach with treatment failure rules applied; all the other endpoints in Table 2 were based on the conservative ITT analysis approach.

Unless noted otherwise, the data presented in these sections are based on the ITT analysis approach.

Table 2: Maintenance of Key Efficacy Endpoints at Week 92 in CNTO1275UCO3001 Maintenance; Randomized Subjects who Were Treated in the LTE

	Ustekinumab 90 mg q12w	Ustekinumab 90 mg q8w
Randomized subjects in maintenance who were treated in the LTE [a]	141	143
Symptomatic remission[b]		
Subjects in symptomatic remission	89.5% (94/105)	90.4% (94/104)
Biologic nonfailure	87.7% (64/73)	93.0% (53/57)
Biologic naïve	88.1% (59/67)	92.3% (48/52)
Biologic failure	93.8% (30/32)	87.2% (41/47)
Both anti-TNF and vedolizumab failure	100.0% (8/8)	90.9% (10/11)
Corticosteroid-free symptomatic remission[c]	63.8% (90/141)	64.3% (92/143)
CRP		
Subjects with normalization (≤3 mg/L) among those with abnormal CRP (>3 mg/L) at induction baseline	47.1% (33/70)	40.2% (33/82)
Fecal calprotectin		
Subjects with normalization (≤250 mg/kg) among those with abnormal fecal calprotectin (>250 mg/kg) at induction baseline	43.6% (48/110)	42.6% (49/115)
IBDQ score		
Subjects with a ≥16-point improvement from induction baseline among those with a ≥16-point improvement at maintenance baseline	68.0% (85/125)	61.6% (77/125)
IBDQ remission (IBDQ ≥170)	59.6% (84/141)	51.7% (74/143)
SF-36: Subjects with a ≥5-point improvement from induction baseline among those with a ≥5-point improvement at maintenance baseline in:		
PCS	65.6% (59/90)	60.3% (47/78)
MCS	71.1% (54/76)	48.8% (39/80)

Abbreviations:CRP=C-reactive protein; IBDQ= Inflammatory Bowel Disease Questionnaire; LTE=long-term extension; MCS=mental component summary (score); PCS=physical component summary (score); q8w=every 8 weeks; q12w=every 12 weeks; SF-36=36-item Short Form Health Survey.

a. Subjects who completed the safety and efficacy evaluation at Week 44 and, in the opinion of the investigator, would benefit from continued treatment were treated in the LTE.
b. Symptomatic remission is defined as a stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0.
c. In symptomatic remission and not receiving corticosteroids at Week 92.

Adapted from: TEFCREM12A; TEFCREM15A; TEFCREM14A; TEFCREM13A; TEFCREM12A2; TEFCREM16B; TEFCRP03B; TEFCALP03B; TEFIBDQ09B; TEFIBDQ01B; TEFSF04B; TEFSF07B; Mod5.3.5.1/CNTO1275UCO3001/W96.

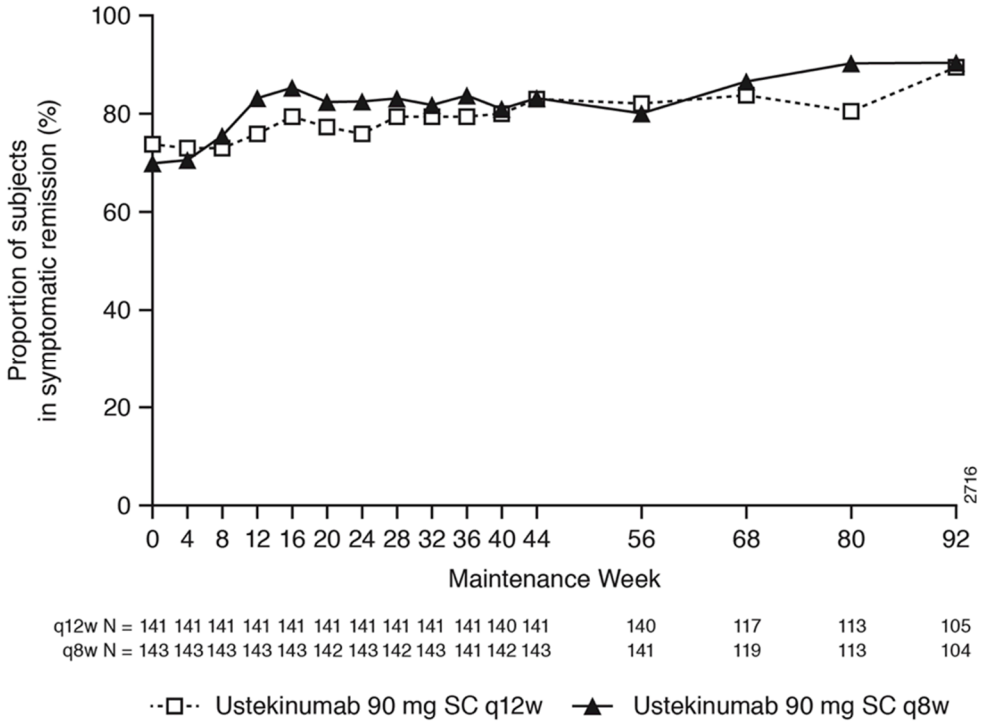
4.4.2.1. Maintenance of Clinical Improvement Among Randomized Subjects in the Long-term Extension

4.4.2.1.1. Symptomatic Remission from Week 44 Through Week 92

Over time, the proportions of subjects in symptomatic remission (defined as having achieved a Mayo stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0) were sustained from Week 44 through Week 92 in the q12w and q8w groups (83.0% and 83.2%, respectively, at Week 44; and 89.5% and 90.4%, respectively, at Week 92; CRD_UC/Mod2.7.3/UC/Sec2.2.1.1.1 and Figure 8). The proportions of subjects in symptomatic remission were sustained from Week 44 to Week 92 among the biologic-naïve, biologic-nonfailure, biologic-failure, and biologic failure to both anti-TNF and vedolizumab populations. At Week 92, the following proportions of subjects were in symptomatic remission in the q12w and q8w groups, respectively, in the following subgroup analyses:

- 87.7% and 93.0% of subjects among the biologic-nonfailure population
  - 88.1% and 92.3% of subjects among the biologic-naïve population
- 93.8% and 87.2% of subjects among the biologic-failure population
  - 100.0% and 90.9% of subjects who failed both anti-TNF and vedolizumab

Figure 8: Proportion of Subjects in Symptomatic Remission Over Time Through Week 92 or Up to the Time of Dose Adjustment (As-Observed With Treatment Failure Rules Applied); Randomized Subjects in Maintenance Who Were Treated in the Long-term Extension (CNTO1275UCO3001)



Abbreviations: q8w=every 8 weeks; q12w=every 12 weeks; SC=subcutaneous

Adapted from: Attachment TEFCREM12A
[TEFCREM12A.RTF] [CNTO1275\UCO3001\DBR_W96\RE_W96\PROD\TEFCREM12A-15A.SAS] 19SEP2019, 18:47

4.4.2.1.2. Partial Mayo Score

4.4.2.1.2.1. Partial Mayo Score Over Time

Over time through Week 92, the mean partial Mayo scores observed at maintenance baseline (1.9 in both the q12w and q8w groups) were generally maintained in the q12w and q8w groups (using the as-observed analysis approach; UC/Mod2.7.3/Sec2.2.1.2.1). At Week 92, the mean changes from maintenance baseline in partial Mayo scores for the q12w and q8w groups were -0.8 and -1.0, respectively.

4.4.2.1.2.2. Mayo Rectal Bleeding and Mayo Stool Frequency Subscores Over Time

The proportions of subjects with a Mayo rectal bleeding subscore of 0 (indicating inactive disease) were comparable in the q12w and q8w groups at maintenance baseline (87.2% and 84.6%, respectively; UC/Mod2.7.3/Sec2.2.1.2.2). At Week 92, the proportions of subjects with a Mayo rectal bleeding subscore of 0 were 70.2% and 68.5% in the q12w and q8w groups, respectively.

The proportions of subjects with a Mayo stool frequency subscore of 0 or 1 (indicating inactive or mild disease) were comparable in the q12w and q8w groups at maintenance baseline (80.9% and 80.4%, respectively). At Week 92, the proportions of subjects with a Mayo stool frequency subscore of 0 or 1 were 66.0% and 67.8% in the q12w and q8w groups, respectively.

4.4.2.1.2.3. Absolute Stool Number Over Time

At maintenance baseline, the mean absolute stool numbers in the q12w and q8w groups were 2.8 and 2.7, respectively, having decreased by at least 3 from induction baseline (UC/Mod2.7.3/Sec2.2.1.2.3). Over time, subjects in the q12w and q8w groups maintained their improvement in absolute stool numbers observed at maintenance baseline (2.4 and 2.3, respectively, at Week 44; and 3.4 and 3.2, respectively, at Week 92).

The proportions of subjects with an absolute stool number ≤3 at maintenance baseline were 68.8% and 63.6% in the q12w and q8w groups, respectively. Over time, the proportions of subjects with an absolute stool number ≤3 in the q12w and q8w groups were generally maintained (78.0% and 80.4% respectively, at Week 44; and 61.0% and 59.4%, respectively, at Week 92).

4.4.2.1.3. Corticosteroid-Related Outcomes

Overall, a majority of subjects were in corticosteroid-free symptomatic remission and were able to eliminate corticosteroids after 2 years of ustekinumab exposure (CRD_UC/Mod2.7.3/UC/Sec2.2.1.3).

4.4.2.1.3.1. Corticosteroid-free Symptomatic Remission

The proportions of randomized subjects in the q12w and q8w groups treated during the LTE who were in symptomatic remission and not receiving corticosteroids at Week 92 were 63.8% and 64.3%, respectively. Among randomized subjects receiving corticosteroids at maintenance baseline, the proportions in symptomatic remission and not receiving corticosteroids at Week 92 were consistent with those of the randomized population (57.4% and 62.0% in the q12w and q8w groups, respectively; Mod5.3.5.1/CNTO1275UCO3001/W96/AttTEFCREM17B).

4.4.2.1.3.2. Elimination of Corticosteroids

Among randomized subjects receiving concomitant corticosteroids (including budesonide and beclomethasone dipropionate) at maintenance baseline, the proportions who were not receiving concomitant corticosteroids at Week 92 were 91.2% and 94.4% in the q12w and q8w groups, respectively.

4.4.2.1.4. Biomarkers of Inflammation

Overall, improvements in inflammatory biomarkers were generally maintained from Week 44 through Week 92 for randomized subjects in the q12w and q8w groups (CRD_UC/Mod2.7.3/UC/Sec2.2.1.4).

4.4.2.1.4.1. C-reactive Protein

Normalization of CRP among Subjects with Abnormal CRP at Induction Baseline

Among randomized subjects with abnormal CRP at induction baseline, CRP normalization (≤3 mg/L) at maintenance baseline was reported in 51.4% and 46.3% of subjects in the q12w and q8w groups, respectively. From Week 44 through Week 92, the proportions of subjects with normalized CRP were generally maintained in both ustekinumab groups, with 47.1% and 40.2% in the q12w and q8w groups, respectively, reporting normalized CRP at Week 92 (Table 2).

Change from Maintenance Baseline in CRP

At maintenance baseline, median CRP concentrations were 1.5 mg/L and 1.8 mg/L in the q12w and q8w groups, respectively. Over time through Week 92, the median CRP concentrations at maintenance baseline were generally maintained. At Week 92, the median changes from maintenance baseline in CRP concentrations were 0.1 mg/L and 0.0 mg/L for the q12w and q8w groups, respectively.

4.4.2.1.4.2. Fecal Calprotectin

Normalization of Fecal Calprotectin Among Subjects with Abnormal Fecal Calprotectin at Induction Baseline

Among randomized subjects with abnormal fecal calprotectin at induction baseline, normalization of fecal calprotectin levels at maintenance baseline was reported in 28.2% and 28.7% of subjects in the q12w and q8w groups, respectively. From Week 44 through Week 92, the proportions of subjects with normalized fecal calprotectin were generally maintained in both ustekinumab groups, with 43.6% and 42.6% of subjects in the q12w and q8w groups, respectively, reporting normalization of fecal calprotectin at Week 92 (Table 2).

Change from Maintenance Baseline in Fecal Calprotectin

At maintenance baseline, median fecal calprotectin concentrations were 431.0 mg/kg and 450.5 mg/kg in the q12w and q8w groups, respectively. Over time through Week 92, the median fecal calprotectin concentrations at maintenance baseline were generally maintained. At Week 92, the median changes from maintenance baseline in fecal calprotectin concentrations were -79.5 mg/kg and -94.5 mg/kg in the q12w and q8w groups, respectively.

4.4.2.1.5. Health-Related Quality of Life

Overall, improvements in measure of health-related quality of life were generally maintained from Week 44 through Week 92 for randomized subjects in the q12w and q8w groups (CRD_UC/Mod2.7.3/UC/Sec2.2.1.5).

4.4.2.1.5.1. IBDQ

A ≥16-point Improvement from Induction Baseline in the Total IBDQ Score

At maintenance baseline, the proportions of subjects who had a ≥16-point improvement from induction baseline in the total IBDQ score were 88.7% and 87.4% in the q12w and q8w groups, respectively. At Week 92, 68.0% and 61.6% of these subjects in the q12w and q8w groups, respectively, maintained their ≥16-point improvement from induction baseline (Table 2).

IBDQ Remission

At maintenance baseline, the proportions of subjects who achieved IBDQ remission (IBDQ ≥170) were 61.7% and 57.3% in the q12w and q8w groups, respectively. At Week 92, the proportions of subjects who achieved IBDQ remission were 59.6% and 51.7% in the q12w and q8w groups, respectively.

Among subjects in IBDQ remission at maintenance baseline, the proportions who maintained IBDQ remission were generally sustained (74.7% and 59.8% in the q12w and q8w groups, respectively, at Week 92).

4.4.2.1.5.2. SF-36

A ≥5-point Improvement from Induction Baseline in the SF-36 Physical Component Score

At maintenance baseline, the proportions of subjects who had a ≥5-point improvement from induction baseline in the SF-36 PCS score were 63.8% and 54.5% in the q12w and q8w groups, respectively. Among these subjects, 65.6% and 60.3% maintained their ≥5-point improvement in the SF-36 PCS score at Week 92 in the q12w and q8w groups, respectively (Table 2).

A ≥5-point Improvement from Induction Baseline in the SF-36 Mental Component Score

At maintenance baseline, the proportions of subjects who had a ≥5-point improvement from induction baseline in the SF-36 MCS score were 53.9% and 55.9% in the q12w and q8w groups, respectively. Among these subjects, 71.1% and 48.8% maintained their ≥5-point improvement in the SF-36 MCS at Week 92 in the q12w and q8w groups, respectively (Table 2).

4.4.2.2. Efficacy in Subjects Who Had a Dose Adjustment

Subjects who were randomized at maintenance Week 0 and treated in the LTE and whose UC disease activity worsened, based on the clinical judgment of the investigator, were eligible for a dose adjustment in the LTE (CRD_UC/Mod2.7.3/UC/Sec2.2.1.6). Subjects who had a dose adjustment prior to or at Week 76 were assessed 16 weeks after the dose adjustment visit to determine if benefit was achieved from the dose adjustment. Interpretation of these data is limited by small sample size.

Among the subjects in the ustekinumab q12w → q8w and ustekinumab q8w → q8w groups who had data at least 16 weeks after dose adjustment, the majority (55.0% [11 of 20 subjects] and 64.3% [18 of 28 subjects], respectively) were in symptomatic remission at the time of dose adjustment and at the first visit at least 16 weeks after dose adjustment (70.0% [14 of 20 subjects]

and 71.4% [20 of 28 subjects], respectively). That a majority of subjects were in symptomatic remission at the time of dose adjustment may be due to the fact that dose adjustment was based on the clinical judgment of the investigator and no other pre-specified criteria (eg, clinical flare based on the partial Mayo score as was applied through Week 44 of the maintenance study) were required during the LTE.

Among the subjects who were not in symptomatic remission at the time of dose adjustment and had data at least 16 weeks after dose adjustment in the ustekinumab q12w → q8w and ustekinumab q8w → q8w groups, approximately half (44.4% [4 of 9 subjects] and 60.0% [6 of 10 subjects], respectively) were in symptomatic remission at the first visit at least 16 weeks after dose adjustment.

Changes in the partial Mayo score and CRP levels also indicated that some benefit of dose adjustment was observed.

4.4.2.3. Dose Adjustment as a Treatment Strategy

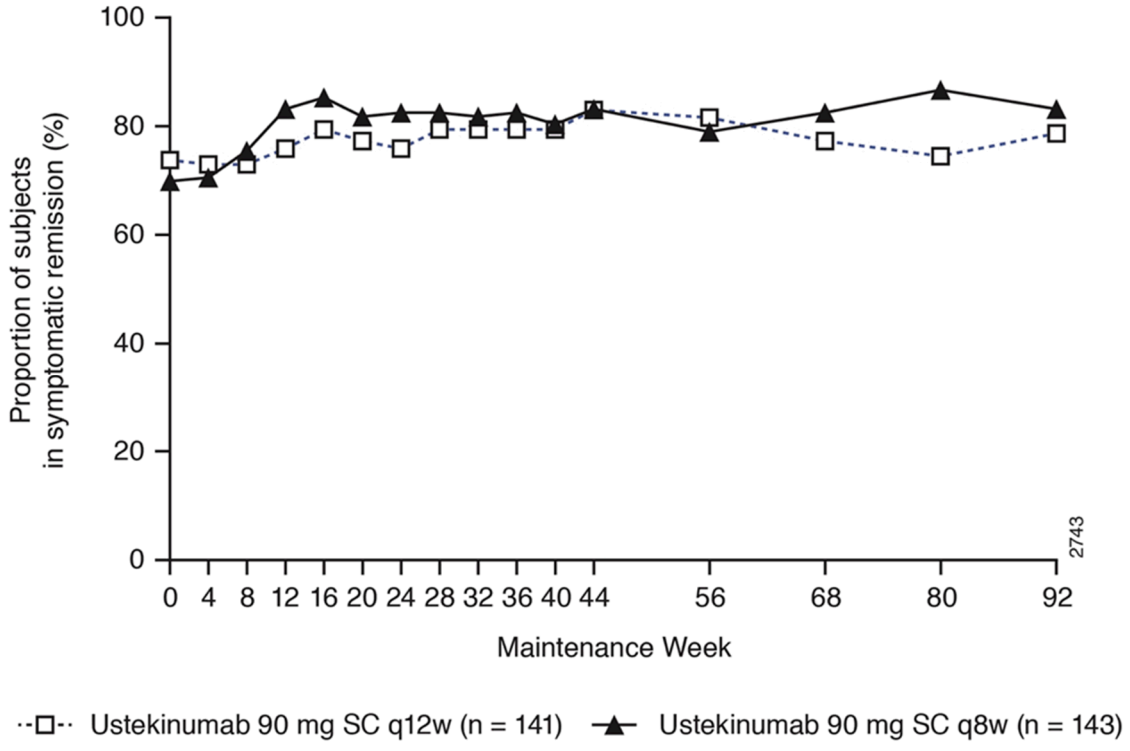
To reflect clinical practice where treatments are optimized either through increases in dose or dosing frequency, the data presented here focus on an analytic approach that treats dose adjustment as a treatment strategy, where subjects who had a dose adjustment during the LTE were not considered to be treatment failures.

Symptomatic Remission

Week 44 through Week 92

From Week 44 through Week 92, the proportions of subjects in symptomatic remission were sustained in the q12w and q8w groups (CRD_UC/Mod2.7.3/UC/Sec2.2.1.7 and Figure 9). Similar results were demonstrated in biologic-naïve, biologic-nonfailure, biologic-failure, and biologic-failure to both anti-TNF and vedolizumab populations.

Figure 9: Number of Subjects in Symptomatic Remission Over Time Through Week 92 (Dose Adjustment Is Not Considered As Treatment Failure); Randomized Subjects in Maintenance Who Were Treated in the Long-term Extension (CNTO1275UCO3001)



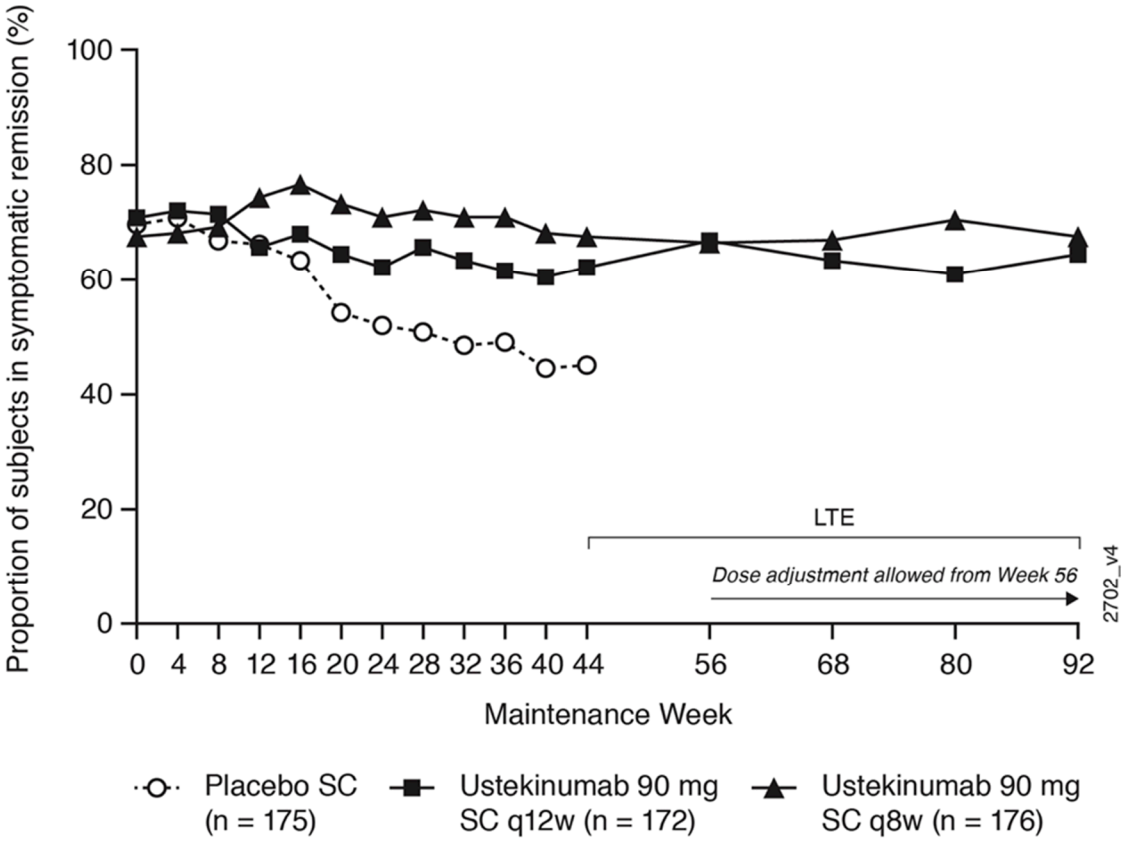
Abbreviations: q8w=every 8 weeks; q12w=every 12 weeks; SC=subcutaneous.

Data source: Attachment TEFCREM12B_S [TEFCREM12B_S.RTF] [CNTO1275\UCO3001\DBR_W96\RE_W96\PROD\TEFCREM12BS.SAS] 23SEP2019, 12:32

Week 0 through Week 92

An additional analysis was conducted in all subjects randomized at Week 0 of the maintenance study, regardless of whether subjects were treated in the LTE. Among these subjects, from Week 0 through Week 92, the proportions of subjects in symptomatic remission were sustained, with 64.5% and 67.6% of subjects in the q12w and q8w groups, respectively, in symptomatic remission at Week 92 (Figure 10).

Figure 10: Number of Subjects in Symptomatic Remission Over Time Through Week 92 (All Randomized: Dose Adjustment Is Not Considered As Treatment Failure); Subjects Randomized at Week 0 of Maintenance (CNTO1275UCO3001)



Abbreviations: LTE=long-term extension; q8w=every 8 weeks; q12w=every 12 weeks; SC=subcutaneous

Data source: Attachment TEFCREM22B
[TEFCREM22B.RTF] [CNTO1275\UCO3001\DBR_W96\RE_W96\PROD\TEFCREM22B.SAS] 03DEC2019, 08:54

4.4.2.4. Efficacy in Subjects Resuming Ustekinumab After Treatment Interruption

Among the subjects who were in clinical response to ustekinumab IV induction, randomized to placebo at maintenance baseline, and treated during the LTE, a total of 42 subjects had a dose adjustment to ustekinumab q8w during the LTE (at least 1 year following their last dose of ustekinumab) and had at least 16 weeks of data after dose adjustment (CRD_UC/Mod2.7.3/UC/Sec2.2.1.8).

Key efficacy results among the subjects in the placebo → ustekinumab q8w group are summarized below.

- Symptomatic Remission
  - Among the subjects who had data at least 16 weeks after dose adjustment, 40.5% were in symptomatic remission at the time of dose adjustment, and 71.4% were in symptomatic remission at the first visit at least 16 weeks after dose adjustment.
  - Among the subjects who were not in symptomatic remission at the time of dose adjustment and had data at least 16 weeks after dose adjustment, 64.0% were in symptomatic remission at the first visit at least 16 weeks after dose adjustment.
- Partial Mayo Score
  - Among the subjects who had data at least 16 weeks after dose adjustment, the mean partial Mayo score was 3.2 at the time of dose adjustment and 1.5 at the first visit at least 16 weeks after dose adjustment.
- Biomarkers of Inflammation
  - Among subjects who had data at least 16 weeks after dose adjustment, the median inflammatory biomarker concentrations at the time of dose adjustment and at the first visit at least 16 weeks after dose adjustment, respectively, were as follows:
    - CRP: 3.6 mg/L, 2.0 mg/L
    - Fecal calprotectin: 1016.5 mg/kg, 355.0 mg/kg

These results demonstrate that in the subset of subjects who responded to the ustekinumab IV induction dose but delayed initiation of the SC ustekinumab maintenance therapy (42 subjects total), benefit can be regained.

4.4.2.5. Efficacy in Ustekinumab Induction Delayed Responders (Nonrandomized Population)

Clinical efficacy measures were summarized for subjects in the ustekinumab induction delayed-responder group who were treated in the LTE. Subjects in this group received ustekinumab 90 mg SC q8w during maintenance (through Week 44) and during the LTE (CRD_UC/Mod2.7.3/UC/Sec2.2.2).

Overall, the clinical benefits observed among the ustekinumab induction delayed-responder group was similar to that observed for randomized subjects treated with ustekinumab q8w in the LTE. Subjects were able to sustain symptomatic remission from Week 44 through Week 92, achieve corticosteroid-free remission at Week 92, and sustain improvement in inflammatory biomarkers and in health-related quality of life from Week 44 through Week 92.

4.4.2.6. Health Economics

From Week 0 of induction through Week 96, few subjects in both ustekinumab groups had a UC disease-related hospitalization or underwent a UC disease-related surgery. The proportions of subjects with a UC disease-related hospitalization or surgery were 4.3% (5 subjects) in the placebo

group and 3.9% (11 subjects) in the combined ustekinumab group (CRD_UC/Mod2.7.3/UC/Sec2.2.3).

The randomized-withdrawal study design, in which all subjects randomized to maintenance were responders to ustekinumab induction, likely explains the low overall rates of these events. Subjects receiving placebo who terminated after study unblinding may further confound the ability to see a significant difference between the ustekinumab and placebo groups as the duration of follow-up for the placebo group is notably shorter.

4.4.2.7. Efficacy and Pharmacokinetics

The population for efficacy and PK analyses was randomized subjects in the UCO3001 maintenance study who received ustekinumab during the LTE, did not have a dose adjustment, and who had appropriate ustekinumab concentration data through Week 92 of the LTE (CRD_UC/Mod2.7.3/UC/Sec2.2.4).

In general, high proportions (≥80%) of subjects were in symptomatic or partial Mayo remission in each concentration quartile. Accordingly, no clear exposure-efficacy relationship was observed between serum ustekinumab concentration and these efficacy endpoints in this population of subjects who were considered to have benefited from maintenance treatment, which suggests that ustekinumab exposure during the LTE was sufficient to maintain efficacy.

With respect to inflammatory biomarkers, in each ustekinumab treatment group and in the combined ustekinumab treatment group, median CRP at Week 92 decreased with increasing serum ustekinumab concentration quartiles and in line with these observations, among subjects with abnormal CRP (>3 mg/L) at induction baseline, the proportions of subjects with normalized CRP at Week 92 tended to increase with increasing serum ustekinumab concentration quartile. A similar pattern was observed for fecal calprotectin; among subjects with abnormal fecal calprotectin (>250 mg/kg) at induction baseline, the proportions of subjects with normalized fecal calprotectin at Week 92 tended to increase with increasing serum ustekinumab concentration quartile.

4.4.2.8. Efficacy and Immunogenicity

Among subjects who received ustekinumab in induction, maintenance, and the LTE, the incidence of antibodies to ustekinumab was low (5.5%) among subjects in the UCO3001 LTE through Week 96 (Section 3.2.2).

In subjects who were randomized in maintenance to ustekinumab and treated in the LTE, the proportions of subjects who were in symptomatic or partial Mayo remission at Week 92 were comparable between those who were positive and those who were negative for antibodies to ustekinumab (CRD_UC/Mod2.7.3/UC/Sec2.2.5). However, these data should be interpreted with caution due to the small number of subjects who were positive for antibodies to ustekinumab.

5. OVERVIEW OF SAFETY

5.1. Safety Profile of the Pharmacologic Class

A first-in-class IL-12/23 antagonist, ustekinumab has an established safety profile elucidated both in clinical studies across multiple indications and in approximately 11 years of postmarketing experience in the approved psoriatic indications (since the first approval of ustekinumab on 12 December 2008). The estimated cumulative global exposure to ustekinumab from launch through 31 December 2019 is 1,667,912 person-years (CRD_UC/Mod2.7.4/Sec6.1).

In the European Union, ustekinumab was approved for the treatment of patients with moderately to severely active Crohn's disease on 11 November 2016 and for the treatment of patients with moderately to severely active UC on 03 September 2019. Ustekinumab continues to have a favorable benefit-risk profile for the treatment of patients with moderate to severe plaque psoriasis, PsA, moderately to severely active Crohn's disease, and/or moderately to severely active UC. The MAH will continue to monitor the safety profile of ustekinumab and report safety findings as appropriate.

No other biologic agents in this class have been approved for any indication.

5.2. Safety of Ustekinumab

The focus is to provide a comprehensive analysis of the safety data from the completed clinical studies of ustekinumab in subjects with Crohn's disease in support of treatment up to 5 years, and from the completed and ongoing clinical studies of ustekinumab in subjects with UC in support of treatment up to 2 years.

Analyses to assess the number of subjects reporting events or the number of events per 100 subject-years of follow-up in ustekinumab-treated subjects compared with placebo-treated subjects are presented using data from the Crohn's disease studies and the UC studies, as well as data from studies in the approved psoriatic disease indications. Taken together, these data support the long-term safety profile of ustekinumab in the treatment of Crohn's disease and UC.

5.2.1. Safety Populations

Crohn's Disease

The safety of ustekinumab in subjects with moderately to severely active Crohn's disease was evaluated across 5 Phase 2 and Phase 3 clinical studies, assessed primarily by standard analyses of AEs and analyses of targeted AEs. Complete descriptions of the datasets used to analyze ustekinumab safety data are provided in the Summary of Clinical Safety (SCS; CRD_UC/Mod2.7.4/Sec1.1.1.1).

While data for all development phases and populations are fully described in the SCS, this Clinical Overview presents standard AEs (all AEs, serious adverse events [SAEs], AEs leading to discontinuation of study agent, deaths, infections, and serious infections), laboratory parameters,

and injection-site reactions with a focus on all subjects treated in the LTE (ie, the all-treated population) of CRD3003.

Ulcerative Colitis

The safety of ustekinumab in subjects with moderately to severely active UC was evaluated across 2 Phase 3 clinical studies (UCO3001 induction and UCO3001 maintenance), assessed primarily by standard analyses of AEs and analyses of targeted AEs. Complete descriptions of the datasets used to analyze ustekinumab safety data are provided in the SCS (CRD_UC/Mod2.7.4/Sec1.1.1.2).

While data for all development phases and populations are fully described in the SCS, this Clinical Overview presents standard AEs (all AEs, SAEs, AEs leading to discontinuation of study agent, deaths, infections, and serious infections), laboratory parameters, and injection-site reactions with a focus on all subjects treated in the LTE (ie, the all-treated population) of UCO3001.

Crohn's Disease and Ulcerative Colitis Pooled with Psoriatic Diseases

The safety experience of ustekinumab across the global Phase 2 and Phase 3 IBD studies (including safety data through 5 years of follow-up for Crohn's disease and through 2 years of follow-up for UC) was assessed alongside the safety experience from the global Phase 2 and Phase 3 psoriatic disease studies (including safety data through 5 years of follow-up for psoriasis and 1 year of follow-up for PsA), as well as all diseases pooled (IBD and psoriatic diseases; CRD_UC/Mod2.7.4/Sec1.1.3.1). This holistic evaluation helped to determine the safety profile of ustekinumab in a large number of exposed subjects.

Additional analyses were performed for targeted AEs including serious infections, malignancies, fatal and nonfatal serious major adverse cardiovascular events (MACE), vascular thrombotic events, anaphylactic and delayed hypersensitivity (serum sickness-like) reactions, tuberculosis (TB), opportunistic infections, serious neurological disorders, and depression and suicidality. These targeted AEs are summarized for IBD (Crohn's disease and UC), psoriatic diseases (psoriasis and PsA), and all diseases pooled.

5.2.2. Exposure and Safety Follow-up

Crohn's Disease

For all treated subjects across the induction and maintenance phases in studies C0379T07, C0743T26, CRD3001, CRD3002, and CRD3003, 1,749 subjects with Crohn's disease were exposed to ustekinumab, with a total of 2,897 subject-years of follow-up (CRD_UC/Mod2.7.4/Sec1.2, Table 6). Among these 1,749 subjects, 592 subjects were exposed to ustekinumab for at least 1 year, 496 subjects were exposed for at least 2 years, and 310 subjects were exposed for at least 5 years. The average duration of treatment was 69.81 weeks. The mean total dose in the combined Crohn's disease studies was 923.7 mg.

Ulcerative Colitis

For all treated subjects across the induction and maintenance phases in the UCO3001 study, 826 subjects with UC were exposed to ustekinumab, with a total of 1,063 subject-years of follow-up (CRD_UC/Mod2.7.4/Sec1.2, Table 6). Among these 826 subjects, 497 subjects were exposed for at least 1 year and 430 subjects were exposed for at least 2 years. The average duration of treatment was 62.02 weeks. The mean total dose in the UCO3001 study was 881.7 mg.

Crohn's Disease and Ulcerative Colitis Pooled with Psoriatic Diseases

Across all diseases pooled, a total of 6,710 subjects were treated with ustekinumab (2,575 subjects in the Phase 2 and Phase 3 IBD studies [1,749 subjects in the Crohn's disease studies and 826 subjects in the UC studies] and 4,135 subjects in the Phase 2 and Phase 3 psoriatic diseases studies), with a total of 13,807 subject-years of follow-up (CRD_UC/Mod2.7.4/Sec1.2, Table 6). Of these 6,710 subjects, 3,471 subjects were exposed to ustekinumab for at least 1 year, 2,579 subjects were exposed to ustekinumab for at least 2 years, and 1148 subjects were exposed to ustekinumab for at least 5 years. The average duration of treatment was 89.90 weeks. The mean total dose of ustekinumab in all diseases pooled was 842.5 mg.

5.2.3. Adverse Events

5.2.3.1. Crohn's Disease

Among all treated subjects in the LTE of CRD3003, the overall safety profile from Week 44 through Week 272 was generally consistent with the known safety profile of ustekinumab (CRD_UC/Mod2.7.4/Sec2.1.1):

- The total number of subjects reporting 1 or more AEs per hundred subject-years of follow-up (AE subject rate) was numerically higher for subjects treated with placebo (64.54) as compared with subjects treated with ustekinumab (28.97). The system-organ classes (SOCs) with the highest AE subject rates were Infections and infestations and Gastrointestinal disorders.
  - The AE subject rates in the Infection and infestations SOC were 39.06, 21.94, and 22.98 in the placebo, q12w, and q8w groups, respectively. Nasopharyngitis was the most frequently reported infection in all treatment groups, with subject rates of 9.06, 8.00, and 9.01 in the placebo, q12w, and q8w groups, respectively.
  - The AE subject rates in the Gastrointestinal disorders SOC were 39.06, 20.16, and 20.28 subjects per hundred subject-years in the placebo, q12w, and q8w groups, respectively. Crohn's disease was the most frequently reported AE among subjects in all treatment groups, with subject rates of 19.25, 7.86, and 8.38 in the placebo, q12w, and q8w groups, respectively.
- Six subjects died while receiving ustekinumab (2 subjects died of cardiovascular causes, 1 from suicide, 1 from septic shock, 1 from end stage renal disease, and 1 was a sudden death due to a ventricular arrythmia); all 6 deaths were deemed unrelated to ustekinumab treatment.

- The total number of subjects with 1 or more SAEs per hundred subject-years of follow-up (SAE subject rate) was 14.72 in the placebo group and 9.36 in the combined ustekinumab treatment group, and was comparable for subjects in the q12w (10.08) and q8w (8.92) groups. The most frequently reported SAEs were related to Crohn's disease, with SAE subject rates of 6.79 and 2.75 in the placebo and combined ustekinumab groups, respectively.
- The total numbers of subjects with 1 or more AEs leading to discontinuation of study agent per hundred subject-years of follow-up were 7.36 and 4.54 in the placebo and combined ustekinumab groups, respectively. The most frequent AEs leading to discontinuation were gastrointestinal disorders related to Crohn's disease for all treatment groups.
- The number of subjects with 1 or more infections per hundred subject-years of follow-up (infection subject rate) was numerically higher for subjects in the placebo group (37.36) as compared with the combined ustekinumab group (22.25), and was comparable between subjects in the q12w (21.19) and q8w (22.89) groups. The most frequently reported treatment-emergent infections were nasopharyngitis (subject rates of 8.49 and 8.07 in the placebo and combined ustekinumab groups, respectively) and upper respiratory tract infection (subject rates of 7.93 and 5.72 in the placebo and combined ustekinumab groups, respectively).
  - The numbers of subjects with 1 or more infections requiring oral or parenteral antimicrobial therapy per hundred subject-years of follow-up were 23.21 in the placebo group and 16.31 in the combined ustekinumab group. The infections with the highest subject rates requiring oral or parenteral antimicrobial treatment were upper respiratory tract infection and urinary tract infection.
- The number of subjects with 1 or more serious infections per hundred subject-years of follow-up was comparable between subjects in the placebo (3.40) and combined ustekinumab (2.69) groups, and comparable between subjects in the q12w (3.41) and q8w (2.25) groups.
- The proportions of injections with injection-site reactions were 0.4% among the total number of ustekinumab injections and 0.2% among the total number of placebo injections.

As shown in Table 3, key safety findings during the LTE of CRD3003 (Weeks 44 through Week 272) compared with the findings from Week 0 through Week 44 in the same population demonstrate that maintenance therapy for Crohn's disease through approximately 5 years is not associated with a change in the safety profile for ustekinumab; no new safety concerns were identified.

Table 3: Number of Subjects With Key Safety Events Per Hundred Subject Years of Follow-Up from Week 0 Through Week 44 and From Week 44 Through the Final Safety Visit; Subjects Who Entered Into the Long-Term Extension in CNTO1275CRD3003

	Week 0 Through Week 44				Week 44 through Final Safety Visit			
		Ustekinumab 90 mg SC				Ustekinumab 90 mg SC		
	Placebo SC [a]	q12w [b]	q8w [c]	Combined	Placebo SC [a]	q12w [b]	q8w [c]	Combined
Analysis set: subjects who entered the long-term extension	151	213	354	567	151	213	354	567
Average duration of follow-up (weeks)	44.4	44.3	44.3	44.3	60.8	164.7	163.0	163.6
Total subject-years of follow-up	128.8	181.4	301.7	483.2	176.6	674.7	1109.7	1784.4
Subjects who died	0	0	0	0	0	2	4	6
Number of subjects with specified events per hundred subject-years of follow-up								
Adverse events	97.02	95.35	102.41	99.76	64.54	28.16	29.47	28.97
Serious adverse events	14.75	13.78	14.25	14.07	14.72	10.08	8.92	9.36
Infections [d]	70.63	61.73	68.27	65.81	37.36	21.19	22.89	22.25
Serious infections [d]	3.10	6.61	2.65	4.14	3.40	3.41	2.25	2.69

Abbreviations: q8w=every 8 weeks; q12w=every 12 weeks; SC=subcutaneous.

[a] Includes: 1) Subjects who were in clinical response to ustekinumab IV induction dosing, were randomized and received placebo SC on entry into this maintenance study, and did not meet loss of response criteria from Week 8 through Week 32; and 2) Subjects who were in clinical response to placebo IV induction dosing and received placebo SC on entry into this maintenance study.

[b] Includes: 1) Subjects who were in clinical response to ustekinumab IV induction dosing, were randomized and received ustekinumab 90 mg SC q12w, and did not meet loss of response criteria from Week 8 through Week 32; and 2) Subjects who were not in clinical response to placebo IV induction dosing, received ustekinumab 130 mg IV at Week 0, achieved clinical response at Week 8, and initiated ustekinumab 90 mg SC q12w.

[c] Includes: 1) Subjects who were in clinical response to ustekinumab IV induction dosing, were randomized on entry into this maintenance study, received ustekinumab 90 mg SC q8w, or met loss of response criteria from Week 8 through Week 32 and received ustekinumab 90 mg SC q8w thereafter; and 2) Subjects who were not in clinical response to ustekinumab IV induction dosing, received ustekinumab 90 mg SC at Week 0, achieved clinical response at Week 8, and initiated ustekinumab 90 mg SC q8w.

[d] Infections as assessed by the investigator.

Adapted from:
[TSFAE13D1B1.RTF] [CNTO1275\CRD3003\DBR_W272\RE_W272\PREPROD\TSFAE13D1B1.SAS] 04MAY2020, 14:23
[TSFAE13D2.RTF] [CNTO1275\CRD3003\DBR_W272\RE_W272\PROD\TSFAE13D2.SAS] 18NOV2019, 18:45

5.2.3.2. Ulcerative Colitis

Among all treated subjects in the LTE of UCO3001, the overall safety profile from Week 44 through Week 96 was generally consistent with the known safety profile of ustekinumab (CRD_UC/Mod2.7.4/Sec2.2.1):

- The number of subjects reporting AEs per hundred subject-years of follow-up (AE subject rate) was generally comparable for subjects treated with ustekinumab as compared with subjects treated with placebo. The Infections and infestations and the Gastrointestinal disorders SOCs had the highest AE subject rates.
  - The AE subject rates in the Infections and infestations SOC were 43.29, 48.91, and 46.48 in the placebo, q12w, and q8w groups, respectively. Nasopharyngitis was the most frequently reported AE, with subject rates of 14.93, 21.55, and 19.83 in the placebo, q12w, and q8w groups, respectively.
  - The AE subject rates in the Gastrointestinal disorders SOC per hundred subject-years were 55.23, 34.82, and 31.53 in the placebo, q12w, and q8w groups, respectively. Ulcerative colitis was the most frequently reported AE, with a greater subject rate in the placebo group (35.08) compared with the q12w and q8w groups (14.09 and 15.60, respectively).
- One subject died. The subject had received 1 dose of ustekinumab after dose adjustment from placebo; the immediate cause of death was attributed to cardiac arrest and was deemed unrelated to ustekinumab treatment. Prior to cardiac arrest, the subject with multiple comorbidities reported AEs of cytomegalovirus (CMV) colitis, worsening UC, and failure to thrive.
- The number of subjects with at least 1 SAE per hundred subject-years of follow-up (SAE subject rate) was 10.45 in the placebo group and 6.30 in the combined ustekinumab 90 mg SC treatment group, which was comparable for those subjects in the q12w (5.80) and q8w (6.50) groups. The highest SAE subject rates were related to ulcerative colitis: 5.22 in the placebo group and 1.63 in the combined ustekinumab group.
- The numbers of subjects who discontinued study agent because of 1 or more AEs per hundred subject-years of follow-up were 7.46, 4.97, and 4.23 in the placebo, q12w, and q8w groups, respectively. Ulcerative colitis was the most frequently reported AE leading to discontinuation, reported in 7.46, 2.49, and 2.28 subjects per hundred subject-years of follow-up in the placebo, q12w, and q8w groups, respectively.
- The numbers of subjects with 1 or more infections per hundred subject-years of follow-up (infection subject rate) were 45.53 in the placebo group and 49.73 in the combined ustekinumab group, which was comparable for those subjects in the q12w (50.57) and q8w (50.71) groups. The most frequently reported treatment-emergent infections were nasopharyngitis (subject rates of 14.18 and 19.15 in the placebo and combined ustekinumab groups, respectively) and upper respiratory tract infection (subject rates of 5.22 and 6.54 in the placebo and combined ustekinumab groups, respectively).

  - The numbers of subjects with 1 or more infections requiring oral or parenteral antimicrobial therapy per hundred subject-years of follow-up were 18.66 in the placebo group and 24.98 in the combined ustekinumab group. The infections with the highest subject rates requiring oral or parenteral antimicrobial treatment were nasopharyngitis, bronchitis, sinusitis, and upper respiratory tract infection.

- Serious infections were reported infrequently; the numbers of subjects with 1 or more serious infections per hundred subject-years of follow-up were 2.24 in the placebo group and 2.33 in the combined ustekinumab group. No specific event was reported in more than 1 subject.
- Among ustekinumab-treated subjects, the proportions of injections with injection-site reactions were 0.5% among the total number of ustekinumab injections and 0.3% among the total number of placebo injections.

Among the limited number of subjects who had a dose adjustment to ustekinumab q8w, the safety profile was generally consistent with that observed in subjects randomized in maintenance to ustekinumab q8w. Serious AEs and AEs leading to discontinuation of study agent were infrequent events among subjects who had a dose adjustment to ustekinumab q8w, with ulcerative colitis as generally the most frequently reported event.

The overall safety profile of ustekinumab for subjects who were delayed responders and were treated in the LTE was consistent with that observed in the randomized ustekinumab q8w group.

During the LTE of UCO3001, from Week 44 through Week 96, the numbers of subjects with AEs, SAEs, infections, and serious infections per hundred subject-years of follow-up were comparable between ustekinumab-treated subjects and placebo-treated subjects. As shown in Table 4, key safety findings during the LTE of UCO3001 (Weeks 44 through Week 96) compared with the findings from Week 0 through Week 44 in the same population demonstrate that a second year of maintenance therapy for UC is not associated with a change in the safety profile for ustekinumab; no new safety concerns were identified.

Table 4: Number of Subjects With Key Safety Events Per Hundred Subject Years of Follow-Up from Week 0 Through Week 44 and From Week 44 Through Week 96; Subjects Who Entered Into the Long-Term Extension in CNTO1275UCO3001

	Week 0 Through Week 44				Week 44 through Week 96			
		Ustekinumab 90 mg SC				Ustekinumab 90 mg SC		
	Placebo SC [a]	q12w [b]	q8w [c]	Combined	Placebo SC [d]	q12w [e]	q8w [f]	Combined
Analysis set: subjects who entered the long-term extension	188	141	259	400	188	141	353	454
Average duration of follow-up (weeks)	39.2	44.3	44.1	44.2	37.1	44.5	45.3	49.1
Total subject-years of follow-up	141.8	120.0	219.7	339.7	134.0	120.6	307.6	428.3
Subjects who died	0	0	0	0	0	0	1	1
Number of subjects with specified events per hundred subject-years of follow-up								
Adverse events	93.82	79.97	86.96	84.49	93.29	78.75	78.66	74.95
Serious adverse events	5.64	5.83	5.46	5.59	10.45	5.80	6.50	6.30
Infections [g]	55.73	40.82	52.81	48.57	45.53	50.57	50.71	49.73
Serious infections [g]	2.12	2.50	1.37	1.77	2.24	3.32	1.95	2.33

Abbreviations: q8w=every 8 weeks; q12w=every 12 weeks; SC=subcutaneous.

[a] Includes 1) Data from maintenance Week 8 through Week 44 for subjects who were in clinical response to ustekinumab IV induction dosing and were randomized to placebo SC on entry into the maintenance study; and 2) Data from maintenance Week 0 through Week 44 for subjects who were in clinical response to placebo IV induction dosing and received placebo SC on entry into the maintenance study.

[b] Includes data from maintenance Week 0 through Week 44 for subjects who were in clinical response to ustekinumab IV induction dosing and were randomized to ustekinumab 90 mg SC q12w on entry into the maintenance study.

[c] Includes: 1) Data from maintenance Week 0 through Week 44 for subjects who were in clinical response to ustekinumab IV induction dosing and were randomized to ustekinumab 90 mg SC q8w on entry into the maintenance study; and 2) Data from maintenance Week 0 through Week 44 for subjects who were not in clinical response to ustekinumab at induction Week 8 but were in clinical response at induction Week 16 after a SC administration of ustekinumab at induction Week 8 and received ustekinumab 90 mg SC q8w on entry into the maintenance study.

[d] Includes 1) Data from Week 44 through Week 96, or up to the dose adjustment if subjects had a dose adjustment during the long-term extension, for subjects who were in clinical response to ustekinumab IV induction dosing and were randomized to placebo SC on entry into the maintenance study; and 2) Data from Week 44 through Week 96 for subjects who were in clinical response to placebo IV induction dosing and received placebo SC on entry into the maintenance study.

[e] Includes data from Week 44 through Week 96, or up to the dose adjustment if subjects had a dose adjustment during the long-term extension for subjects who were in clinical response to ustekinumab IV induction dosing and were randomized to ustekinumab 90 mg SC q12w on entry into the maintenance study.

[f] Includes: 1) Subjects who were in clinical response to ustekinumab IV induction dosing and were randomized to receive ustekinumab 90 mg SC q8w on entry into the maintenance study, with data from Week 44 through Week 96; and 2) Subjects who were in clinical response to ustekinumab IV induction dosing, randomized to receive placebo SC or ustekinumab 90 mg SC q12w on entry into the maintenance study, and had a dose adjustment to ustekinumab 90 mg SC q8w, with data from the time of dose adjustment onward; 3) Subjects who were not in clinical response to ustekinumab at induction Week 8 but were in clinical response at induction Week 16 after a SC administration of ustekinumab at induction Week 8 and received ustekinumab 90 mg SC q8w on entry into the maintenance study with data from Week 44 through Week 96.

[g] Infection as assessed by the investigator.

Adapted from:
[TSFAE25B.RTF] [CNTO1275\UCO3001\DBR_W96\RE_W96\PROD\TSFAE25B.SAS] 04MAY2020, 18:30; [TSFAE22C1.RTF] [CNTO1275\UCO3001\DBR_W96\RE_W96\PROD\TSFAE22C1.SAS] 04MAY2020, 18:29; [TSFAE21C.RTF] [CNTO1275\UCO3001\DBR_W96\RE_W96\PROD\TSFAE21ABC.SAS] 10DEC2019, 18:09

5.2.3.3. Crohn's Disease and Ulcerative Colitis Pooled with Psoriatic Diseases

5.2.3.3.1. Overview of Key Safety Findings

5.2.3.3.1.1. Common Adverse Events

Overall, supportive analyses that examined pooled Phase 2 and Phase 3 safety data for all diseases pooled (IBD [UC and Crohn's disease] and psoriatic diseases [psoriasis and PsA]) demonstrate that the additional maintenance safety data from the Crohn's disease and UC studies have not altered the well characterized ustekinumab safety profile previously established for the approved indications of Crohn's disease, UC, psoriasis, and PsA.

A summary of subjects with key safety events per hundred subject-years of follow-up through the end of the respective reporting periods across Phase 2 and Phase 3 IBD (including Crohn's disease and UC separately) studies and Phase 2 and Phase 3 psoriatic disease (psoriasis and PsA) studies is presented in Table 5.

Through the end of the respective reporting periods for the all diseases pooled population, the number of subjects with AEs per 100 subject-years (ie, AE subject rate) was lower in ustekinumab-treated subjects (40.50) compared with placebo-treated subjects (130.18; CRD_UC/Mod2.7.4/Sec2.3.1.3). Similarly, across disease populations, the AE subject rate was consistently lower in the ustekinumab group compared with the placebo group. The AE subject rate in the pooled IBD population was 54.40 for ustekinumab-treated subjects and 111.74 for placebo-treated subjects. The SOCs with the highest AE subject rates for all diseases pooled were Infections and infestations (28.74 for ustekinumab- and 62.96 for placebo-treated subjects) and Gastrointestinal disorders (16.27 for ustekinumab- and 52.10 for placebo-treated subjects). Across indications, the AE subject rate was generally lower for ustekinumab-treated subjects compared with placebo-treated subjects in both the Infections and infestations and Gastrointestinal disorders SOCs.

Table 5: Number of Subjects With Key Safety Events Per Hundred Subject-Years of Follow-Up Through Five Years of Follow Up for Crohn's Disease Studies, Through Two Years[a] of Follow Up for the Ulcerative Colitis Study, Through One Year of Follow Up for Psoriatic Arthritis Studies, and Through Five Years of Follow Up for Psoriasis Studies; Treated Subjects in Inflammatory Bowel Disease (Crohn's Disease and Ulcerative Colitis) and Psoriatic Diseases (Psoriasis and Psoriatic Arthritis) Studies[b]

	Crohn's Disease		Ulcerative Colitis		Inflammatory Bowel Disease		Psoriatic Diseases		All Diseases Pooled	
	Placebo[c]	Ustekinumab[d]	Placebo[c]	Ustekinumab[d]	Placebo[c]	Ustekinumab[d]	Placebo[e]	Ustekinumab[f]	Placebo[c,e]	Ustekinumab[d,f]
Subjects treated	943	1749	446	826	1389	2575	1112	4135	2501	6710
Avg duration of follow-up (weeks)	29.01	86.13	45.50	66.92	34.31	79.97	15.30	123.83	25.86	107.00
Avg duration of treatment (weeks)	19.96	69.13	35.25	57.44	25.24	65.38	7.31	103.97	16.91	89.16
Total subject-years of follow-up	526	2897	390	1063	916	3960	327	9847	1244	13807
Number of subjects with events per 100 subject-years (number of subjects with events)										
Adverse events	132.66 (698)	51.88 (1503)	83.53 (326)	61.24 (651)	111.74 (1024)	54.40 (2154)	181.81 (595)	34.91 (3438)	130.18 (1619)	40.50 (5592)
Serious adverse events	26.80 (141)	14.40 (417)	15.37 (60)	9.69 (103)	21.93 (201)	13.13 (520)	8.25 (27)	4.81 (474)	18.33 (228)	7.20 (994)
Infections[g]	66.90 (352)	32.59 (944)	43.30 (169)	37.44 (398)	56.85 (521)	33.89 (1342)	84.64 (277)	26.93 (2652)	64.16 (798)	28.93 (3994)
Serious infections[g]	5.70 (30)	3.90 (113)	3.33 (13)	2.92 (31)	4.69 (43)	3.64 (144)	1.22 (4)	0.96 (95)	3.78 (47)	1.73 (239)
Serious MACE[h]	0.19 (1)	0.28 (8)	0.51 (2)	0.38 (4)	0.33 (3)	0.30 (12)	0.61 (2)	0.44 (43)	0.40 (5)	0.40 (55)
Discontinuation of study agents because of 1 or more adverse events	11.40 (60)	6.56 (190)	11.02 (43)	4.33 (46)	11.24 (103)	5.96 (236)	11.92 (39)	2.51 (247)	11.42 (142)	3.50 (483)
Death	0.00 (0)	0.21 (6)	0.00 (0)	0.28 (3)	0.00 (0)	0.23 (9)	0.00 (0)	0.20 (20)	0.00 (0)	0.21 (29)
Malignancies (excluding NMSC)	0.19 (1)	0.41 (12)	0.51 (2)	0.47 (5)	0.33 (3)	0.43 (17)	0.31 (1)	0.56 (55)	0.32 (4)	0.52 (72)

Table 5: Number of Subjects With Key Safety Events Per Hundred Subject-Years of Follow-Up Through Five Years of Follow Up for Crohn's Disease Studies, Through Two Years[a] of Follow Up for the Ulcerative Colitis Study, Through One Year of Follow Up for Psoriatic Arthritis Studies, and Through Five Years of Follow Up for Psoriasis Studies; Treated Subjects in Inflammatory Bowel Disease (Crohn's Disease and Ulcerative Colitis) and Psoriatic Diseases (Psoriasis and Psoriatic Arthritis) Studies[b]

Abbreviations: MACE=major adverse cardiovascular event; NMSC=nonmelanoma skin cancer.

[a] 104 (112) weeks for subjects who entered maintenance at Week 8 (Week 16) of the induction study in Ulcerative Colitis CNTO1275UCO3001.

[b] Crohn's: C0379T07 (only placebo-controlled IV population in population 1; through Week 28), C0743T26 (through Week 36), CNTO1275CRD3001 (through Week 8 for subjects who entered CNTO1275CRD3003; through Week 20 for subjects who did not enter CNTO1275CRD3003), CNTO1275CRD3002 (through Week 8 for subjects who entered CNTO1275CRD3003; through Week 20 for subjects who did not enter CNTO1275CRD3003), CNTO1275CRD3003 (through Week 272); Ulcerative Colitis: CNTO1275UCO3001 (through induction Week 20 for subjects who did not enter maintenance and did not receive treatment at induction Week 8; through induction Week 28 for subjects who did not enter maintenance and received treatment at induction Week 8; through maintenance Week 96 for subjects who entered maintenance); Psoriasis: C0379T04 (through Week 52), C0743T08 (through Week 264), C0743T09 (through Week 264), C0743T12 (through Week 64); Psoriatic Arthritis: C0743T10 (through Week 36), CNTO1275PSA3001 (through Week 52), CNTO1275PSA3002 (through Week 60).

[c] Crohn's disease and Ulcerative Colitis: includes data up to the first ustekinumab dose for subjects who were initially treated with placebo; includes data at or after 16 weeks from the first ustekinumab dose onward, up to the dose adjustment if subjects had a dose adjustment, for subjects who were crossed over or rerandomized to placebo maintenance.

[d] Crohn's disease and Ulcerative Colitis: includes data up to 16 weeks from the first ustekinumab dose for subjects who were crossed over or rerandomized to placebo, and from the dose adjustment onward if subjects had a dose adjustment from placebo SC to ustekinumab 90 mg SC q8w.

[e] Psoriatic diseases: includes data up to the time of early escape or crossover.

[f] Psoriatic diseases: includes data from the first ustekinumab dose onward for subjects who early escaped or crossed over from placebo.

[g] Infection as assessed by the investigator.

[h] MACE events were independently adjudicated through five years of follow up for Psoriasis indication, through one year for Psoriatic Arthritis and Crohn's indications. MACE events were identified by clinical review and were not independently adjudicated for the UC indication and beyond one year of follow up for the Crohn's indication.

[TSFKEY02E.RTF] [CNTO1275\Z_SCS\DBR_2020_07\RE_2020_07\PROD\TSFKEY02E.SAS] 05MAR2020, 18:56

5.2.3.3.1.2. Deaths

Overall, there were few deaths reported through the end of the reporting period in the clinical programs evaluating ustekinumab (CRD_UC/Mod2.7.4/Sec2.3.1.4). While all the deaths were reported in ustekinumab-treated subjects, this observation is likely attributable to the notably longer observation period for ustekinumab-treated compared to placebo-treated subjects. When normalized for the different observation periods, the death event rate for each of the disease indications (Crohn's disease, UC, IBD pooled, psoriatic diseases, and all diseases pooled) is low and ranges from 0.20 to 0.28 events per hundred subject-years. It should be noted that, due to the shorter duration of follow-up in the placebo groups, a single subject death in each of the placebo treatment groups would yield death event rates in the placebo treatment groups that would be comparable with the reported ustekinumab-treated rates. Additionally, the rates reported for ustekinumab-treated Crohn's disease, UC, and the pooled IBD populations are below rates that have been reported in the literature, ranging from 0.8 to 2.0 per 100 subject-years.[2,9,11] Lastly, in the Psoriasis Longitudinal Assessment and Registry (PSOLAR) study, all-cause mortality event rates, as well as cardiovascular mortality and unexplained death rates were comparable across all treatment groups that included 27,938 patient-years of ustekinumab exposure, 34,502 patient-years of exposure to anti-TNF biologic therapy, and 10,693 patient-years of exposure to non-biologic treatments. Therefore, based on the available clinical study data, there is no evidence to suggest an increased risk of death with ustekinumab treatment.

Crohn's Disease

Through approximately 5 years of follow-up, there were 6 subjects who died in CRD3003. Five of the 6 subjects received ustekinumab 90 mg SC q8w and 1 subject received ustekinumab 90 mg SC q12w. Three subjects died prior to Week 96 while receiving ustekinumab and are described in the Week 96 SCS (CRD W96/Mod2.7.4/Sec2.3.1.4.3). Two subjects died of cardiovascular causes and 1 from suicide; all 3 deaths were deemed unrelated to ustekinumab. Three deaths were reported after Week 96 and through Week 272:

- A 45- to 50-year-old ustekinumab-treated subject died from an acute myocardial infarction on Day 977. The subject had a history of smoking, hyperlipidemia, and hypertension. The subject reported a nonserious AE of unstable angina and was seen by a general practitioner after refusing to go to the emergency room. No treatment was reported for this event. Ten days later, the subject's condition worsened and the subject died of acute myocardial infarction.
- A 30- to 35-year-old ustekinumab-treated subject died from septic shock several months after discontinuation from the study at the Principal Investigator's discretion on Day 955. The sepsis was determined to be a postoperative complication following the repair of an abdominal hernia. The subject had a history of peripheral vascular disease, hypertension, osteoporosis, sclerosis of the left kidney, smoking, tonsillectomy, left hemicolectomy due to a gastrointestinal perforation, recurrent urinary tract infections, factor V Leiden mutation, acute pancreatitis related to mesalazine use, acute renal failure related to tacrolimus use, and increased pancreatic enzymes due to AZA and 6-MP use. The subject had initially received ustekinumab IV induction and went on to receive 90 mg SC q8w as maintenance therapy.

- A 70- to 75-year-old ustekinumab-treated subject died from end stage renal disease after discontinuing dialysis on Day 809. The subject had a history of smoking, bladder disorder, acute kidney injury, chronic kidney disease, a renal cyst, essential hypertension, coronary artery disease, gastroesophageal reflux disease, hyperphosphatemia, hypocalcemia, metabolic acidosis, nephrogenic anemia, and proteinuria.

Ulcerative Colitis

Through approximately 2 years of follow-up, 3 deaths were reported in ustekinumab-treated subjects in UCO3001. The 2 deaths reported through the first year of treatment (1 sudden death due to oesophageal varices hemorrhage and 1 death due to acute respiratory failure) were described in the initial SCS (UC/Mod2.7.4/Sec2.1.2), and the additional death reported through 2 years of follow-up is as follows:

- A 65- to 74-year-old subject with multiple comorbidities (including diagnoses of CMV colitis and erosive esophagitis, and recurrent admissions for UC exacerbation, with subsequent development of failure to thrive) died on Day 573 due to cardiac arrest. The subject received placebo IV at Week 0 of induction, followed by ustekinumab ~6 mg/kg IV at Week 8 of induction and was randomized to the placebo group at Week 0 of maintenance. During the LTE, the subject reported an AE of diarrhea approximately 10 days prior to receiving a single dose of ustekinumab.

Psoriatic Diseases

Through the end of the reporting period for psoriatic disease studies, there were 20 deaths that were previously reported (Psoriasis 5-Year Module 2.7.4, Section 2.1.2.1).

Through the end of the reporting period for all diseases pooled, the subject rates (95% CI) of death were 0.21 (0.14, 0.30) in ustekinumab-treated subjects and 0.00 (0.00, 0.24) in placebo-treated subjects.

5.2.3.3.1.3. Other Serious Adverse Events

Through the end of the respective reporting periods for all diseases pooled, the number of subjects with SAEs per 100 subject-years (ie, SAE subject rate) was lower in ustekinumab-treated subjects (7.20) compared with placebo-treated subjects (18.33; CRD_UC/Mod2.7.4/Sec2.3.1.5). Similarly, across disease populations, the SAE subject rate was consistently lower in the ustekinumab group compared with the placebo group. The SAE subject rate in the pooled IBD population was 13.13 for ustekinumab-treated subjects and 21.93 for placebo-treated subjects.

The SOCs with the highest SAE subject rates for all diseases pooled were Gastrointestinal disorders (driven by events of Crohn's disease and UC) and Infections and infestations. As expected, in the SOC of Gastrointestinal Disorders, the SAE subject rates were higher in the pooled IBD population than in the pooled psoriatic diseases population and the all diseases pooled population; the SAE subject rates were numerically lower in ustekinumab-treated subjects than in placebo-treated subjects (7.02 and 13.42, respectively, in the pooled IBD population, 0.58 and 0.61, respectively, in the pooled psoriatic diseases population, and 2.43 and 10.05, respectively, in the all diseases pooled population). Across indications, the SAE subject rate in the Infections and

infestations SOC was generally comparable for ustekinumab-treated subjects compared with placebo-treated subjects.

All SAEs reported were at a rate of less than 1 subject per 100 subject-years within the all diseases pooled and pooled IBD populations, with the exception of events associated with IBD. In the all diseases pooled population, the events with the highest subject rates in ustekinumab-treated subjects were Crohn's disease (1.16), small intestinal obstruction (0.25), and anal abscess (0.16; each predominately in Crohn's disease subjects), ulcerative colitis (0.25; in UC subjects), and myocardial infarction (0.20) and coronary artery disease (0.16; predominately in the psoriatic disease indications). All of these events occurred at generally lower rates in ustekinumab-treated subjects compared with placebo-treated subjects.

5.2.3.3.1.4. Discontinuations of Study Agent Due to Adverse Events

Overall, the number of subjects who discontinued study agent due to an AE through the end of the respective reporting period for all diseases pooled was low (CRD_UC/Mod2.7.4/Sec2.3.1.6.1). For all diseases pooled, the number of subjects who discontinued study agent due to an AE per hundred subject-years of follow-up (subject rate of discontinuations due to AE) was lower for ustekinumab-treated subjects (3.50) than for placebo-treated subjects (11.42). Similarly, the subject rate of discontinuations due to AEs was lower among ustekinumab-treated subjects compared with placebo-treated subjects across disease populations. In the pooled IBD population, the subject rates of discontinuations due to AE were 5.96 and 11.24 among ustekinumab- and placebo-treated subjects, respectively.

For all diseases pooled, the SOC with the highest subject rates of discontinuations of study agent due to AE was Gastrointestinal disorders, with rates of 1.08 and 6.35 among ustekinumab- and placebo-treated subjects, respectively. The rates for Gastrointestinal disorders were mainly driven by subjects with the AE of Crohn's disease in the Crohn's disease studies and the AE of ulcerative colitis in the UC studies.

5.2.3.3.1.5. Infections and Serious Infections

Infections as reported below represent AEs that were designated as an infection by the investigator on the electronic case report form (eCRF) and are not limited to the Medical Dictionary for Regulatory Activities Infections and infestations SOC. Infections and serious infections through the end of the respective reporting periods for all diseases pooled are as follows:

- Infections (CRD_UC/Mod2.7.4/Sec2.3.1.7.1):
  - The number of subjects with AEs of infection per 100 subject-years (infection subject rate) was lower in ustekinumab-treated subjects (28.93) compared with placebo-treated subjects (64.16). A similar pattern was observed across disease populations.
  - In the pooled IBD population, the infection subject rates were 33.89 and 56.85 among ustekinumab- and placebo-treated subjects, respectively.

  - Among AEs designated as infections on the eCRF by the investigators, the preferred terms with the highest subject rates for all diseases pooled were nasopharyngitis (10.13 and 15.28 in ustekinumab- and placebo-treated subjects, respectively) and upper respiratory tract infection (8.27 and 11.26 in ustekinumab- and placebo-treated subjects, respectively).

- Serious infections (CRD_UC/Mod2.7.4/Sec2.3.1.7.2):
  - The number of subjects with serious infections per 100 subject-years was 1.73 in ustekinumab-treated subjects and 3.78 in placebo-treated subjects.
  - The overall serious infection subject rate was higher in the pooled IBD population compared with the pooled psoriatic diseases population and the all diseases pooled population; however, the rates in the pooled IBD population were comparable between ustekinumab-treated subjects (3.64) and placebo-treated subjects (4.69).
  - All serious infections in ustekinumab-treated subjects across all indications occurred at a rate of less than 1 subject per 100 subject-years. Among SAEs designated as infections on the eCRF by the investigators, the most frequently reported serious infections by preferred terms in all diseases pooled were anal abscess (with serious infection subject rates of 0.14 and 0.72 in ustekinumab- and placebo-treated subjects, respectively; these were driven by subjects in the Crohn's disease and UC populations) and pneumonia (with serious infection subject rates of 0.14 and 0.32 in ustekinumab- and placebo-treated subjects, respectively).

5.2.3.3.2. Targeted Adverse Events

The targeted AEs of serious infections, malignancies, serious MACE, and vascular thrombotic events were analyzed across the pooled IBD, pooled psoriatic diseases, and all diseases pooled populations. Additionally, targeted AEs that occurred infrequently (ie, anaphylactic and serum sickness-like reactions, TB and opportunistic infections, serious neurologic disorders, and depression and suicidality) are also described. Note that serious infections are discussed in Section 5.2.3.3.1.5; all other targeted AEs are discussed within this section.

Overall, in the evaluation of targeted AEs, there were no findings that suggested a new safety concern or a change in the ustekinumab safety profile.

5.2.3.3.2.1. Malignancy

The incidence of overall malignancies, nonmelanoma skin cancers (NMSCs; basal cell and squamous cell skin cancers), and cancers other than NMSCs through the end of the respective reporting periods are presented below. Additional details are available in the SCS (CRD_UC/Mod2.7.4/Sec2.3.1.8.1).

All Indications

For all diseases pooled through the end of the respective reporting periods, the number of subjects with 1 or more malignancies per 100 subject-years of follow-up (subject rate) for all malignancies (including NMSC) was low and generally comparable between ustekinumab-treated subjects (1.00 [95% CI: 0.84, 1.18]) and placebo-treated subjects (0.73 [95% CI: 0.33, 1.38]). The subject rate

for NMSCs was 0.48 (95% CI: 0.37, 0.61) among ustekinumab-treated subjects and 0.40 (95% CI: 0.13, 0.94) among placebo-treated subjects. Not unexpectedly, given the use of ultraviolet light therapy for the treatment of psoriasis, the majority of NMSC events were reported in the pooled psoriatic diseases population with comparable rates between treatment groups. Of note, among all indications, 56 subjects reported basal cell cancer and 18 subjects reported squamous cell skin cancer, which is consistent with the ratio of basal cell to squamous cell skin cancers reported in immunocompetent individuals.

For all diseases pooled, the subject rate for malignancies other than NMSC was low and comparable between ustekinumab-treated subjects (0.52 [95% CI: 0.41, 0.66]) and placebo-treated subjects (0.32 [95% CI: 0.09, 0.82]).

Pooled IBD

In the pooled IBD population through the end of the respective reporting periods, the subject rate for all malignancies was low and comparable between ustekinumab-treated subjects (0.84 [95% CI: 0.58, 1.18]) and placebo-treated subjects (0.66 [95% CI: 0.24, 1.43]). The subject rate for NMSCs was 0.43 (95% CI: 0.25, 0.69) among ustekinumab-treated subjects and 0.33 (95% CI: 0.07, 0.96) among placebo-treated subjects. Subject rates for malignancies other than NMSCs were also low, with rates of 0.43 (95% CI: 0.25, 0.69) in ustekinumab-treated subjects and 0.33 (95% CI: 0.07, 0.96) in placebo-treated subjects.

Crohn's Disease

Through approximately 5 years of follow-up in the Crohn's disease studies, the subject rate for all malignancies was low and comparable between ustekinumab-treated subjects (0.80 [95% CI: 0.51, 1.20]) and placebo-treated subjects (0.57 [95% CI: 0.12, 1.68]). The subject rate for NMSCs was 0.42 (95% CI: 0.22, 0.73) in ustekinumab-treated subjects and 0.38 (95% CI: 0.05, 1.38) in placebo-treated subjects. The subject rate for malignancies other than NMSCs was also low, with a rate of 0.41 (95% CI: 0.21, 0.72) in ustekinumab-treated subjects and 0.19 (95% CI: 0.00, 1.06) in placebo-treated subjects.

There were 14 malignancies (other than NMSCs) reported in 12 ustekinumab-treated subjects and 1 placebo-treated subject. All were single events except for 2 small intestine adenocarcinomas:

- Four malignancies were reported in 3 subjects in the combined studies through Week 44 (multiple myeloma, small intestine adenocarcinoma, incidental carcinoid tumor, and prostate cancer) and were described in the initial SCS (CRD/Mod2.7.4/Sec2.3.1.8.1.2).
- Two malignancies were reported in 2 subjects after Week 44 and through Week 96 (testicular seminoma and papillary thyroid cancer [the latter in a placebo-treated subject]) and were described in the Week 96 SCS (CRD W96/Mod2.7.4/Sec2.3.1.8.1.3).
- Eight malignancies were reported in 8 subjects after Week 96 and through Week 272 (intraocular melanoma, renal cell carcinoma, endometrial adenocarcinoma, small intestine adenocarcinoma, chronic myeloid leukemia, lentigo maligna melanoma, lobular breast cancer

in situ, and pancreatic carcinoma); full subject narratives are provided in the Week 272 clinical study report.

Ulcerative Colitis

Through approximately 2 years of follow-up in the UCO3001 studies, the subject rate for all malignancies was low and comparable between ustekinumab-treated subjects (0.95 [95% CI: 0.45, 1.74]) and placebo-treated subjects (0.77 [95% CI: 0.16, 2.25]). The subject rate for NMSCs was 0.47 (95% CI: 0.15, 1.10) in ustekinumab-treated subjects and 0.26 (95% CI: 0.01, 1.43) in placebo-treated subjects. The subject rate for malignancies other than NMSCs was 0.47 (95% CI: 0.15, 1.10) in ustekinumab-treated subjects and 0.51 (95% CI: 0.06, 1.85) in placebo-treated subjects.

There were 7 malignancies (other than NMSCs) in 5 ustekinumab-treated subjects and 2 placebo-treated subjects:

- Five malignancies were reported through Week 44 (prostate cancer, rectal adenocarcinoma, colon cancer, papillary renal cell carcinoma, and testis cancer [the latter in a placebo-treated subject]) and were described in the initial SCS (UC/Mod2.7.4/Sec2.1.5.8).
- Two malignancies were reported after Week 44 and through Week 96 (malignant melanoma in a ustekinumab-treated subject who entered but was not treated during the LTE, and lentigo malignant melanoma for a subject who received placebo only).

Comparison with External Data or Background Rates

To assess the incidence of malignancies in the ustekinumab studies compared with the expected incidence in the general US population, standardized incidence ratios (SIR) were evaluated using the National Institutes of Health Surveillance, Epidemiology, and End Results (SEER) database. The SIR is the ratio of the observed number of subjects with 1 or more malignancies to the expected number of subjects with 1 or more malignancies in the general US population adjusting for age, sex, and race. When the SIR is greater than 1, the observed number of subjects with malignancies is higher than the expected number of cases.

Through the end of the respective reporting periods, for all diseases pooled, the SIR was 0.96 (95% CI: 0.75, 1.22) in ustekinumab-treated subjects and 0.58 (95% CI: 0.12, 1.69) in placebo-treated subjects. In the pooled IBD population, the SIR was 1.10 (95% CI: 0.63, 1.78) in ustekinumab-treated subjects and 0.58 (95% CI: 0.07, 2.10) in placebo-treated subjects.

Taken together, these analyses do not provide evidence of an increased risk of malignancy in subjects with Crohn's disease, UC, or psoriatic diseases who were treated with ustekinumab over the treatment periods studied.

5.2.3.3.2.2. Major Adverse Cardiovascular Events

Overall, there has been no evidence that ustekinumab increases cardiovascular risk in psoriatic diseases, as previously reported in the 5-year update for moderate to severe psoriasis, in the 1-year SCS for PsA, in the initial SCS for Crohn's disease, or in the initial SCS for UC.

Serious MACE beyond 1 year of follow-up for the Crohn's indication and in the UCO3001 induction and maintenance studies were identified by the MAH by clinical review without independent adjudication and were pooled with the independently adjudicated serious MACE in the first year of follow-up for the Crohn's indication and in the approved psoriasis and PsA indications (CRD_UC/Mod2.7.4/Sec2.3.1.8.2).

Overall, across all indications through the end of the respective reporting periods, the number of serious MACE (ie, nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death) per 100 subject-years of follow-up (incidence of serious MACE) was comparable between ustekinumab- and placebo-treated subjects. For all diseases pooled, the incidence of serious MACE was 0.42 (95% CI: 0.32, 0.54) in ustekinumab-treated subjects and 0.40 (95% CI: 0.13, 0.94) in placebo-treated subjects. Among subjects in the pooled IBD population, the incidence of serious MACE was 0.30 (95% CI: 0.16, 0.53) in ustekinumab-treated subjects and 0.33 (95% CI: 0.07, 0.96) in placebo-treated subjects.

Through approximately 5 years of follow-up in the Crohn's disease studies, the incidence of serious MACE was low in ustekinumab-treated subjects (0.28 [95% CI: 0.12, 0.54]) and placebo-treated subjects (0.19 [95% CI: 0.00, 1.06]). There were 9 serious MACE reported in 8 ustekinumab-treated subjects and 1 placebo-treated subject. One serious MACE was reported through 1 year of follow-up (subarachnoid hemorrhage due to aneurysm rupture that was adjudicated as a nonfatal stroke in a ustekinumab-treated subject) and was described in the initial SCS (CRD/Mod2.7.4/Sec2.3.1.8.2). Eight serious MACE were reported after Week 44 and through Week 272 (ventricular arrythmia and probable ischemic heart disease leading to death, cardiopulmonary arrest leading to death, 4 events of myocardial infarction [1 in a placebo-treated subject], cerebral infarction, and ischemic stroke). All subjects with MACE had underlying risk factors for cardiovascular disease.

Through approximately 2 years of follow-up in the UC studies, the incidence of serious MACE was low in ustekinumab-treated subjects (0.38 [95% CI: 0.10, 0.96]) and placebo-treated subjects (0.51 [95% CI: 0.06, 1.85]). There were 6 serious MACE reported in 5 subjects treated with ustekinumab and 1 subject in the placebo group. Three of these serious MACE were reported through 1 year of follow-up (nonfatal cardiac arrest, postoperative anterior wall myocardial infarction, and ischemic stroke [the latter in a placebo-treated subject]) and were described in the initial SCS (UC/Mod2.7.4/Sec2.1.5.9). The other 3 serious MACE were reported after Week 44 and through Week 96 (cardiac arrest leading to death and 2 events of nonfatal myocardial infarction). All subjects with MACE had underlying risk factors for cardiovascular disease.

Overall, in up to 5 years for Crohn's disease and 2 years for UC, there is no consistent evidence that ustekinumab increases cardiovascular risk. Therefore, results from the Crohn's disease and UC studies did not change the previous assessment of the lack of impact of ustekinumab on serious MACE.

Vascular Thrombotic Events

Through the end of the respective reporting periods for all diseases pooled, the number of vascular thrombotic events per 100 subject-years of follow-up (incidence of vascular thrombotic events) was 0.36 (95% CI: 0.27, 0.48) in ustekinumab-treated subjects and 0.32 (95% CI: 0.09, 0.82) in placebo-treated subjects (CRD_UC/Mod2.7.4/Sec2.3.1.8.2.1). Across all indications, the incidences of deep vein thrombosis (DVT) and pulmonary embolism among ustekinumab-treated subjects were 0.19 and 0.08, respectively. Among placebo-treated subjects, the incidence of pulmonary embolism was 0.24; no cases of DVT were identified.

Consistent with an increased risk of vascular thrombotic events in IBD patients (estimated to be 2 to 3-fold higher than in the general population,[12,14] the incidence of vascular thrombotic events in the pooled IBD population was higher than that in the pooled psoriatic diseases population. In the pooled IBD population, the incidence of vascular thrombotic events was 0.78 (95% CI: 0.53, 1.11) in ustekinumab-treated subjects and 0.44 (95% CI: 0.12, 1.12) in placebo-treated subjects. Rates for additional events that are not considered to be thrombotic or embolic events (ie thrombophlebitis, thrombophlebitis superficial, and retinal vein occlusion) are also included in the overall rates for completeness in the SCS (CRD_UC/Mod2.7.4/ Sec2.3.1.8.2.1).

Through approximately 5 years of follow-up in the Crohn's disease studies, the overall incidence of vascular thrombotic events was 0.76 (95% CI: 0.48, 1.15) in ustekinumab-treated subjects and 0.57 (95% CI: 0.12, 1.67) in placebo-treated subjects.

- The incidence of DVT events was 0.45 in ustekinumab-treated subjects and 0.00 in placebo-treated subjects, while the incidence of PE events was lower in ustekinumab-treated subjects (0.07) than in placebo-treated subjects (0.57).
- Events of venous embolism and May-Thurner syndrome were reported, each with an incidence of 0.03; the latter event was reported concurrently with an event of DVT.

Through approximately 2 years of follow-up in the UC studies, the overall incidence of vascular thrombotic events was 0.85 (95% CI: 0.39, 1.61) in ustekinumab-treated subjects and 0.26 (95% CI: 0.01, 1.43) in placebo-treated subjects.

- Among ustekinumab-treated subjects, the incidences of DVT and PE were 0.38 and 0.19, respectively. It should be noted that no DVT or PE events were reported from Week 44 through Week 96 of the LTE. The DVT and PE events observed through 1 year of follow-up in the UC studies program were described in the initial SCS (UC/Mod2.7.4/Sec2.1.3).
- One event of portal vein thrombosis was reported among the ustekinumab-treated subjects with an incidence of 0.09 subjects per hundred subject-years of follow-up.

While there is a slight imbalance across treatment groups in the reporting of all vascular thrombotic events, the overall incidences per hundred subject-years (~0.1 [~1%]) observed among ustekinumab-treated subjects in both the Crohn's disease and UC populations are within the range of 1-8% reported in the IBD literature.[1,4,10] Collectively, rates of DVT and pulmonary embolism were low and generally similar across treatment groups. Of note, review of the individual cases indicated that the majority of ustekinumab-treated subjects from the Crohn's disease and UC

populations had confounding conditions that are associated with increased risk of vascular thrombotic events (eg, smoking, factor V Leiden mutation, May-Thurner syndrome, hypertension, hyperlipidemia, obesity), as well as additional risk factors inherent to underlying active IBD itself, including flare activity and corticosteroid use. Furthermore, the absolute numbers are too small (<1 per hundred subject-years) across treatment groups to be conclusive.

In addition to the review of events reported in clinical trials of venous thromboembolism (VTE), a term which encompasses the closely related conditions of venous thrombosis (eg, DVT) and pulmonary embolism, cases were retrieved from postmarketing reports and the database from the PSOLAR study (CRD_UC/Mod2.7.4/Sec6.2.1). Of the postmarketing cases that were reviewed, almost all of them were confounded by relevant medical history, concomitant conditions, or medications. A review of data from the PSOLAR study did not suggest an increase in DVT and pulmonary embolism reporting rates in the ustekinumab-exposed cohort. The rate of VTE events reported for ustekinumab in the ever-exposed cohort was 0.104 events per hundred patient-years, which did not exceed the 0.125 events per 100 patient-years for non-biologic therapy.

Finally, there is no known biologic mechanism for ustekinumab-induced venous thromboembolism. Ustekinumab inhibits both IL-12 and IL-23, and the inhibition of IL-23 is associated with reduced plasma levels of pro-inflammatory cytokines (TNFα, IL-6, and IL-8) that have been implicated in thrombogenesis. The lower incidence of vascular thrombotic events among ustekinumab-treated subjects in the pooled psoriatic diseases population compared to the IBD population provides additional support that the disease state, along with known confounding factors, may be more important than ustekinumab treatment alone for the risk of vascular thrombotic events. Therefore, there is currently no evidence to suggest biologic plausibility for ustekinumab contributing to the development of thrombosis.

5.2.3.3.2.3. Anaphylactic and Serum Sickness-Like Reactions

The terms anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, anaphylactoid shock, Type I hypersensitivity, and serum sickness or serum sickness-like reaction were utilized to search all reported AEs (CRD_UC/Mod2.7.4/Sec2.3.1.8.3). No events of anaphylactic and delayed hypersensitivity (serum sickness-like) reactions related to ustekinumab were reported from Week 96 through Week 272 of CRD3003 and from Week 44 through Week 96 of UCO3001. Events previously reported in prior submissions were unrelated to ustekinumab.

5.2.3.3.2.4. Tuberculosis and Opportunistic Infections

Tuberculosis

For all diseases pooled through the end of the respective reporting periods, among ustekinumab-treated subjects, there was 1 report of presumed active primary TB in a subject with Crohn's disease 10 months after their last ustekinumab dose and 1 report of active TB through Week 96 of CRD3003 (CRD_UC/Mod2.7.4/Sec2.3.1.8.4.1). There were no new reports of active TB in CRD3003 through Week 272 and no reports of active TB in UCO3001 through Week 96.

Opportunistic Infections

Opportunistic infections reported across the pooled indications through 1 year of treatment are described in the initial UC SCS (UC/Mod2.7.4/2.3.1.8.4.2).

For all diseases pooled through the end of the respective reporting periods, few opportunistic infections were identified by the MAH (CRD_UC/Mod2.7.4/Sec2.3.1.8.4.2). No single serious opportunistic infection was reported in more than 1 subject with the exception of CMV colitis, which was reported in 1 subject receiving placebo maintenance and none of the ustekinumab-treated subjects in the Crohn's disease population, and 3 ustekinumab-treated subjects in the UC population. None of the events reported for the 3 ustekinumab-treated subjects were considered by the investigator to be related to ustekinumab, and 2 of the 3 events were previously described in the initial SCS. It is important to note that the risk of CMV colitis/infection has been reported to be increased in patients with IBD. [7,8] In general, the subjects reporting CMV colitis in these studies presented with confounding risk factors including a history of corticosteroid dependence or refractoriness, concurrent corticosteroid and/or immunomodulator use, and underlying IBD exacerbation at the time of CMV colitis diagnosis.[13] Overall, CMV colitis was reported infrequently (<0.5%) among ustekinumab-treated subjects and is well below rates reported in the IBD population.[3,6]

Among all treated subjects in CRD3003, there were no reports of infections considered to be opportunistic after Week 96 through Week 272.

Among all treated subjects in UCO3001, there were 2 reports of infections (CMV colitis and *Listeria monocytogenes* infection) considered to be opportunistic after Week 44 and through Week 96:

- A 65- to 74-year-old ustekinumab-treated subject was hospitalized (Day 523) for diarrhea secondary to UC, which was complicated by the development of CMV colitis as identified by the presence of CMV inclusion bodies on biopsy. The AE was ongoing at the time of the subject's death due to cardiac arrest.
- A >85-year-old ustekinumab-treated subject was diagnosed with *Listeria monocytogenes* infection (Day 724) 30 days after last dose of ustekinumab. After presenting with a fever and worsening of UC, a blood culture test during follow-up was found to be positive for *L. monocytogenes*. The subject underwent an emergency total colectomy with ileostomy. The subject was diagnosed with disseminated intravascular coagulation and sepsis on the same day as the surgery and with bacterial meningitis a few days later; these were subsequently attributed to the Listeria infection. Study treatment was permanently discontinued due to the SAE of listeriosis. The outcome of the event was reported as resolved with sequelae.

No cases of disseminated Salmonella or atypical mycobacterial infections were observed through the end of the respective reporting periods in the IBD and psoriatic diseases studies or the psoriasis and PsA studies. These 2 types of infections have been described in patients genetically deficient in IL-12/23.[5]

5.2.3.3.2.5. Serious Neurologic Disorders

There were no serious neurologic disorders of reversible posterior leukoencephalopathy, progressive multifocal leukoencephalopathy, or other demyelinating disorders reported during the CRD3003 LTE or from Week 44 through Week 96 of the UCO3001 LTE (CRD_UC/Mod2.7.4/Sec2.3.1.8.5). However, as previously discussed in the initial SCS for UCO3001 (UC/Mod2.7.4/Sec2.1.5.10), a nonserious event of mild multiple sclerosis (MS) progression was reported in the UCO3001 induction study in a subject with a history of relapsing-remitting MS and optic neuritis who received ustekinumab ~6 mg/kg IV induction.

The MAH previously conducted a Phase 2 study of ustekinumab that enrolled 249 subjects with relapsing-remitting MS (C0743T06). During this study, no worsening of MS symptoms or MRI lesions were detected in subjects with MS treated with ustekinumab.

5.2.3.3.2.6. Depression and Suicidality

Depression and suicidality from Week 44 to Week 272 of CRD3003 were previously reported in 1 subject in the ustekinumab q8w group, who committed suicide by [redacted] the same day they were [redacted] for [redacted] under the influence of alcohol (UC/Mod2.7.4/2.3.1.8.6).

Depression and suicidality from Week 44 to Week 96 of UCO3001 were previously reported in 1 ustekinumab-treated subject who was diagnosed with suicidal ideation. The subject had a prior history of depression, anxiety, and obsessive-compulsive disorder.

5.2.4. Adverse Drug Reactions

The MAH maintains a robust pharmacovigilance system and continues to monitor safety information for ustekinumab from clinical studies, registries, and spontaneous postmarketing reports. The methodology used in identifying adverse drug reactions (ADRs) is provided in the SCS (CRD_UC/Mod2.7.4/Sec1.1.6)

The methodology for identifying ADRs from the Crohn's disease and UC studies followed a similar approach to that used for the psoriasis, PsA, and prior Crohn's disease and UC submissions. The primary data used in this assessment were the Crohn's disease clinical study data from treated subjects in the CRD3003 LTE and UC clinical study data from treated subjects in the UCO3001 LTE (CRD_UC/Mod2.7.4/Sec2.3.3).

From the ADR analyses of clinical trial data, including data from CRD3003 through 5 years of follow-up and UCO3001 through 2 years of follow-up, no new ADRs have been identified.

5.3. Laboratory Data

In the Phase 3 studies in Crohn's disease and in UC, the proportions of subjects experiencing markedly abnormal values or reporting maximum National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) toxicity Grade 3 and Grade 4 values, respectively, in hematology and chemistry laboratory test results were low and were generally comparable among the treatment groups (ie, the placebo and all ustekinumab dose groups). These results are consistent with previous observations in the approved Crohn's disease, UC, psoriasis,

and PsA indications, which showed that no clinically meaningful changes in laboratory parameters were detected in subjects treated with ustekinumab; hence, no recommendations for laboratory monitoring during treatment with ustekinumab are warranted.

5.3.1. Crohn's Disease Studies

5.3.1.1. Hematology

From Week 44 through Week 272 in CRD3003, the numbers of subjects with >1 abnormal value hematology were low except for reports of a decrease in absolute lymphocytes (CRD_UC/Mod2.7.4/Sec3.1.1). Low lymphocyte values are not unexpected in Crohn's disease patients who are frequently prescribed immunomodulators as concomitant therapy. Of note, approximately 30% of subjects who entered the LTE were receiving immunomodulators. The number of subjects with markedly low lymphocyte values per hundred subject-years of follow-up were 4.7 and 5.9 in the ustekinumab q12w and ustekinumab q8w groups, respectively, and 6.8 in the placebo group.

5.3.1.2. Clinical Chemistry

From Week 44 through Week 272 in CRD3003, the proportions of subjects with markedly abnormal changes in post-maintenance baseline clinical chemistry laboratory values were low overall, and subjects with more than 1 markedly abnormal post-maintenance baseline clinical chemistry value were generally infrequent (CRD_UC/Mod2.7.4/Sec3.1.2).

5.3.2. Ulcerative Colitis Studies

5.3.2.1. Hematology

From Week 44 through Week 96 of the UCO3001 LTE, the maximum NCI-CTCAE toxicity grades for hematology laboratory values were similar in the placebo and combined ustekinumab groups, and most were Grade 1 or Grade 2 events (CRD_UC/Mod2.7.4/Sec3.2.1). There were few ustekinumab-treated subjects with Grade 3 hematology events and no Grade 4 events. The most frequently reported Grade 3 event was absolute lymphocytes decreased, reported for 1 (0.7%) and 3 (0.9%) subjects in the ustekinumab q12w and q8w groups, respectively; no clinically important decreases in neutrophils were observed, and all 4 subjects were receiving concomitant immunomodulator therapy (ie, AZA or 6-MP). Three subjects from the placebo group also presented with Grade 3 absolute lymphocytes decreased during the LTE. Grade 3 events for hemoglobin decreased were reported in 0 and 3 (0.9%) subjects in the ustekinumab q12w and q8w groups, respectively. Two subjects from the placebo group presented with Grade 4 events for hemoglobin decreased during the LTE.

5.3.2.2. Clinical Chemistry

From Week 44 through Week 96 of the UCO3001 LTE, the maximum NCI-CTCAE toxicity grades for chemistry laboratory values were similar in the placebo and combined ustekinumab groups, and most were Grade 1 or Grade 2 events (CRD_UC/Mod2.7.4/Sec3.2.2). There were few ustekinumab-treated subjects with Grade 3 chemistry events and no Grade 4 events. The most frequently reported Grade 3 event was phosphate decreased, reported for 0 and 9 (2.6%) subjects

in the ustekinumab q12w and q8w groups, respectively. One subject (ustekinumab q12w group) presented with a transient Grade 3 elevation in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase, and 1 subject (ustekinumab q12w group) presented with a Grade 3 bilirubin elevation unaccompanied by elevations in ALT or AST. No cases meeting Hy's law criteria were identified. No Grade 4 chemistry events were observed.

5.4. Other Observations Related to Safety

5.4.1. Crohn's Disease

5.4.1.1. Effect of Immunogenicity on Safety

In the initial SCS (CRD/Mod2.7.4/Sec4.2), it was noted that, overall, the incidence of antibodies to ustekinumab and incidence of study agent administration-related events (eg, injection-site reactions and AEs temporally associated with an infusion reaction) in the Crohn's disease studies were low.

Through the final safety visit of CRD3003, among the 532 subjects who received ustekinumab in maintenance and continued on ustekinumab in the LTE, 31 (5.8%) were positive for antibodies to ustekinumab between induction Week 0 and the final safety visit of the LTE (CRD_UC/Mod2.7.4/Sec4.1.1).

From Week 44 through Week 272 in the LTE, 1 of 575 ustekinumab SC injections (0.2%) was associated with an injection-site reaction among those who were positive for antibodies to ustekinumab in comparison to 38 of 8977 ustekinumab SC injections (0.4%) among those who were negative for antibodies to ustekinumab. There were no injection-site reactions associated with the 490 placebo SC injections among those who were positive for antibodies to ustekinumab in comparison to 12 of 6809 placebo SC injections (0.2%) among those who were negative for antibodies to ustekinumab.

Overall, no relationship between the development of antibodies to ustekinumab and injection-site reactions following SC administration of ustekinumab was identified during the Crohn's disease studies through Week 272 of the LTE. However, due to the limited number of subjects in these analyses, these results should be interpreted with caution.

5.4.1.2. Exposure-Response Analysis for Safety

The relationship between serum ustekinumab concentration and safety in Crohn's disease is discussed in the SCP (CRD_UC/Mod2.7.2/Sec3.2). Overall, no association was observed between ustekinumab concentration and safety events (ie, infections, serious infections, and SAEs) through the final safety visit of the CRD3003 LTE.

5.4.1.3. Subgroup Analyses

To evaluate whether intrinsic factors such as demographics (sex, race, age, weight, and body-mass index) and baseline disease characteristics (disease severity as measured by CDAI score, disease duration, area of disease involvement) and extrinsic factors such as concomitant Crohn's disease medications (baseline immunomodulators or oral corticosteroids) or biologic failure history had a

differential effect on subject safety, subgroup analyses were performed in the Crohn's disease study population (CRD_UC/Mod2.7.4/Sec5.1.1 and Sec 5.2.1). Comparisons were made between the placebo-treated subjects and ustekinumab-treated subjects.

Overall, the safety profile for ustekinumab in the Crohn's disease population was generally consistent with the previously established safety profile when evaluated by age, sex, race, weight, disease duration, severity, or extent, corticosteroid or immunomodulator use at induction baseline, or history of biologic failure.

5.4.2. Ulcerative Colitis

5.4.2.1. Effect of Immunogenicity on Safety

In the initial SCS (UC/Mod2.7.4/Sec4.2), it was noted that, overall, the incidence of antibodies to ustekinumab and incidence of study agent administration-related events (eg, injection-site reactions and AEs temporally associated with an infusion reaction) in the UC studies were low.

Among the 400 subjects who received ustekinumab in maintenance and continued on ustekinumab in the LTE, 22 (5.5%) were positive for antibodies to ustekinumab between induction Week 0 and Week 96 of the LTE (CRD_UC/Mod2.7.4/Sec4.2.1).

Among subjects who received ustekinumab SC injections from Week 44 through Week 96 in the UCO3001 LTE, 1 of 172 ustekinumab SC injections (0.6%) was associated with an injection-site reaction among those who were positive for antibodies to ustekinumab in comparison to 13 of 2531 ustekinumab SC injections (0.5%) among those who were negative for antibodies to ustekinumab. Among subjects who received placebo SC injections from Week 44 through Week 96 in the UCO3001 LTE, 2 of 125 placebo SC injections (1.6%) were associated with an injection-site reaction among those who were positive for antibodies to ustekinumab in comparison to 3 of 1906 placebo SC injections (0.2%) among those who were negative for antibodies to ustekinumab.

Overall, no relationship between the development of antibodies to ustekinumab and injection-site reactions following SC administration of ustekinumab was identified during the UC studies through Week 96 of the LTE. However, due to the limited number of subjects in these analyses, these results should be interpreted with caution.

5.4.2.2. Exposure-Response Analysis for Safety

The relationship between serum ustekinumab concentration and safety in UC is discussed in the SCP (CRD_UC/Mod2.7.2/Sec3.2). Overall, no association was observed between ustekinumab concentration and the safety events (ie, infections, serious infections, and SAEs) through Week 96 of the UCO3001 LTE.

5.4.2.3. Subgroup Analyses

To evaluate whether intrinsic factors such as demographics (sex, race, age, weight, and body-mass index) and baseline disease characteristics (disease severity as measured by Mayo score, disease duration, extent of disease) and extrinsic factors such as concomitant UC medications (baseline immunomodulators or oral corticosteroids) or biologic failure history had a differential effect on subject safety, subgroup analyses were performed in the UC study population (CRD_UC/Mod2.7.4/Sec5.1.2 and Sec 5.2.2). Comparisons were made between the placebo-treated subjects and ustekinumab-treated subjects and data were analyzed from maintenance Week 0 through up to 96 weeks of maintenance treatment in UCO3001.

Overall, the safety profile for ustekinumab in the UC population was generally consistent with the previously established safety profile when evaluated by age, sex, race, weight, disease duration, severity, or extent, corticosteroid or immunomodulator use at induction baseline, or history of biologic failure.

5.4.3. Geriatric Use

Interpretation of data regarding the impact of age upon safety is limited due to the low number of subjects ≥65 years of age.

In the Crohn's disease studies, there were 23 subjects 65-74 years of age, 2 subjects 75-84 years of age, and no subjects ≥85 years of age (CRD_UC/Mod2.7.4/Sec5.1.1.1.3). No trends were observed with regard to differences in the event rates per hundred subject-years for AEs, SAEs, infections, or discontinuations due to an AE during up to 272 weeks of maintenance treatment when evaluated according to the subject's age.

In the UC studies, there were 29 subjects 65-74 years of age, 4 subjects 75-84 years of age, and no subjects ≥85 years of age (CRD_UC/Mod2.7.4/Sec5.1.2.1.3). No trends were observed with regard to differences in the event rates per hundred subject-years for AEs, infections, or discontinuations due to an AE during up to 96 weeks of maintenance treatment when evaluated according to the subject's age. However, within the ≥65 years-of-age population, a higher event rate per hundred subject-years for SAEs was observed among 22 ustekinumab-treated subjects (54.37; 13 events in 5 subjects) compared with that among 11 placebo-treated subjects (0.00; 0 events); this pattern was not observed in the <65 years-of-age population. On review of the specific SAEs, 3 subjects reported 11 of the 13 SAEs. However, given the low number of subjects in the ≥65 years-of-age subpopulation, particularly in the placebo group, definitive conclusions of the impact of ustekinumab on the risk of SAEs in elderly patients cannot be drawn.

Supportive analyses of the number of subjects with key safety events through the end of the respective reporting periods is provided for subjects <65 years of age and for subjects ≥65 years of age in the SCS.

Through the end of the respective reporting periods across all disease indications, the number of subjects with key safety events per hundred subject-years of follow-up among subjects who were <65 years of age and among subjects ≥65 years of age is presented in the SCS

(CRD_UC/Mod2.7.4/Sec5.1.3). Across disease indications, no overall trends were observed with regard to differences in event rates per hundred subject-years for key safety events through the end of the respective reporting periods when evaluated according to the subject's age. However, while the rates of SAEs were comparable between ustekinumab-treated subjects in the Crohn's disease and UC populations, the rate of SAEs among ustekinumab-treated subjects in the UC population tended to be slightly higher than that among placebo-treated subjects among subjects ≥65 years of age. Of note, among subjects ≥65 years of age, the rate of SAEs among placebo-treated subjects in the UC population was lower compared to what was observed in the Crohn's disease or the pooled psoriatic diseases populations.

5.4.4. Use in Pregnancy and Lactation

No studies of ustekinumab were conducted in pregnant or lactating women. The ustekinumab protocols mandated the use of effective contraception during the studies. Discontinuation of study agent was mandated in the event a subject became pregnant.

As of 31 December 2019, 171 reports of pregnancy were identified in studies of ustekinumab in UC, Crohn's disease, psoriasis, PsA, MS, ankylosing spondylitis, and healthy volunteers: 92 maternal pregnancies and 79 pregnancies with paternal exposure. In general, the outcomes seen in the ustekinumab pregnancies are comparable with what is expected in the general population. Additional details are provided in the SCS (CRD_UC/Mod2.7.4/Sec5.4).

5.5. Experience from Approved Indications for Ustekinumab

As presented in the initial Crohn's disease submission (CRD/Mod2.5/Sec5.5), the Crohn's disease 2-year update (CRD W96/Mod2.5/Sec5.5), and the initial UC submission (UC/Mod2.5/Sec5.5), extensive clinical safety data supported the approval of ustekinumab for UC, Crohn's disease, psoriasis, and PsA.

As noted previously (Section 5.2.2), through 5 years of follow-up for Crohn's disease studies, 2 years of follow-up for UC, 5 years of follow-up for psoriasis studies, and 1 year of follow-up for PsA studies, across all pooled indications, a total of 6,710 subjects were treated with ustekinumab, with a total of 13,807 subject-years of follow-up (CRD_UC/Mod2.7.4/Sec1.2):

- 1,749 subjects in the combined Crohn's disease studies
- 826 subjects in the UC studies
- 4,135 in the combined psoriatic disease studies

The SCS presents analyses of safety data from the pooled indications in detail (CRD_UC/Mod2.7.4/Sec2.3). Overall, additional safety data through 5 years of follow-up in Crohn's disease and through 2 years of follow-up in UC does not appear to have altered the well-characterized ustekinumab safety profile established in the approved indications of psoriasis, PsA, Crohn's disease, and UC as reflected in the current Summary of Product Characteristics.

5.6. Worldwide Postmarketing Safety Experience

Postmarketing information has been accruing since the first approval of ustekinumab on 12 Dec 2008. As of 31 December 2019, ustekinumab has received marketing authorization globally, including countries in North America, Europe, South America, and the Asia Pacific regions. Global postmarketing exposure through 31 December 2019 is 1,667,912 person-years (CRD_UC/Mod2.7.4/Sec6.1). Annual Periodic Safety Update reports generated for ustekinumab reflect the assessment of active, ongoing postmarketing surveillance of targeted safety events as described in clinical study safety analyses, as well as broad overall safety surveillance.

6. BENEFITS AND RISKS CONCLUSIONS

Crohn's Disease

The benefit-to-risk of ustekinumab in subjects with moderately to severely active Crohn's disease was described in the initial submission (CRD/Mod2.5/Sec6) and was updated through 2 years of treatment (CRD W96/Mod2.5/Sec6). It was shown to be favorable based on the data available from 2 adequate, well-controlled induction studies and 1 maintenance study through at least 2 years of exposure.

Additional data accrued through 252 weeks of treatment continue to support the favorable benefit-to-risk profile of ustekinumab in Crohn's disease. Treatment with ustekinumab 90 mg SC q12w or q8w maintained clinical remission and clinical response through 5 years of treatment. Furthermore, improvements in inflammatory markers of disease and health-related quality of life measures were also generally maintained.

Ustekinumab continued to be well tolerated in subjects with Crohn's disease, with generally similar safety profiles across the q12w and q8w groups. The 5-year safety data from the Crohn's disease studies were consistent with the previously reported safety data through 2 years of treatment. No new types or patterns of AEs were identified and there was no clear impact of ustekinumab on safety events, including serious infection and malignancy. No new ADRs were identified during 5 years of follow-up in Crohn's disease.

Because Crohn's disease is a chronic immune-mediated disease and life-long therapy may be required, it is important that prescribers be aware of long-term efficacy and safety data. As such, the MAH proposes to update the current information on long-term efficacy in the EU Product Information to include maintenance of efficacy through 5 years of treatment, in subjects with and without prior TNF antagonist failure, and include the most relevant endpoints of clinical remission, clinical response, and quality of life. The MAH also proposes to update the information on maintained decreases in inflammatory markers to include the study extension. In addition, the MAH proposes to update the current information on long-term safety in Crohn's disease to state that no new safety concerns were identified with up to 5 years of treatment.

Ulcerative Colitis

The benefit-to-risk of ustekinumab in subjects with moderately to severely active UC was described in the initial submission (UC/Mod2.5/Sec6). It was shown to be favorable based on the data available from a well-controlled induction study and maintenance study through at least 1 year of ustekinumab exposure.

Additional data accrued through 96 weeks of treatment continue to support the favorable benefit-to-risk profile of ustekinumab in UC. Treatment with ustekinumab 90 mg SC q12w or q8w maintained symptomatic and partial Mayo remission through 2 years of treatment. Furthermore, improvements in inflammatory markers of disease and health-related quality of life measures were also generally maintained.

Ustekinumab continued to be well tolerated in subjects with UC, with generally similar safety profiles across the q12w and q8w groups. The 2-year safety data from the UC studies were consistent with the previously reported safety data through 1 year of treatment. No new types or patterns of AEs were identified and there was no clear impact of ustekinumab on safety events, including serious infection and malignancy. No new ADRs were identified during 2 years of follow-up in UC.

Ulcerative colitis is also a chronic immune-mediated disease and life-long therapy may be required, therefore it is important that prescribers be aware of long-term efficacy and safety data. As such, the MAH proposes that information be included in the label for the most relevant endpoints captured in the LTE. These include maintenance of symptomatic remission, maintenance of reductions in inflammatory markers, and maintenance of improvements in quality of life. Also, given the different populations studied, the MAH considers it relevant to indicate that efficacy was maintained in the conventional therapy failure population (including biologic naïve and biologic nonfailure) and the biologic-failure population (including failure to both anti-TNF and vedolizumab). Efficacy was also regained in subjects who resumed treatment after treatment interruption. In addition, the MAH proposes to update product labeling to include a statement that no new safety concerns were identified with up to 2 years of treatment for UC.

Conclusions

No new safety risks or ADRs were identified and the benefit-risk of ustekinumab in Crohn's disease and UC continues to be positive. For patients living with moderately to severely active Crohn's disease, ustekinumab meets an important medical need for those who have either failed conventional therapies or have failed or are intolerant to TNF antagonists. For patients living with moderately to severely active UC, ustekinumab meets an important unmet medical need for those who have either failed conventional therapies or have failed or are intolerant to biologic therapies including anti-TNF and anti-integrin agents. Ustekinumab also continues to have a favorable benefit-risk profile across all indications, including psoriatic diseases. No additional pharmacovigilance activities or additional risk-minimization measures are proposed for the European Union Risk Management Plan.

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