CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761044Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	BLA 761-044
Drug Name:	Stelara®(ustekinumab) IV or SC
Indication(s):	The treatment of adult patients (18 years or older) with moderately to severely active Crohn's disease who have: 1) failed or were intolerant to immunomodulators or corticosteroids, but never failed (b) (4) 2) failed or were intolerant to (b) (4)
Applicant:	Janssen Biotech, Inc.
Date(s):	Stamp date: 11/25/2015 PDUFA Goal date: 09/25/2016
Review Priority:	Standard
Biometrics Division:	DBIII
Statistical Reviewer:	Min Min, Ph.D.
Concurring Reviewers:	Yeh-Fong Chen, Ph.D.
Medical Division:	Division of Gastrointestinal and Inborn Error Products (DGIEP)
Clinical Team:	Medical Officer: Kerry Jo Lee, M.D. Medical Team Leader: Juli Tomaino, M.D.
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1 EXECUTIVE SUMMARY

The sponsor submitted two Phase 3 induction studies (CNTO1275CRD3001 and CNTO1275CRD3002) and one Phase 3 maintenance study (CNTO1275CRD3003) to support the use of ustekinumab in treating adult patients (18 years or older) with moderately to severely active Crohn's disease. In particular, these patients had:

- failed or were intolerant to immunomodulators or corticosteroids, but never failed (b) (4)
- failed or were intolerant to (b) (4)

In addition to these three studies, the sponsor also conducted an endoscopy sub-study (b) (4) (b) (4)

During an IND meeting with the FDA on the clinical development of this product, the FDA notified the sponsor that the pre-specified clinical remission as primary endpoint for Crohn Disease is preferred and "maintenance of remission" (b) (4) should be based on remitters at Week 44 from induction studies. However, this "maintenance of remission" endpoint was only pre-specified as a key secondary endpoint in the protocol and SAP. According to the pre-specified testing procedure, the low dose (90mg q12w) failed to demonstrate ustekinumab's maintenance effect of remission with p-value of 0.189.

Before this BLA was submitted, the FDA also informed the sponsor that the data of the endoscopic sub-study from the two induction studies needs to be analyzed separately first, before any statistical inference can be made from the pooled data. Moreover, in order to control the overall Type I error rate, the sponsor was recommended to perform a sequential test dealing with different populations and doses. Nevertheless, no detailed information for multiplicity adjustment procedure was included in the protocol and SAP.

The statistical reviewer had carefully reviewed this application and was able to confirm the sponsor's analysis results for the primary endpoint, all of the key secondary endpoints as well as those for the alternative clinical remission and/or response efficacy endpoints for induction studies. In order to assure the robustness of the efficacy findings, the statistical reviewer also conducted additional exploratory analysis based on clinical remission in at least 80% of maintenance visits from Week 0 through Week 44.

After thorough review, we concluded that data of the three efficacy studies indeed supported the efficacy of ustekinumab in treating patients with Crohn's disease (b) (4) (b) (4)

2 INTRODUCTION

2.1 OVERVIEW

The sponsor is seeking the following indications for STELARA® (ustekinumab), a human interleukin-12 and -23 antagonist, for the treatment of adult patients (18 years or older) with moderately to severely active Crohn's disease who have:

- failed or were intolerant to immunomodulators or corticosteroids, but never failed (b) (4) (b) (4) or;
- failed or were intolerant to (b) (4)

Ustekinumab is US Food and Drug Administration (FDA) approved for the treatment of adults with moderate to severe psoriasis and the treatment of adults with active psoriatic arthritis (PsA).

Crohn's disease is a chronic immune-mediated inflammatory bowel disease (IBD) and clinically characterized as a relapsing, remitting disease, with annual incidence rates ranging from 6 to 8 per 100,000 and a prevalence of ~100 to 200 per 100,000 in the United States and annual incidence rates ranging from 0.3 to 12.7 per 100,000 and a prevalence of ~0.6 to 322 per 100,000 in Europe. Peak age-specific incidence occurs between ages 15 and 30 years, thereby disproportionally affecting young adults during their prime working years; a second, smaller peak occurs in the sixth and seventh decades of life. Crohn's disease is associated with substantial morbidity and mortality.

TNF antagonist therapies (infliximab, adalimumab, and certolizumab pegol) have been the first line biologic agents in Crohn's disease. Although many patients initially respond to TNF antagonist therapy, many others do not, and secondary failures due to intolerance or loss of initial response are common. For patients who have failed TNF antagonists, only one other class of biologic agent is available for the treatment of moderate to severe Crohn's disease, the integrin inhibitors, which interfere with lymphocyte trafficking. This class includes natalizumab and, more recently vedolizumab. With only two classes of biologic agents available for patients who have failed or are intolerant to conventional systemic therapies, there is an unmet need for additional treatment options for a disease that largely affects younger patients during their most formative and productive years.

Ustekinumab binds with high affinity and specificity to the p40 subunit common to both human IL-12 and human IL-23 and inhibits their binding to the IL-12 receptor β1 chain and subsequent intracellular signaling by both cytokines. IL-12 induces immune cells toward a T helper 1 (Th1) phenotype (stimulates interferon-gamma [IFN-γ] production), while IL-23 induces a T helper 17 (Th17) pathway (promotes secretion of IL-17A, IL-21, and IL-22). Both cytokines stimulate TNF production, resulting in the intestinal inflammation and epithelial cell injury typical of Crohn's disease.

The sponsor submitted two 8-week IV induction studies, CNTO1275CRD3001 and CNTO1275CRD3002, and one SC maintenance study, CNTO1275CRD3003 to support the treatment of adult patients (18 years or older) with moderately to severely active Crohn's disease

(see Table 1). In addition, an endoscopy substudy was also conducted which aimed at demonstrating and quantifying endoscopic healing of the mucosa in the Phase 3 development program for ustekinumab in Crohn's disease. In this statistical review, only the three efficacy studies, i.e., CNTO1275CRD3001, CNTO1275CRD3002 and CNTO1275CRD3003 were thoroughly evaluated. The analysis results for ustekinumab endoscopy substudy were briefly described in Sections 3.2.4 and 3.2.5.

Table 1: Phase 3 Pivotal Studies

CNTO1275CRD3001 (Induction study) 8 weeks	Moderately to severely active Crohn's disease; TNF antagonist failure population	**Single IV induction dose at Week 0 (n=741):** Placebo (n=247). Ustekinumab 130 mg (n=245). Tiered (weight-based) ustekinumab doses ~6 mg/kg (n=249).
CNTO1275CRD3002 (Induction study) 8 weeks	Moderately to severely active Crohn's disease; conventional therapy (corticosteroids and/or immunomodulators) failure population.	**Single IV induction dose at Week 0 (n=628):** Placebo (n=210). Ustekinumab 130 mg (n=209). Tiered ustekinumab doses ~6 mg/kg (n=209).
CNTO1275CRD3003 (Maintenance study) Data through Week 44 (272 weeks total duration when completed)	Subjects from both Phase 3 induction studies could continue into this maintenance study	**Subjects in response to ustekinumab induction at Week 8 (Randomized subjects; n=388):** Placebo SC (n=133). Ustekinumab 90 mg SC q12w (n=132). Ustekinumab 90 mg SC q8w (n=132). *Other populations (Nonrandomized subjects; n=884):* Placebo SC (responders to placebo IV induction, n=123). Ustekinumab 90 mg SC q8w (nonresponders to ustekinumab IV induction, n=476). Ustekinumab 90 mg SC q12w (nonresponders to placebo IV induction, n=285).

Source: Sponsor's Table 1 of summary-clin-efficacy.pdf

2.2 DATA SOURCES

The sponsor's original BLA submission including the data sets is stored in the following link: \\cdsesub1\evsprod\BLA761044\0000.

The sponsor temporarily suspended dosing of subjects in November 2011 because a stability issue was identified with the batch of the IV drug used in the induction studies (130 mg ustekinumab in 26 mL [5 mg/mL; (b) (4) mL fill of liquid]). To maintain the originally planned sample size in each of the induction studies, an additional 40 subjects were to be enrolled in the induction studies. Because knowledge of the stability issue could potentially bias the assessments, data from subjects who were enrolled before this study was temporarily suspended

(28 from study CNTO1275CRD3001 and 12 from study CNTO1275CRD3002; among the 40 patients, 9 of them were included in the study CNTO1275CRD3003) were not used in the planned efficacy analyses accordingly.

During the review, the FDA requested the sponsor to provide the list of the subjects who were no longer in clinical response to ustekinumab IV induction dosing based on using Week 8 Hematocrit instead of Week 6 Hematocrit for calculation of the CDAI at maintenance baseline; The IR response is stored in the link: \\cdsesub1\evsprod\BLA761044\0018\. In addition, the reviewer identified 6 misclassified responders to ustekinumab that were included in the maintenance study. Furthermore, based on the inclusion criteria as baseline CDAI score between 220 and 450 inclusively, there were 58 patients who had this inclusion criteria violation. In order to assess the impact of protocol violation and misclassification, the reviewer conducted additional analyses whose results were included in the Section of Reviewer's Findings and Conclusions.

3 STATISTICAL EVALUATION

3.1 DATA and ANALYSIS QUALITY

The statistical reviewer confirmed the sponsor's analysis results for the three pivotal studies. Overall, the data and analysis quality of this BLA submission are acceptable.

3.2 EVALUATION of EFFICACY

The following sections contain the study description, where mostly was extracted directly from the sponsor's Clinical Study Report (CSR). If there is any major discrepancy between the CSR and the study protocol or amendments, the detailed discussion will be included in the Section of Reviewer's Findings and Conclusions.

3.2.1 Study CNTO1275CRD3001

Study CNTO1275CRD3001 is titled "A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Induction Therapy in Subjects with Moderately to Severely Active Crohn's Disease Who Have Failed or Are Intolerant to TNF Antagonist Therapy." It was conducted from June 23 2011 through July 03 2013 in 178 worldwide sites.

3.2.1.1 Study Objective and Study Design

This was a phase 3, multicenter, multinational, randomized, double-blind, placebo-controlled parallel group, stratified study in patients with moderately to severely active Crohn's disease who have failed or are intolerant to TNF antagonist therapy. The stratification criteria were with study region (Asia, Eastern Europe, or rest of world), CDAI score (≤ 300 or > 300), and initial response to TNF antagonist therapy (yes or no) as the stratification variables. For subjects who had received multiple TNF antagonist therapies, their initial response status (yes or no) was to be determined by whether they had initially responded to the first TNF antagonist therapy received.

The primary objective of Study CNTO1275CRD3001 was to evaluate the efficacy and safety of IV induction regimens of ustekinumab in inducing clinical response in subjects with moderately to severely active Crohn's disease who have failed or are intolerant to one or more TNF antagonist therapies.

The target population consisted of men or women aged 18 years or older at the time of informed consent with moderately to severely active Crohn's disease (of at least 3 months' duration), defined as a CDAI score ≥220 but ≤450, who had received infliximab (REMICADE®), adalimumab (HUMIRA®), or certolizumab pegol (CIMZIA®) at a dose approved for the treatment of Crohn's disease, and were documented to have not responded initially, responded initially but then lost response, or were intolerant to the medication. Subjects had to have colitis, ileitis, or ileocolitis previously confirmed at some time in the past by radiography, histology, and/or endoscopy, and had to allow a washout period of at least 8 weeks for prior TNF antagonist use. Patients were to be randomized in a 1:1:1 ratio to receive a single IV administration of either placebo or 1 of 2 induction doses of ustekinumab at Week 0:

- Group 1: Placebo
- Group 2: Ustekinumab 130 mg
- Group 3: Tiered ustekinumab doses approximating ustekinumab 6 mg/kg:
    - Ustekinumab 260 mg (weight ≤ 55 kg)
    - Ustekinumab 390 mg (weight > 55 kg and ≤ 85 kg)
    - Ustekinumab 520 mg (weight > 85 kg)

Allocation to treatment group was to be performed using a central randomization center by means of an interactive voice response system (IVRS)/interactive web response system (IWRS). At Week 6, all subjects were to be evaluated for the primary endpoint of clinical response. At Week 8, subjects who had been randomized to ustekinumab induction therapy at Week 0 and had been induced into clinical response at Week 8 in this study were eligible to enter the maintenance study, CNTO1275CRD3003, as the primary efficacy population.

Regarding the sample size planning, with a total of 615 subjects – 205 subjects per treatment group, the power of the study was estimated to be 90%. These calculations assumed a Week 6 responder rate of 40% in the ustekinumab 6 mg/kg group, and 25% in the placebo group. The power for detecting a significant difference between the ustekinumab high dose group and placebo was also examined for the first major secondary endpoint of clinical remission at Week 8. Assuming a 10% clinical remission rate at Week 8 in the placebo group, and a rate of 20% in the ustekinumab high-dose group, 205 subjects per treatment group were predicted to yield an overall power of 81%, at a significance level of 0.05 (2-sided). To increase the power to detect a significant difference for the clinical remission endpoint, the sample size for the key efficacy analyses was increased to 225 subjects per treatment group (total sample size of 675), which provides 85% power for the clinical remission endpoint. A fixed-sequence testing procedure was used to control the overall Type I error rate at the 0.05 level for the comparisons of the 2 ustekinumab dose groups with the placebo group for the primary endpoint. Therefore, the sample size/power calculations were based on the chi-square test (2-sided) for detecting a significant

difference between subjects receiving the high dose (tiered dose approximating ustekinumab 6 mg/kg) and those receiving placebo.

A total of 28 subjects were randomized prior to the study being placed on hold. Because knowledge of the stability issue could potentially bias the assessments, data from these 28 subjects will not be used in the key efficacy analyses (primary and major secondary efficacy analyses). Consequently, to maintain the planned sample size of 675 subjects for the key efficacy analyses, a target of 703 (675+28) subjects will be enrolled in the study.

3.2.1.2 Efficacy Endpoints and Analyses

According to the protocol, the primary efficacy endpoint was clinical response at Week 6 is defined as a reduction from baseline in the CDAI score of ≥100 points. Subjects with a baseline CDAI score of ≥ 220 to ≤ 248 are considered to be in clinical response if a CDAI score of < 150 is attained. The primary hypothesis is that ustekinumab (130 mg or weight-range based doses approximating 6 mg/kg) is superior to placebo in inducing clinical response at Week 6 in subjects with moderately to severely active Crohn's disease who have failed or are intolerant to one or more TNF antagonist therapies.

Based on a request from the Agency, a United States (US)-specific testing procedure was put in place to provide strong control of the overall Type I error rate over the primary and major secondary endpoints. Within each induction study, a sequential testing procedure was employed, and each comparison of an ustekinumab group with placebo was tested at the 0.05 (2-sided) level.

The following list details the order of the testing that was performed within each study. Testing continued to the next endpoint in the list, provided the preceding endpoint was significant.

- Clinical response at Week 6 - tiered ustekinumab dose group ~6 mg/kg
- Clinical response at Week 6 - ustekinumab 130 mg group
- Clinical remission at Week 8 - tiered ustekinumab dose group ~6 mg/kg
- Clinical remission at Week 8 - ustekinumab 130 mg group
- Clinical response at Week 8 - tiered ustekinumab dose group ~6 mg/kg
- Clinical response at Week 8 - ustekinumab 130 mg group
- 70-point response at Week 6 - tiered ustekinumab dose group ~6 mg/kg
- 70-point response at Week 6 - ustekinumab 130 mg group
- 70-point response at Week 3- tiered ustekinumab dose group ~6 mg/kg
- 70-point response at Week 3 - ustekinumab 130 mg group

In addition to the clinical response status at Week 6 based on the CDAI score, the treatment failure rules will be applied to determine the final response status for a subject. The treatment failure rules override the response from the CDAI score. Subjects who have any of the following events prior to the Week 6 visit will be considered not to be in clinical response at Week 6, regardless of the actual CDAI score:

- A Crohn's disease-related surgery (with the exception of drainage of an abscess or seton placement) thought to be a result of lack of efficacy of study agent.

- Specified changes in concomitant Crohn's disease medications.

In addition, subjects with a missing CDAI score at Week 6 will also be considered to not have achieved clinical response at Week 6.

The proportion of subjects in clinical response at Week 6 will be compared between each of the ustekinumab treatment groups and the placebo group using a 2-sided Cochran-Mantel-Haenszel chi-square test, stratified by study region (Asia, Eastern Europe, or Rest of World), CDAI score (≤ 300 or > 300), and initial response to TNF antagonist therapy (yes or no) at a significance level of 0.05.

Efficacy analyses will include all subjects randomized at Week 0, excluding the 28 subjects randomized prior to the study restart. In addition, selected efficacy analyses will also be provided for the population of subjects randomized prior to the study restart. Efficacy analyses will be based on an intent-to-treat principle. Therefore, the efficacy data for each subject will be analyzed according to the assigned treatment regardless of the actual treatment received.

The study will be considered positive if the ustekinumab high dose group is significantly different from the placebo group for the primary endpoint.

Reviewer's Note:
As stated in the FDA's February 17, 2011 meeting minutes: (b) (4) ssuming that they can establish that clinical response in the intended patient population is meaningful, we made the following comments: in order to demonstrate maintenance of response or remission, subjects would need to meet the definitions of clinical response or remission, respectively, at the time of enrollment into Study CNTO1275CRD3003 at Week 8." This explained why the primary efficacy endpoint for induction studies was assessed at Week 6 but only ustekinumab responders at Week 8 were re-randomized into maintenance study.

3.2.1.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 769 subjects were randomly assigned to receive study agent. Unless otherwise specified, analyses discussed in this section are based on the 741 subjects who were randomized after the study was restarted, at 177 sites in Asia (8.0%), Eastern Europe (3.2%), and other countries (88.8%) in North America, Western Europe, Israel, South Africa, Australia, New Zealand, and Brazil. Table 2 displays the number of patients randomized into each treatment group, patient disposition and the reasons for early discontinuation.

Patient retention was excellent; 95.5% of the randomized patients and 95.7% of the treated patients completed the study.

Table 2 Patient Disposition for Study CNTO1275CRD3001 Exclude Those Enrolled Prior to Study Restart (Total=741)

	Placebo n (%)	Ustekinumab 130 mg n (%)	Ustekinumab 6 mg/kg n (%)
Randomized	247 (100)	245 (100)	249 (100)
Never treated	1 (0.4)	0 (0.0)	0 (0.0)
Treated	246 (99.6)	245 (100)	249 (100)
Completed induction study	237 (96.0)	236 (96.3)	235 (94.4)
Entered maintenance study	214 (86.6)	229 (93.5)	227 (91.2)
Terminated prior to Week 8	7 (2.8)	7 (2.9)	9 (3.6)
Reason for termination			
Withdrawal of consent	4 (1.6)	4 (1.6)	8 (3.2)
Death	0 (0.0)	0	0 (0.0)
Lost to follow up	1 (0.4)	1 (0.4)	0 (0.0)
Other reason	2 (0.8)	2 (0.8)	1 (0.4)
Terminated between Week 8 and Week 20	3 (1.2)	2 (0.8)	5 (2.0)
Reason for termination			
Withdrawal of consent	2 (0.8)	1 (0.4)	2 (0.8)
Death	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow up	1 (0.4)	0 (0.0)	2 (0.8)
Other	0 (0.0)	1 (0.4)	1 (0.4)

Source: Sponsor's Table 1 of cnto1275crd3001-study-report.pdf

Table 3 Patients' Baseline Demographics based on Randomized Subjects Excluding Those Enrolled Prior to Study Re-start for Study CNTO1275CRD3001 (Total=741)

Parameter	Placebo (N=247)	Ustekinumab 130 mg (N=245)	Ustekinumab 6 mg/kg (N=249)
Gender			
Male	118 (47.8%)	98 (40.0%)	101 (40.6%)
Female	129 (52.2 %)	147 (60.0%)	148 (59.4%)
Age (years), mean (SD)	37.3 (11.8)	37.4 (11.8)	37.3 (12.5)
Weight (kg), mean (SD)	71.5 (17.7)	68.4 (17.4)	69.5 (19.5)
Race			
White	210 (85.0%)	202 (82.4%)	211 (84.7%)
African American	8 (3.2%)	7 (2.9%)	8 (3.2%)
Asian	20 (8.1%)	20 (8.2%)	23 (9.2%)
Other	5 (2.0%)	6 (2.4%)	3 (1.2%)
Not reported	4 (1.6%)	8 (3.3%)	4 (1.6%)
Unknown	0 (0.0%)	2 (0.8%)	0 (0.0%)

Source: Sponsor's Table 2 of cnto1275crd3001-study-report.pdf

3.2.1.4 Sponsor's Efficacy Results & Conclusions

The sponsor's results for all primary and four major secondary efficacy endpoints based on randomized 741 subjects excluding those enrolled prior to study re-start are shown in Table 4.

Table 4 Sponsor's Results for Primary and Secondary Efficacy Endpoints on Randomized Subjects Excluding Those Enrolled Prior to Study Re-start for Study CNTO1275CRD3001 (Total=741)

	Placebo (N=247)	Ustekinumab 130 mg (N=245)	Ustekinumab 6 mg/kg* (N=249)
Primary efficacy endpoint (clinical response at Week 6)			
Number (%)	53 (21.5)	84 (34.3)	84 (33.7)
p-value by CMH test**		0.002	0.003
Four ranked key secondary efficacy endpoints			
1. Clinical remission at Week 8			
Number (%)	18 (7.3)	39 (15.9)	52 (20.9)
p-value by CMH test**		0.003	<0.001
2. Clinical response at Week 8			
Number (%)	50 (20.2)	82 (33.5)	94 (37.8)
p-value by CMH test**		0.001	<0.001
3. 70-point response at Week 6			
Number (%)	75 (30.4)	113 (46.1)	109 (43.8)
p-value by CMH test**		<0.001	0.002
4. 70-point response at Week 3			
Number (%)	67 (27.1)	94 (38.4)	101 (40.6)
p-value by CMH test**		0.009	0.001

Source: Sponsor's Tables 6, 7, 8, 9 and 10 in cnto1275crd3001-study-report.pdf (Pages 66, 68 and 69) *Weight-range based ustekinumab doses approximating 6 mg/kg: 260 mg (weight ≤ 55kg), 390 mg (weight >55 kg and ≤ 85 kg), 520 mg (weight > 85 kg); **stratified by study region (Asia, Eastern Europe, or Rest of World), CDAI score (≤ 300 or > 300), and initial response to TNF antagonist therapy (yes or no) at significance level of 0.05.

The sponsor's summary is that "ustekinumab induced clinical response and clinical remission. Based on the pre-specified global and US-specific multiple testing procedures, statistical significance can be claimed for both ustekinumab doses (~6 mg/kg and 130 mg) for the primary endpoint as well as all 4 major secondary endpoints."

Exploratory analyses

In addition, as requested by the FDA, exploratory analyses based on alternative clinical response / remission for stool frequency and abdominal pain were done by the sponsor. The Table 5 shows the summary of the results for Weeks 6 and 8.

Of 741 randomized subjects in the primary population, 3.1% (23 subjects) discontinued study agent prior to Week 8. The sponsor performed many sensitivity analyses of the primary endpoint using the observed case, last observation carried forward, multiple imputation, and the worst case missing data methods. The results of all the planned sensitivity analyses supported the conclusion that ustekinumab induced clinical response. These results are not shown in this review.

Table 5 Sponsor's Results for Additional Analysis Results (Stool Frequency and Abdominal Pain) on Randomized Subjects Excluding Those Enrolled Prior to Study Re-start for Study CNTO1275CRD3001 (Total=741)

	Placebo (N=247)	Ustekinumab 130 mg (N=245)	Ustekinumab 6 mg/kg* (N=249)
WEEK 8 alternative clinical remission and response			
Combined abdominal pain and stool frequency score <75 points			
Number (%)	NA	24.5	29.7
Both an abdominal pain mean daily score ≤1 and a stool frequency mean daily score ≤3			
Number (%)	23 (9.3)	42 (17.1)	52 (20.9)
p-value by CMH test**		0.009	<0.001
≥50 point decrease from baseline in the combined abdominal pain and stool frequency score			
Number (%)	48 (19.4)	82 (33.5)	94 (37.8)
p-value by CMH test**		<0.001	<0.001
WEEK 6 alternative clinical remission and response			
Both an abdominal pain mean daily score ≤1 and a stool frequency mean daily score ≤3			
Number (%)	24 (9.7)	40 (16.3)	45 (18.1)
p-value by CMH test**		0.028	0.008
≥50 point decrease from baseline in the combined abdominal pain and stool frequency score			
Number (%)	54 (21.9)	81 (33.1)	91 (36.5)
p-value by CMH test**		<0.001	<0.001

Source: page 115 of summary –clin-efficacy.pdf and \\cdsesub1\evsprod\BLA761044\0013\m1\us IR response to Tables TEFAPSF11 and 02. *Weight-range based ustekinumab doses approximating 6 mg/kg: 260 mg (weight ≤ 55kg), 390 mg (weight >55 kg and ≤ 85 kg), 520 mg (weight > 85 kg); **stratified by study region (Asia, Eastern Europe, or Rest of World), CDAI score (≤ 300 or > 300), and initial response to TNF antagonist therapy (yes or no).

3.2.2 Study CNTO1275CRD3002

Study CNTO1275CRD3002 is titled as "A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Induction Therapy in Subjects with Moderately to Severely Active Crohn's Disease." It was conducted from June 23 2011 through October 28 2014 at 175 sites worldwide.

3.2.2.1 Study Objective and Study Design

This was a phase 3, multicenter, multinational, randomized, double-blind, placebo-controlled parallel group, stratified study in patients with moderately to severely active Crohn's disease who failed or were intolerant to immunomodulators or corticosteroids, but never failed anti-TNF-α treatment. The stratification criteria were with study region (Asia, Eastern Europe, or rest of world), and CDAI score (≤ 300 or > 300) as the stratification variables.

The primary objective of Study CNTO1275CRD3002 was to evaluate the efficacy and safety of IV induction regimens of ustekinumab in inducing clinical response in subjects with moderately to severely active Crohn's disease who failed or were intolerant to immunomodulators or corticosteroids, but never failed anti-TNF-α treatment.

The target population consisted of men or women aged 18 years or older at the time of informed consent with moderately to severely active Crohn's disease (of at least 3 months duration), defined as a Crohn's Disease Activity Index (CDAI) score ≥220 and ≤450 with either elevated CRP of >3.0 mg/L (i.e., >0.3 mg/dL), fecal calprotectin >250 mg/kg, or endoscopic evidence of active Crohn's disease. Subjects had to have colitis, ileitis, or ileocolitis previously confirmed at any time in the past by radiography, histology, and/or endoscopy. Subjects must have demonstrated an inadequate response to or failed to tolerate corticosteroids or immunomodulators (6-mercaptopurine [6-MP], azathioprine [AZA], and methotrexate [MTX]). Subjects who demonstrated corticosteroid dependence were also eligible for entry into the study. Subjects with prior exposure to TNF antagonists were permitted to enter the study; however subjects must not have demonstrated inadequate response or intolerance to such therapy. Patients were to be randomized in a 1:1:1 ratio to receive a single IV administration of either placebo or 1 of 2 induction doses of ustekinumab at Week 0:

- Group 1: Placebo
- Group 2: Ustekinumab 130 mg
- Group 3: Tiered ustekinumab doses approximating ustekinumab 6 mg/kg:
    - Ustekinumab 260 mg (weight ≤ 55 kg)
    - Ustekinumab 390 mg (weight > 55 kg and ≤ 85 kg)
    - Ustekinumab 520 mg (weight > 85 kg)

Allocation to treatment group was to be performed by a central randomization center by means of an interactive voice response system (IVRS)/interactive web response system (IWRS). At Week 6, all subjects were evaluated for the primary endpoint of clinical response. At Week 8, subjects who had been randomized to ustekinumab induction therapy at Week 0 and had been induced into clinical response at Week 8 in this study were eligible to enter the maintenance study CNTO1275CRD3003, as the primary efficacy population. Subjects who were not in clinical response to ustekinumab induction therapy, as well as all subjects who were initially receiving placebo (both in clinical response and not in clinical response), were also eligible to enter the CNTO1275CRD3003 study at Week 8, but were not included in the primary efficacy population.

Regarding the sample size planning, with a total of 600 subjects – 200 subjects per treatment group, the power of the study was estimated to be 90%. These calculations assumed a Week 6 responder rate of 50% in the ustekinumab 6 mg/kg group, and 33% in the placebo group. The power for detecting a significant difference between the ustekinumab high dose group and placebo was also examined for the first major secondary endpoint of clinical remission at Week 8. Assuming a 12% clinical remission rate at Week 8 in the placebo group, and a rate of 25% in the ustekinumab high-dose group, 200 subjects per treatment group were predicted to yield an overall power of 90%, at a significance level of 0.05 (2-sided).

3.2.2.2 Efficacy Endpoints and Analyses

The primary endpoint was clinical response at Week 6 was defined as a reduction from baseline in the CDAI score of ≥ 100 points. Subjects with a baseline CDAI score of ≥220 to ≤248 points were considered to be in clinical response if a CDAI score of <150 was attained.

A fixed sequence testing procedure was used to control the overall Type 1 error rate at the 0.05 level for the comparisons of the 2 ustekinumab dose groups with the placebo group for the primary endpoint. Therefore, the sample size/power calculations were based on the chi-square test (2-sided) for detecting a significant difference between subjects receiving the high dose (tiered dosing approximating ustekinumab 6 mg/kg) and those receiving placebo.

The following list details the order of the testing that was performed within each study. Testing continued to the next endpoint in the list, provided the preceding endpoint was significant.

- Clinical response at Week 6 - tiered ustekinumab dose group ~6 mg/kg
- Clinical remission at Week 8 - tiered ustekinumab dose group ~6 mg/kg
- Clinical response at Week 6 - ustekinumab 130 mg group
- Clinical remission at Week 8 - ustekinumab 130 mg group
- Clinical response at Week 8 - tiered ustekinumab dose group ~6 mg/kg
- Clinical response at Week 8 - ustekinumab 130 mg group
- 70-point response at Week 6 - tiered ustekinumab dose group ~6 mg/kg
- 70-point response at Week 6 - ustekinumab 130 mg group
- 70-point response at Week 3- tiered ustekinumab dose group ~6 mg/kg
- 70-point response at Week 3 - ustekinumab 130 mg group

In addition to the clinical response status at Week 6 based on the CDAI score, treatment failure rules were applied to determine each subject's final response status. As specified in the SAP, treatment failure rules overrode the response from the CDAI score. Subjects who had any of the following events prior to the Week 6 visit were considered to not be in clinical response at Week 6, regardless of the actual CDAI score:

- A Crohn's disease-related surgery (with the exception of drainage of an abscess or seton placement) thought to be a result of lack of efficacy of study agent.
- Specified changes in concomitant Crohn's disease medications.

The CDAI score was calculated for a visit only if 4 or more of the 8 components were available at that visit. When at least 4 of the 8 components were available, any missing components were imputed by carrying forward the last non-missing component, with the exception of a missing hematocrit value. For missing baseline hematocrit values, the hematocrit value obtained closest to and before the date of the Week 0 infusion was used. For all other visits, the hematocrit value obtained closest to the date of the visit was used, provided that it was obtained within 7 days of the visit. If the laboratory value was not available within the ±7-day window, then the closest previous hematocrit value was carried forward. The weight component of the CDAI was based on the standard weight table.

If the CDAI score could not be calculated (i.e., <4 components available) at a visit, the CDAI score was considered missing. Subjects with a missing CDAI score at Week 6 were considered to not have achieved clinical response at Week 6.

The proportion of subjects in clinical response at Week 6 was compared between each of the ustekinumab treatment groups and the placebo group using a 2-sided Cochran-Mantel-Haenszel chi-square test, stratified by study region (Asia, Eastern Europe, or rest of world) and CDAI score (≤ 300 or >300), at a significance level of 0.05.

Efficacy analyses included all subjects randomized at Week 0, excluding the 12 subjects randomized prior to the study restart. Efficacy analyses were to be based on an intent-to-treat principle. Therefore, the efficacy data for each subject were analyzed according to the assigned treatment, regardless of the actual treatment received.

The study was considered to be positive if the ustekinumab high dose group was significantly different from the placebo group for the primary endpoint.

Reviewer's Note:
The sponsor agreed to use remission at Week 8 for Study CNTO1275CRD3002 as the primary efficacy endpoint, but the FDA stated "DGIEP prefers clinical remission as the pre-specified primary endpoint for CD trials, however considering the current stage of your ongoing induction trial (estimated to complete enrollment in the second quarter of 2014) we recommend you do not amend your protocol or SAP." This further explained why the primary efficacy endpoint for induction studies was assessed at Week 6 but only ustekinumab responders at Week 8 were re-randomized into maintenance study.

3.2.2.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 640 subjects were randomly assigned to receive study agent. Unless otherwise specified, analyses discussed in this section are based on the 628 or 627 subjects who were randomized after the study was restarted, at 174 sites in Asia (7.3%), Eastern Europe (23.4%), and other countries (69.3%) in North America, Western Europe, Israel, South Africa, Australia, New Zealand, and Brazil. Tables 6 and 7 display the number of patients randomized into each treatment group, patient disposition, the reasons for early discontinuation and patient baseline demographics.

Patient retention was excellent; 96.3% of the randomized patients and 96.5% of the treated patients completed the study.

Table 6 Patient Disposition for Study CNTO1275CRD3002 Exclude Those Enrolled Prior to Study Restart (Total=628)

	Placebo n (%)	Ustekinumab 130 mg n (%)	Ustekinumab 6 mg/kg n (%)
Randomized	210 (100)	209 (100)	209 (100)
Never treated	1 (0.5)	0 (0.0)	0 (0.0)
Treated	209 (99.5)	209 (100)	209 (100)
Completed induction study	198 (94.3)	200 (95.7)	207 (99.0)
Entered maintenance study	186 (88.6)	196 (93.8)	203 (97.1)
Terminated study	12 (5.7)	9 (4.3)	2 (1.0)
Terminated prior to Week 8	9 (4.3)	3 (1.4)	2 (1.0)
Reason for termination			
Withdrawal of consent	6 (2.9)	3 (1.4)	1 (0.5)
Death	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow up	2 (1.0)	0 (0.0)	1 (0.5)
Other reason	1 (0.5)	0 (0.0)	0 (0.0)
Terminated between Week 8 and Week 20	3 (1.4)	6 (2.9)	0 (0.0)
Reason for termination			
Withdrawal of consent	1 (0.5)	4 (1.9)	-
Death	0 (0.0)	0 (0.0)	-
Lost to follow up	2 (1.0)	2 (1.0)	-
Other	0 (0.0)	0 (0.0)	-

Source: Sponsor's Table 1 of cnto1275crd3002-study-report.pdf

Table 7 Patients' Baseline Demographics based on Randomized Subjects Excluding Those Enrolled Prior to Study Re-start for Study CNTO1275CRD3002 (Total=628)

Parameter	Placebo (N=210)	Ustekinumab 130 mg (N=209)	Ustekinumab 6 mg/kg (N=209)
Gender			
Male	99 (47.1%)	104 (49.8%)	90 (43.1%)
Female	111 (52.9 %)	105 (50.2%)	119 (56.9%)
Age (years), mean (SD)	40.2 (13.1)	39.1 (13.8)	38.4 (13.1)
Weight (kg), mean (SD)	74.0 (19.9)	74.4 (21.3)	71.9 (18.8)
Race			
White	177 (84.3%)	175 (83.7%)	174 (83.3%)
African American	7 (3.3%)	6 (2.9%)	7 (3.3%)
Asian	17 (8.1%)	17 (8.1%)	16 (7.7%)
Other	7 (3.3%)	10 (4.8%)	6 (2.9%)
Not reported	0 (0.0%)	1 (0.5%)	3 (1.4%)
Unknown	2 (1.0%)	0 (0.0%)	0 (0.0%)

Source: Sponsor's Table 2 of cnto1275crd3002-study-report.pdf

3.2.2.4 Sponsor's Efficacy Results & Conclusions

Superiority of the ustekinumab compared to placebo was demonstrated using a two-sided CMH test with study region (Asia, Eastern Europe, or Rest of World) and CDAI score (≤ 300 or > 300) as strata.

Of 628 randomized subjects in the primary population, 2.2% (14 subjects) discontinued study agent prior to Week 8. The sponsor also conducted sensitivity analyses of primary efficacy endpoint using the observed case, last observation carried forward, multiple imputation, and the worst case missing data methods (results are not shown in this review), and concluded that the primary efficacy analysis results are robust.

The sponsor's results for all primary and secondary efficacy endpoints based on randomized 627 subjects excluding those enrolled prior to study re-start and site 1127 are shown in Table 8.

Table 8 Sponsor's Results for Primary and Secondary Efficacy Endpoints on Randomized Subjects Excluding Those Enrolled Prior to Study Re-start and Excluding Site 1127 for Study CNTO1275CRD3002 (Total=627)

	Placebo (N=209)	Ustekinumab 130 mg (N=209)	Ustekinumab 6 mg/kg* (N=209)
Primary efficacy endpoint (clinical response at Week 6)			
Number (%)	60 (28.7)	108 (51.7)	116 (55.5)
p-value by CMH test**		<0.001	<0.001
Four ranked key secondary efficacy endpoints			
1. Clinical remission at Week 8			
Number (%)	41 (19.6)	64 (30.6)	84 (40.2)
p-value by CMH test**		0.009	<0.001
2. Clinical response at Week 8			
Number (%)	67 (32.1)	99 (47.4)	121 (57.9)
p-value by CMH test**		<0.001	<0.001
3. 70-point response at Week 6			
Number (%)	81 (38.8)	123 (58.9)	135 (64.6)
p-value by CMH test**		<0.001	<0.001
4. 70-point response at Week 3			
Number (%)	66 (31.6)	103 (49.3)	106 (50.7)
p-value by CMH test**		<0.001	<0.001

Source: Sponsor's Tables 6, 7, 8, 9 and 10 in cnto1275crd3001-study-report.pdf (Pages 71, 72, 73 and 74) *Weight-range based ustekinumab doses approximating 6 mg/kg: 260 mg (weight ≤ 55kg), 390 mg (weight >55 kg and ≤ 85 kg), 520 mg (weight > 85 kg); **stratified by study region (Asia, Eastern Europe, or Rest of World) and CDAI score (≤ 300 or > 300) at significance level of 0.05.

The sponsor's summary is that "ustekinumab induced clinical response and clinical remission in a population of Crohn's disease patients with moderately to severely active disease who had previously failed or were intolerant to conventional systemic therapy."

Exploratory analyses

The FDA recommended the sponsor conduct exploratory analyses based on the following three efficacy endpoints (Week6 and Week8):

- Combined abdominal pain and stool frequency score < 75 points
- Both an abdominal pain mean daily score ≤ 1 and a stool frequency mean daily score ≤ 3
- ≥ 50 points decrease from baseline in the combined abdominal pain and stool frequency score

The sponsor's results for the exploratory efficacy endpoints (stool frequency and abdominal pain) based on randomized 627 subjects excluding those enrolled prior to study re-start and site 1127 are shown in Table 9.

Table 9 Sponsor's Results for Additional Analysis Results (Stool Frequency and Abdominal Pain) on Randomized Subjects Excluding Those Enrolled Prior to Study Re-start and Excluding Site 1127 for Study CNTO1275CRD3002 (Total=627)

	Placebo (N=209)	**Ustekinumab 130 mg (N=209)**	**Ustekinumab 6 mg/kg* (N=209)**
WEEK 8 alternative clinical remission and response			
Combined abdominal pain and stool frequency score <75 points			
Number (%)	67 (32.1)	86 (41.1)	111 (53.1)
p-value by CMH test**		0.047	<0.001
Both an abdominal pain mean daily score ≤1 and a stool frequency mean daily score ≤3			
Number (%)	40 (19.1)	58 (27.8)	78 (37.3)
p-value by CMH test**		0.030	<0.001
≥50 point decrease from baseline in the combined abdominal pain and stool frequency score			
Number (%)	68 (32.5)	83 (39.7)	93 (44.5)
p-value by CMH test**		0.110	0.010
WEEK 6 alternative clinical remission and response			
Combined abdominal pain and stool frequency score <75 points			
Number (%)	60 (28.7)	89 (42.6)	106 (50.7)
p-value by CMH test**		0.002	<0.001
Both an abdominal pain mean daily score ≤1 and a stool frequency mean daily score ≤3			
Number (%)	43 (20.6)	60 (28.7)	73 (34.9)
p-value by CMH test**		0.047	<0.001
≥50 point decrease from baseline in the combined abdominal pain and stool frequency score			
Number (%)	58 (27.8)	88 (42.1)	101 (48.3)
p-value by CMH test**		0.001	<0.001

Source: Sponsor's Tables TEFCDAI07, TEFCDAI08 and TEFCDAI09 in cnto1275crd3002-study-report.pdf (pages 179, 180 and 181) *Weight-range based ustekinumab doses approximating 6 mg/kg: 260 mg (weight ≤ 55kg), 390 mg (weight >55 kg and ≤ 85 kg), 520 mg (weight > 85 kg); **stratified by study region (Asia, Eastern Europe, or Rest of World) and CDAI score (≤ 300 or > 300).

3.2.3 Study CNTO1275CRD3003

Study CNTO1275CRD3003 is titled as "A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Maintenance Therapy in Subjects with Moderately to Severely Active Crohn's Disease." The study was conducted from September 13 of 2011 to June 10 of 2015 with 260 study sites worldwide.

3.2.3.1 Study Objective and Study Design

This was a phase 3, multicenter, multinational, randomized, double-blind, placebo-controlled parallel group, stratified study in patients with moderately to severely active Crohn's disease who were in clinical response to IV ustekinumab induction therapy (at Week 8 of the induction studies). The stratification criteria were with clinical remission at Week 0 (yes or no), the induction study (CNTO1275CRD3001 or CNTO1275CRD3002) and ustekinumab induction dose (130 mg or tiered dosing approximating 6 mg/kg ustekinumab) as stratification variables. The primary objective of the study was to evaluate clinical remission for the 2 subcutaneous (SC) maintenance regimens of ustekinumab in subjects with moderately to severely active Crohn's disease induced into clinical response with ustekinumab in the induction studies, CNTO1275CRD3001 and CNTO1275CRD3002 and to evaluate the safety of 2 SC maintenance regimens of ustekinumab in subjects with moderately to severely active Crohn's disease..

The IV induction studies were temporarily suspended by the sponsor in November 2011 because of a stability issue identified with the batch of the IV drug (130 mg ustekinumab in 26 mL [5 mg/mL; (b) (4) mL fill of liquid]) used in the studies. As a consequence of this, this maintenance study was also temporarily suspended. A total of 40 subjects had been randomized in the induction studies prior to the studies being temporarily suspended. Nine of them were included in the study CNTO1275CRD3003.

The primary population for efficacy analyses was subjects with a history of moderately to severely active Crohn's disease who were in clinical response to IV ustekinumab induction therapy (at Week 8 of the induction studies, CNTO1275CRD3001 and CNTO1275CRD3002). Subjects in clinical response to ustekinumab induction dosing were randomized in a 1:1:1 ratio at Week 0 of this maintenance study (Week 8 of induction studies) to receive placebo or 1 of the following SC regimens:

- Group 1: Placebo
- Group 2: Ustekinumab 90 mg SC q12w (with last dose at Week 36)
- Group 3: Ustekinumab 90 mg SC q8w (with last dose at Week 40)

Subjects who were in clinical response to ustekinumab induction in either study CNTO1275CRD3001 or CNTO1275CRD3002 were randomly assigned to 1 of 3 treatment groups (placebo, ustekinumab 90 mg SC q12w, and ustekinumab 90 mg SC q8w) based on a computer-generated randomization schedule prepared before the study under the supervision of the sponsor.

The number of subjects in the primary analysis population was dependent on the number of subjects in clinical response to ustekinumab at Week 8 in the induction studies who consented to participate in the maintenance study. Assuming clinical response rates of 35% and 40% in the 2 ustekinumab dose groups in the CNTO1275CRD3001 study, and clinical response rates of 45% and 50% in the CNTO1275CRD3002 study, and an assumption of 10% dropout rate, approximately 322 responders (approximately 107 per treatment group) were predicted to enter into the maintenance study. Note that this calculation excludes the subjects who were randomized in the induction studies prior to them being placed on hold by the sponsor in November 2011.

Regarding the sample size planning, with a total of 322 responders – 107 per treatment group, the power of the study was estimated to be 90%. These calculations assumed a Week 44 clinical remission rate of 35% in the ustekinumab 90 mg q8w group, and 15% in the placebo group.

3.2.3.2 Efficacy Endpoints and Analyses

The primary endpoint was clinical remission at Week 44. Clinical remission was defined as a CDAI score of <150 points.

A fixed sequence testing procedure was used to control the overall Type I error rate at the 0.05 level for the comparisons of the 2 ustekinumab dose groups with the placebo group for the primary endpoint. Therefore, the sample size/power calculations were based on the chi-square test (2-sided) for detecting a significant difference between subjects receiving the high dose (tiered dosing approximating ustekinumab 6 mg/kg) and those receiving placebo.

The following list the order of the testing that was performed within Study CNTO1275CRD3003. Testing continued to the next endpoint in the list, provided the preceding endpoint was significant.

- Clinical remission at Week 44 in the ustekinumab high dose group (90 mg SC q8w)
- Clinical response at Week 44 in the ustekinumab high dose group (90 mg SC q8w)
- Clinical remission at Week 44 (among subjects in clinical remission at Week 0 maintenance) in the ustekinumab high dose group (90 mg SC q8w)
- Clinical remission at Week 44 in the ustekinumab low dose group (90 mg SC q12w)
- Clinical response at Week 44 in the ustekinumab low dose group (90 mg SC q12w)
- Clinical remission at Week 44 (among subjects in clinical remission at Week 0 maintenance) in the ustekinumab low dose group (90 mg SC q12w)
- Corticosteroid-free remission at Week 44 in the ustekinumab high dose group (90 mg SC q8w) Corticosteroid-free remission at Week 44 in the ustekinumab low dose group (90 mg SC q12w)
- Clinical remission at Week 44 (among subjects who were refractory or intolerant to
- TNF-antagonist therapy) in the ustekinumab high dose group (90 mg SC q8w)
- Clinical remission at Week 44 (among subjects who were refractory or intolerant to
- TNF-antagonist therapy) in the ustekinumab low dose group (90 mg SC q12w)

Subjects who had any of the following events prior to Week 44 were not considered to be in clinical remission for the primary endpoint analysis, regardless of the actual CDAI score:

- A Crohn's disease-related surgery due to lack of efficacy of study agent (with the exception of minor procedures such as drainage of a superficial abscess or seton placement).
- Discontinuation of study agent due to lack of efficacy or due to an AE of worsening Crohn's disease.
- Loss of clinical response, defined as a CDAI score ≥220 points AND a ≥100 point increase from the Week 0 CDAI score (i.e., Week 8 in the induction study

CNTO1275CRD3001 or CNTO1275CRD3002), which was assessed between Week 8 and Week 32 in IVRS.

- Specified changes in concomitant Crohn's disease medications

In addition, subjects who did not return for evaluation or had insufficient data to assess their clinical remission status at Week 44 (i.e., <4 components of the CDAI are available) were also considered to not have achieved clinical remission.

The primary efficacy analysis was based on the 2-sided stratum adjusted Cochran-Mantel-Haenszel (CMH) method on the proportion of patients in clinical remission at Week 44. The model included clinical remission status at Week 0 (yes or no), ustekinumab induction dose (130 mg or tiered dosing approximating ustekinum 6 mg/kg), and induction study (CNTO1275CRD3001 or CNTO1275CRD3002). To control the overall Type I error rate, the primary endpoint was tested in a fixed sequence. Specifically, the ustekinumab 90 mg SC q8w group was first compared with the placebo group at the 2-sided 0.05 level of significance. If the ustekinumab 90 mg SC q8w group was significantly different from the placebo group, then the ustekinumab 90 mg SC q12w group was compared with the placebo group at the 2-sided 0.05 level of significance.

Reviewer's Note:
The FDA stated "In addition, we strongly recommend that you pre-specify exploratory analyses that evaluate definitions of clinical remission without the CDAI. For example, this could include a definition based on abdominal pain (AP) and frequency of loose/watery stools (SF) (both components of the CDAI)." This explained the importance of assessing the second major secondary efficacy endpoint and exploring alternative clinical remission/response based on abdominal pain and frequency of loose/watery stools for Studies CNTO1275CRD3001 and CNTO1275CRD3002. Note that similar analyses were not conducted for the maintenance study.

3.2.3.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 397 subjects were randomly assigned to receive study agent. Unless otherwise specified, analyses discussed in this section are based on the 388 subjects who were randomized after the study was restarted and also ustekinumab responders at Week 8, at 137 sites in Asia (7.3%), Eastern Europe (18.4%), and other countries (74.3%) in North America and Western Europe, and countries including Israel, South Africa, Australia, New Zealand, and Brazil. Tables 10 and11 display the number of patients randomized into each treatment group, patient disposition, the reasons for early discontinuation and baseline demographics.

Table 10 Patient Disposition for Study CNTO1275CRD3003 Exclude Those Enrolled Prior to Study Restart (Total=397)

	Placebo n (%)	**Ustekinumab 90mg q12w n (%)**	**Ustekinumab 90mg q8w n (%)**
Randomized	133 (100)	132 (100)	132 (100)
Never treated	0 (0.0)	0 (0.0)	1 (0.8)
Treated	133 (100)	132 (100)	131 (99.2)
Subjects who discontinued study agent prior to Week 44	31 (23.3)	29 (22.0)	30 (22.7)
Reason for discontinuation			
Adverse event	9 (6.8)	12 (9.1)	6 (4.5)
Death	0 (0.0)	0 (0.0)	0 (0.0)
Lack of efficacy	15 (11.3)	14 (10.6)	15 (11.4)
Protocol violation	0 (0.0)	1 (0.8)	1 (0.8)
Study terminated by sponsor	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow up—not due to lack of efficacy or AE	1 (0.8)	0 (0.0)	1 (0.8)
Withdrawal of consent for administration of study agent – not due to lack of efficacy or AE	6 (4.5)	2 (1.5)	7 (5.3)

Source: Sponsor's Table TSIDS03A of cnto1275crd3003-study-report.pdf

Table 11 Patients' Baseline Demographics based on Randomized Subjects Excluding Those Enrolled Prior to Study Re-start for Study CNTO1275CRD3002 (Total=397)

Parameter	**Placebo (N=133)**	**Ustekinumab 130 mg (N=132)**	**Ustekinumab6 mg/kg (N=132)**
Gender			
Male	59 (44.4%)	58 (43.9%)	56 (42.4%)
Female	74 (55.6 %)	74 (56.1%)	76 (57.6%)
Age (years), mean (SD)	39.5 (12.7)	38.6 (13.7)	37.9 (13.2)
Weight (kg), mean (SD)	72.3 (17.3)	70.0 (19.6)	70.6 (16.9)
Race			
White	115 (86.5%)	111 (84.1%)	111 (84.1%)
African American	5 (3.8%)	5 (3.8%)	3 (2.3%)
Asian	7 (5.3%)	12 (9.1%)	13 (9.8%)
Other	2 (1.5%)	2 (1.5%)	4 (3.0%)
Not reported	2 (1.5%)	2 (1.5%)	1 (0.8%)
Unknown	2 (1.5%)	0 (0.0%)	0 (0.0%)

Source: Sponsor's TSIDEM02A of cnto1275crd3003-study-report.pdf

3.2.3.4 Sponsor's Efficacy Results & Conclusions

The primary endpoint was clinical remission at Week 44 was defined as Week 44 CDAI score < 150 points. The sponsor's results for all primary and secondary efficacy endpoints based on randomized 388 subjects excluding those enrolled prior to study re-start are shown in Table 12.

Table 12 Sponsor's Results for Primary and Secondary Efficacy Endpoints on Randomized Subjects (Week 8 Ustekinumab responders) Excluding Those Enrolled Prior to Study Re-start (Total=388)

	Placebo SC (N=131)	Ustekinumab 90 mg SC q12w (N=129)	Ustekinumab 90 mg SC q8w (N=128)
Primary efficacy endpoint (clinical remission at Week 44)			
Number (%)	47 (35.9)	63 (48.8)	68 (53.1)
p-value by CMH test**		0.040	0.005
Four ranked key secondary efficacy endpoints			
1. Clinical response at Week 44			
Number (%)	58 (44.3)	75 (58.1)	76 (59.4)
p-value by CMH test**		0.033	0.018
2. Clinical remission at Week 44 among Week 8 remitters			
	Placebo SC (N=79)	**Ustekinumab 90 mg SC q12w (N=78)**	**Ustekinumab 90 mg SC q8w (N=78)**
Number (%)	36 (45.6)	44 (56.4)	52 (66.7)
p-value by CMH test**		0.189*	0.007
3. Corticosteroid-free remission at Week 44			
Number (%)	39 (29.8)	55 (42.6)	60 (46.9)
p-value by CMH test**		0.035	0.004
4. Clinical remission at Week 44 in the subset of subjects who were refractory or intolerant to TNF antagonist therapy			
	Placebo SC (N=61)	**Ustekinumab 90 mg SC q12w (N=57)**	**Ustekinumab 90 mg SC q8w (N=56)**
Number (%)	16 (26.2)	22 (38.6)	23 (41.1)
p-value by CMH test**		0.140	0.102

Source: Sponsor's Tables 5, 6, 7, 8 and 9 in cnto1275crd3003-study-report.pdf (Pages 85, 88, 89, 90 and 91) *Based on the pre-specified fixed testing sequence, it failed at this endpoint for low dose and 3rd & 4th secondary efficacy endpoints should not be tested; **stratified by clinical remission status at Week 0 (yes or no), ustekinumab induction dose (130 mg or tiered dosing approximating ustekinumab 6 mg/kg), and the induction study (CNTO1275CRD3001 or CNTO1275CRD3002) at a significance level of 0.05.

The sponsor's summary is that "Study CNTO1275CRD3003 was a positive study demonstrating efficacy in the maintenance of clinical response and remission at Week 44 for both the ustekinumab SC 90 mg q12w and 90 mg q8w dose regimens. The totality of the data, including robustness of the primary endpoint, supports q8w dosing as the primary regimen. This q8w regimen had larger treatment effects than the q12w regimen across many of the endpoints."

Of 397 randomized subjects in the primary population, 22.7% (90 subjects) discontinued study agent prior to Week 44. The proportions of subjects who discontinued study agent were similar across treatment groups (23.3%, 22.0%, and 22.7% in the placebo SC and ustekinumab 90 mg SC 12w, and q8w groups, respectively). The most common reasons for discontinuation of study agent among subjects in the primary population were lack of efficacy or an AE.

The sponsor performed many sensitivity analyses of the primary endpoint using the observed case, last observation carried forward, multiple imputation, and the worst case missing data methods. Sensitivity analyses were robust for the q8w dosing regimen (i.e., all but the worst-case analysis were significant); however, while treatment effects were in the same direction and of generally similar magnitude to those in the primary analysis, the sensitivity analyses for the q12w regimen were generally not significant. These results are shown in Table 34 of the Appendix.

3.2.4 Ustekinumab Endoscopic Substudy

Ustekinumab endoscopy substudy was a dedicated study aimed at demonstrating and quantifying endoscopic healing of the mucosa in the Phase 3 development program for ustekinumab in Crohn's disease.

3.2.4.1 Study Objective and Study Design

The primary objectives of the endoscopy substudy were to conduct a systematic and comprehensive evaluation of:

- The efficacy of ustekinumab compared with placebo to induce endoscopic healing of the mucosa.
- The benefit of continued ustekinumab maintenance compared with placebo on the achievement of endoscopic healing of the mucosa among subjects who had a clinical response to ustekinumab induction.

Subjects from participating sites within the Phase 3 development program could consent to participate in the endoscopy substudy and undergo endoscopic assessments at screening (induction baseline), at the end of the induction study (Week 8 of induction), and at the end of the maintenance study (Week 44 of maintenance). A single reader at a central facility evaluated and scored all video endoscopies in a blinded manner. Two measures were used for the evaluation of endoscopic healing of the mucosa: changes in the Simplified Endoscopic Disease Severity Score for Crohn's Disease (SES-CD) score and detection of presence/absence of mucosal ulceration. In addition, biopsies were collected to support exploratory histologic evaluation.

The primary analysis population for endoscopy endpoints in induction was the integrated induction population from the CNTO1275CRD3001 and CNTO1275CRD3002 induction studies, and data for ustekinumab were pooled across the induction dose groups. The primary analysis population for endoscopy endpoints in maintenance was the randomized maintenance population in the CRD3003 maintenance study (i.e., ustekinumab induction responders who were randomized to ustekinumab 90 mg SC every 12 weeks (q12w), ustekinumab 90 mg SC every 8 weeks (q8w), or placebo maintenance); data for ustekinumab were pooled across maintenance dose groups.

It was estimated about 210 randomized subjects from CNTO1275CRD3001 and CNTO1275CRD3002 study had eligible endoscopy data at baseline. Assuming a change in SESCD score of -2 (SD ±7) at Week 8 in the placebo group and -5 (SD ±7) in the ustekinumab

group, 70 subjects in placebo and 140 subjects in ustekinumab treatment group will yield an overall power approximately 80%, at a significance level of 0.05 (2-sided).
The power for detecting a significant difference between ustekinumab and placebo was also examined for the first major secondary endpoint of change in SES-CD score from induction baseline at Week 44 of CNTO1275CRD3003 study. It was estimated about 80 of the 210 subjects with eligible endoscopy data at baseline were in clinical response at week 8 of induction. Assuming 75% of these subjects were in ustekinumab treatment groups (based on clinical response rate assumption in the sample size estimation in CNTO1275CRD3001 and CNTO1275CRD3002), then 60 subjects were in the primary population in CNTO1275CRD3003.

Assuming a change in SES-CD score of -4 (SD ±6.5) at Week 44 in the placebo group and -10 (SD ±9) in the ustekinumab group, 20 subjects in placebo and 40 subjects in ustekinumab treatment group will yield an overall power of approximately 80% for the first major secondary endpoint of change in SES-CD score at Week 44, at a significance level of 0.05 (2-sided).

3.2.4.2 Efficacy Endpoints and Analyses

The primary endpoint was the change from baseline in SES-CD score at Week 8 in subjects with eligible endoscopy data at baseline from the pooled CNTO1275CRD3001 and CNTO1275CRD3002 studies.

The following are the major secondary endpoints, which are presented in the order in which they will be tested:

1. The change from baseline of the induction study in the SES-CD score at Week 44 in CNTO1275CRD3003 in subjects with eligible endoscopy data at baseline of induction.
2. The proportion of subjects with mucosal healing at Week 44 in CNTO1275CRD3003 in subjects with ulcerations at baseline of the induction study.
3. The proportion of subjects with mucosal healing at Week 8 in subjects with ulcerations at baseline from pooled CNTO1275CDR3001 and CNTO1275CRD3002.

The following subgroups will be evaluated for the primary endpoint in this study:

- By individual study (CNTO1275CRD3001, CNTO1275CRD3002)
- By induction dose (ustekinumab 130 mg, ustekinumab 6 mg/kg)

<u>Treatment failure rules:</u>
Treatment failure rules will be applied for all endoscopy endpoints and will be applied separately in induction and maintenance. If a treatment failure event occurred during induction, baseline values for SES-CD score (at Week 0 of induction) will be assigned for Week 8 of induction, regardless of the observed data, and subjects will be considered as not achieving mucosal healing at Week 8 of induction. If a treatment failure event occurred during maintenance, baseline values for SES-CD score (at Week 0 of induction) will be assigned for Week 44 of maintenance, regardless of the observed data, and subjects will be considered as not achieving mucosal healing at Week 44 of maintenance. Treatment failure rules override other data handling rules.

Subjects who have any of the following events will be considered to be a treatment failure from

the time of the event, regardless of the actual endoscopy assessment:

- A Crohn's disease-related surgery thought to be a result of lack of efficacy of study agent (with the exception of minor procedures such as drainage of a superficial abscess or seton placement).
- An initiation of any of the following prohibited medications after Week 0 of induction or maintenance due to worsening Crohn's disease:
    a. Immunomodulatory agents other than 6-MP/AZA or MTX (including but not limited to 6-TG, cyclosporine, tacrolimus, sirolimus, mycophenolate mofetil).
    b. Immunomodulatory biologic agents (including but not limited to TNF-antagonists, natalizumab, vedolizumab, abatacept).
    c. Experimental Crohn's disease medications (including but not limited to thalidomide, briakinumab, traficet, AMG-827).
- For endoscopy endpoints in CNTO1275CRD3003, the following event will also be considered to be a treatment failure from the time of the event through Week 44, regardless of the actual endoscopy assessment.
    - Loss of clinical response, defined as a CDAI score ≥ 220 points AND a ≥ 100 point increase from the Week 0 CDAI score (i.e., Week 8 in the induction study CNTO1275CRD3001 or CNTO1275CRD3002).
    - Of note, this corresponds to the protocol-specified trigger for cross-over back to active ustekinumab treatment in subjects assigned to placebo maintenance. So as not to introduce bias, this criterion is applied to all maintenance treatment groups equally.

Missing data rules:

The SES-CD score at baseline will be calculated based on all segments scored at baseline. The SES-CD score at post-baseline visit(s) will be calculated based on segments scored at baseline only. Segments that are scored only at post-baseline visit(s) will be excluded, since it is not possible to evaluate the improvement in a segment without a baseline measurement. For missing segments at post-baseline visit(s), the baseline score for each of the missing segments will be carried forward.

The determination of ulceration status at baseline and post baseline visit(s) will be based on the presence or absence of ulceration across all segments evaluated at that visit. Furthermore, at post-baseline visit(s), any segments that are not evaluated or missing will have their ulceration status at baseline carried forward, if available. Segments that are scored only at post-baseline visit(s) will be included in the determination of the ulceration status at that visit.

The endoscopic substudy will be considered positive if the combined ustekinumab treatment group is significantly different from the placebo group for the primary endpoint.

Reviewer's Note:

In May 12 2015 pre-BLA meeting minutes, the FDA recommended endoscopic substudy data from the two induction trials (CNTO1275CRD3001 and CNTO1275CRD3002) be analyzed separately first, before any statistical inference is made for the pooled data from both studies. The FDA was open to reviewing more detailed justification for pooling the endoscopic

substudy data. The FDA recommended the sponsor submit their Statistical Analysis Plan (SAP) as soon as possible, and prior to the BLA submission.

To control the overall Type I error rate, the FDA recommended the sponsor either perform a sequential test by testing the overall population first and then the subset, or split alpha level for these two tests. In addition, the FDA suggested the sponsor propose another procedure for controlling multiplicity due to multiple doses. Whether or not pooling the endoscopic substudy data to assess endoscopic endpoints, as proposed, valid and interpretable results will be a review issue. Of note, in the SAP (November 07 2015) submitted by the sponsor, no multiplicity procedure was proposed to control overall type I error. In addition, the sponsor did not incorporate FDA's recommendations into the SAP.

3.2.4.3 Patient Disposition, Demographic and Baseline Characteristics

Nearly 90% (252/289) of subjects from Studies CNTO1275CRD3001 and CNTO1275CRD3002 with evaluable endoscopy data had eligible SES-CD scores or ulceration at baseline. Tables 13-16 display the number of patients randomized into each treatment group, patient disposition and demographics.

Table 13 Summary of Endoscopy Information at Baseline: Randomized Subjects Enrolled in the Endoscopy Substudy from the CNTO1275CRD3001 and CNTO1275CRD3002 Studies

	Placebo n	Ustekinumab 130mg and 6 mg/kg combined n
Randomized	124	210
Subjects with evaluable endoscopy data	104	185
Subjects with eligible SES-CD score or ulcerations	97 (93.3%)	155 (87.2%)
Subjects who had eligible SES-CD score at baseline	97	155
Subjects who had ulcerations at baseline	97	155

Source: Sponsor's Table 3 of endoscopy-substudy-report.pdf

Table 14 Summary of Endoscopy Information at Baseline: Randomized Subjects Enrolled in the Endoscopy Substudy from the CNTO1275CRD3003 Study

	Placebo n	Ustekinumab 130mg and 6 mg/kg combined
Randomized	32	63
Subjects with evaluable endoscopy data	29	54
Subjects with eligible SES-CD score or ulcerations	24 (82.8%)	46 (85.2%)
Subjects who had eligible SES-CD score at baseline	24	46
Subjects who had ulcerations at baseline	24	46

Source: Sponsor's Table 10 of endoscopy-substudy-report.pdf

Table 15 Patients' Baseline Demographics based on Randomized Subjects with Eligible SES-CD Score or Ulcerations at Baseline From CNTO1275CRD 3001 and CNTO1275CRD 3002 Studies (Total=252)

Parameter	Placebo (N=97)	Ustekinumab 130 mg and 6 mg/kg combined (N=155)
Gender		
Male	51 (52.6%)	68 (43.9%)
Female	46 (47.4 %)	87 (56.1%)
Age (years), mean (SD)	40.2 (13.6)	40.3 (12.9)
Weight (kg), mean (SD)	76.6 (17.7)	72.4 (17.2)
Race		
White	82 (84.5%)	128 (82.6%)
African American	5 (5.2%)	11 (7.1%)
Asian	5 (5.2%)	7 (4.5%)
American Indian or Alaska Native	0 (0.0%)	1 (0.6%)
Other	5 (5.2%)	4 (2.6%)
Not reported	0 (0.0%)	4 (2.6%)
Unknown	0 (0.0%)	0 (0.0%)

Source: Sponsor's Table 5 of endoscopy-substudy-report.pdf

Table 16 Patients' Baseline Demographics based on Randomized Subjects with Eligible SES-CD Score or Ulcerations at Baseline From CNTO1275CRD 3003 Study (Total=70)

Parameter	Placebo (N=24)	Ustekinumab 130 mg and 6 mg/kg combined (N=46)
Gender		
Male	12 (50.0%)	17 (37.0%)
Female	12 (50.0%)	29 (63.0%)
Age (years), mean (SD)	40.5 (12.1)	39.5 (14.5)
Weight (kg), mean (SD)	72.4 (15.5)	73.4 (16.5)
Race		
White	16 (66.7%)	37 (80.4%)
African American	3 (12.5%)	1 (2.3%)
Asian	3 (12.5%)	4 (8.7%)
American Indian or Alaska Native	0 (0.0%)	0 (0.0%)
Other	0 (0.0%)	3 (6.5%)
Not reported	2 (8.3%)	1 (2.2%)
Unknown	0 (0.0%)	0 (0.0%)

Source: Sponsor's Table 12 of endoscopy-substudy-report.pdf

3.2.4.3 Sponsor's Efficacy Results & Conclusions

The primary endpoint was the change from baseline in SES-CD score at Week 8 in subjects with eligible endoscopy data at baseline from the pooled CNTO1275CRD3001 and CNTO1275CRD3002 studies. The sponsor's results for all primary and secondary efficacy endpoints based on randomized subjects with eligible endoscopy data at baseline are shown in Table 17.

Table 17 Sponsor's Results for Primary and Secondary Efficacy Endpoints on Randomized Subjects with Eligible SES-CD Scores or Ulceration at Baseline (N=252 or 70)

	Placebo SC (N=97)	Ustekinumab* (N=155)
Primary efficacy endpoint (change from baseline in SES-CD score at Week 8) * **		
Mean (SD)	-0.7 (4.97)	-2.8 (5.68)
p-value		0.012

Primary efficacy endpoint by individual study * **				
	CNTO1275CRD3001		**CNTO1275CRD3002**	
	Placebo SC (N=41)	**Ustekinumab* (N=66)**	**Placebo SC (N=56)**	**Ustekinumab* (N=89)**
Mean (SD)	0.2 (3.24)	-2.3 (5.22)	-1.4 (5.85)	-3.1 (6.00)
p-value		0.010		0.234

Primary efficacy endpoint by induction dose * **			
	Placebo (N=97)	**Ustekinumab 130 mg (N=72)**	**Ustekinumab 6 mg/kg (N=83)**
Mean (SD)	-0.7 (4.97)	-2.5 (6.15)	-3.0 (5.26)
p-value		0.096	0.009

Three ranked key secondary efficacy endpoints		
1. Change from baseline in SES-CD score at Week 44 of maintenance		
	Placebo SC (N=24)	**Ustekinumab** (N=46)**
Mean (SD)	-1.9 (4.06)	-2.5 (3.73)
p-value		0.176
2. Mucosal healing at Week 44		
Number (%)	1 (4.2%)	6 (13.0%)
p-value		0.409
3. Mucosal healing at Week 8		
	Placebo SC (N=97)	**Ustekinumab* (N=155)**
Number (%)	4 (4.1%)	14 (9.0%)
p-value		0.141

Source: Sponsor's Tables 15, 16, 17, 18, 19 and 20 in endoscopy-substudy-report.pdf (Pages 48, 50, 52, 51 54 and 55) *Ustekinumab 130 mg and 6 mg/kg combined.; ** Ustekinumab 90 mg q12w and q8w combined.; ***Subjects with missing segments at the designated analysis time point had their baseline score for the missing segment(s) carried forward and subjects who, prior to the designated analysis time point, had a Crohn's disease-related surgery due to lack of efficacy or had an initiation of specified prohibited medication had their baseline value carried forward.

[redacted] (b) (4) The primary endpoint, reduction from baseline in SES-CD score at Week 8 of induction, was met and confirmed that ustekinumab induction is more effective in reducing endoscopic disease activity compared with placebo. The significant reductions in endoscopic disease activity were corroborated by reductions in the underlying histologic inflammation.

3.2.5 Statistical Reviewer's Findings and Comments

1. (Re-Analysis Results for Ustekinumab Endoscopic Substudy) the statistical reviewer confirmed the sponsor's analysis results for the primary and secondary endpoints based on total of 252 patients in the clinical study report.

Recall that there are 40 patients with stability issues were excluded from the primary analysis populations for the three pivotal studies. The statistical reviewer performed analyses based on both 252 and 239 patients after excluding those enrolled prior to study re-start without combining two dose groups as one. In addition, the analyses of maintenance Week 44 efficacy endpoints were conducted based on pooled induction Studies (CNTO1275CRD3001 and CNTO1275CRD3002) by using either CMH test stratified by study or ANCOVA with baseline SES-CD, study and induction doses as covariates. The analyses of induction Week 8 efficacy endpoints were conducted based on combined induction studies and each induction study, separately.

Of note, the sponsor had been notified that endoscopic substudy data from the two induction studies (CNTO1275CRD3001 and CNTO1275CRD3002) should be analyzed separately first, before any statistical inference can be made for the pooled data from both studies. They were also notified that to control the overall Type 1 error rate, either a sequential test by testing the overall population first and then the subset, or split alpha level for these two tests should be performed besides controlling multiplicity due to multiple doses . However, the detailed multiplicity procedure was not specified in neither of the protocol and SAP.

As we have three populations (combined two induction studies and each one of them) with two dose groups, in order to control overall type I error, a pre-specified testing procedure needs be proposed and agreed upon. Without that, the sponsor's conclusion would be changed by different testing procedures. For example, we may consider splitting alpha level of 0.05 into 0.025 for each dose group. In order to pool the trials, both induction trials need to win on either dose. Now, based on reviewer's results of each induction study without combining two dose groups as one (not shown in this review), it failed for high dose group (90 mg q8w) for Study CNTO1275CRD3001 at significance level of 0.025. Therefore, data from doses cannot be pooled to make inference as trials are heterogeneous.

2. (Sensitivity Analysis Results for Studies CNTO1275CRD3001, CNTO1275CRD3001 and CNTO1275CRD3003)

To further investigate the protocol inclusion criteria violation (baseline CDAI score between 220 and 450 inclusively), fifty eight patients (32 from CNTO1275CRD3001 and 26 from CNTO1275CRD3002), 6 misclassified responders in the maintenance study and misclassification due to using Week 8 Hematocrit instead of Week 6 Hematocrit for calculation of the CDAI at maintenance baseline were excluded, the statistical reviewer performed the sensitivity analyses for all three pivotal studies.

Based on the statistical reviewer's sensitivity analyses results (not shown in this review), we

concluded that the impact of inclusion criteria violation and misclassification on the efficacy of ustekinumab in the two doses should not be a concern although not all the efficacy results shown for the Ustekinumab 90mg q8w and 12w are statistically significant.

3. (Additional analyses for Study CNTO1275CRD3003) To ensure the robustness of the efficacy findings, the statistical reviewer also conducted post-hoc analysis based on Week 8 clinical responders for the efficacy endpoint: proportion of patients who achieved clinical remission for at least 80% of visits (from Week 0 through Week 44) at maintenance stage to determine whether remission was "maintained" throughout the 44-week study. As seen in Table 36 in appendix, only the proportion of the remitters in high dose group (90 mg q8w) is statistically significant higher than those of placebo group.

4. (Efficacy Findings for Study CNTO1275CRD3001 and CNTO1275CRD3002) The statistical reviewer confirmed the sponsor's analysis results for the primary endpoint and four major secondary endpoints. We concluded that the study data support the superiority of ustekinumab over placebo for all primary and four major secondary efficacy endpoints of induction phase.

5. (Efficacy Results for Study CNTO1275CRD3003) The statistical reviewer confirmed the sponsor's analysis results for the primary endpoint and four major secondary endpoints. The superiority only won over placebo for primary efficacy endpoint of clinical remission at Week 44, first secondary efficacy endpoint of clinical response at Week 44 and high dose group for the second secondary efficacy endpoint of clinical remission at Week 44 among Week 8 remitters for maintenance phase.

6. (**US Results for Study CNTO1275CRD3003**) Although this study demonstrated significant treatment effect of utekinumab 90 mg q8w for primary (clinical remission at Week 44), first (clinical response at Week 44) and second (clinical remission at Week 44 among Week 8 remitters) major secondary efficacy endpoints and utekinumab 90 mg q12w for primary and first major secondary efficacy endpoints. This reviewer would like to note that Study CNTO1275CRD3003 was conducted worldwide with 29% (114 out of 388) of patients from the U.S. and the observed treatment difference between the study drug and placebo in the U.S. was not consistent with the rest of the world (see Table 35 of appendix).

3.3. Evaluation of Safety

The safety evaluation is not conducted in this review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1. Gender, Race, Age, Baseline CDAI Scores, Studies and Geographic Region

4.1.1 For Study CNTO1275CRD3001

The following Tables 18 to 22 present the statistical reviewer's subgroup analysis results for the primary and four major secondary efficacy endpoints. Of note, the sponsor only

provided odds ratios of each ustekinumab dose group versus placebo and corresponding 95% confidence intervals for each subgroups.

Table 18 Statistical Reviewer's Gender Subgroup Analysis Results for Primary and Secondary Efficacy Endpoints on Randomized Subjects Excluding Those Enrolled Prior to Study Re-start (Total=741)

	Placebo SC N=247	**Ustekinumab 130 mg N=245**	**Ustekinumab 6 mg/kg N=249**
Female (N)	N=129	N=147	N=148
Primary efficacy endpoint (clinical response at Week 6)			
Number (%)	28 (21.7%)	52 (35.4%)	59 (39.9%)
Difference from placebo		13.7%	18.2%
1. *Clinical remission at Week 8*			
Number (%)	7 (5.4%)	22 (15.0%)	34 (23.0%)
Difference from placebo		9.6%	17.6%
2. *Clinical response at Week 8*			
Number (%)	21 (16.3%)	49 (33.3%)	59 (39.9%)
Difference from placebo		17.0%	23.6%
3. *70-point response at Week 6*			
Number (%)	39 (30.2%)	69 (46.9%)	72 (48.7%)
Difference from placebo		16.7%	18.5%
4. *70-point response at Week 3*			
Number (%)	40 (31.0%)	63 (42.9%)	64 (43.2%)
Difference from placebo		11.9%	12.2%
Male (N)	N=118	N=98	N=101
Primary efficacy endpoint (clinical response at Week 6)			
Number (%) of Subjects	25 (21.2%)	32 (32.7%)	25 (24.8%)
Difference from placebo		11.5%	3.6%
1. *Clinical remission at Week 8*			
Number (%)	11 (9.3%)	17 (17.4%)	18 (17.8%)
Difference from placebo		8.1%	8.5%
2. *Clinical response at Week 8*			
Number (%) of Subjects	29 (24.6%)	33 (33.7%)	35 (34.7%)
Difference from placebo		9.1%	10.1%
3. *70-point response at Week 6*			
Number (%) of Subjects	36 (30.5%)	44 (44.9%)	37 (36.6%)
Difference from placebo		14.4%	6.1%
4. *70-point response at Week 3*			
Number (%)	27 (22.9%)	31 (31.6%)	37 (36.6%)
Difference from placebo		8.7%	13.7%

Table 19 Statistical Reviewer's Age Subgroup Analysis Results for Primary and Secondary Efficacy Endpoints on Randomized Subjects Excluding Those Enrolled Prior to Study Re-start (Total=741)

	Placebo SC N=247	Ustekinumab 130 mg N=245	Ustekinumab 6 mg/kg N=249
Age ≤ median age (36)	N=130	N=122	N=129
Primary efficacy endpoint (clinical response at Week 6)			
Number (%)	21 (16.2%)	42 (34.4%)	40 (31.0%)
Difference from placebo		18.2%	14.8%
1. *Clinical remission at Week 8*			
Number (%)	8 (6.2%)	20 (16.4%)	25 (19.4%)
Difference from placebo		10.2%	13.2%
2. *Clinical response at Week 8*			
Number (%)	23 (17.7%)	43 (35.3%)	43 (33.3%)
Difference from placebo		17.6%	15.6%
3. *70-point response at Week 6*			
Number (%)	30 (23.1%)	58 (47.5%)	51 (39.5%)
Difference from placebo		24.4%	16.4%
4. *70-point response at Week 3*			
Number (%)	32 (24.6%)	46 (37.7%)	53 (41.1%)
Difference from placebo		13.1%	16.5%
Age > median age (36)	N=117	N=123	N=120
Primary efficacy endpoint (clinical response at Week 6)			
Number (%)	32 (27.4%)	42 (34.2%)	44 (36.7%)
Difference from placebo		6.8%	9.3%
1. *Clinical remission at Week 8*			
Number (%)	10 (8.6%)	19 (15.5%)	27 (22.5%)
Difference from placebo		6.9%	13.9%
2. *Clinical response at Week 8*			
Number (%)	27 (23.1%)	39 (31.7%)	51 (42.5%)
Difference from placebo		8.6%	19.4%
3. *70-point response at Week 6*			
Number (%)	45 (38.5%)	55 (44.7%)	58 (48.3%)
Difference from placebo		6.2%	9.8%
4. *70-point response at Week 3*			
Number (%)	35 (29.9%)	48 (39.0%)	48 (40.0%)
Difference from placebo		9.1%	10.1%

Table 20 Statistical Reviewer's Race Subgroup Analysis Results for Primary and Secondary Efficacy Endpoints on Randomized Subjects Excluding Those Enrolled Prior to Study Re-start (Total=741)

	Placebo SC N=247	Ustekinumab 130 mg N=245	Ustekinumab 6 mg/kg N=249
White	N=210	N=202	N=211
Primary efficacy endpoint (clinical response at Week 6)			
Number (%)	43 (20.5%)	68 (33.7%)	74 (35.1%)
Difference from placebo		13.2%	14.6%
1. *Clinical remission at Week 8*			
Number (%)	14 (6.7%)	31 (15.4%)	44 (20.9%)
Difference from placebo		8.7%	14.2%
2. *Clinical response at Week 8*			
Number (%)	38 (18.1%)	67 (33.2%)	81 (38.4%)
Difference from placebo		15.1%	20.3%
3. *70-point response at Week 6*			
Number (%)	61 (29.1%)	94 (46.5%)	94 (44.6%)
Difference from placebo		17.4%	15.5%
4. *70-point response at Week 3*			
Number (%)	53 (25.2%)	77 (38.1%)	87 (41.0%)
Difference from placebo		2.9%	15.8%
Non-white	N=37	N=43	N=38
Primary efficacy endpoint (clinical response at Week 6)			
Number (%)	10 (27.0%)	16 (37.2%)	10 (26.3%)
Difference from placebo		10.2%	-0.7%
1. *Clinical remission at Week 8*			
Number (%)	4 (10.8%)	8 (18.6%)	8 (21.1%)
Difference from placebo		7.8%	10.3%
2. *Clinical response at Week 8*			
Number (%)	12 (32.4%)	15 (34.9%)	13 (34.2%)
Difference from placebo		2.5%	1.8%
3. *70-point response at Week 6*			
Number (%)	14 (37.8%)	19 (44.2%)	15 (39.5%)
Difference from placebo		6.4%	1.7%
4. *70-point response at Week 3*			
Number (%)	14 (37.8%)	17 (39.5%)	14 (36.8%)
Difference from placebo		1.7%	-1.0%

Table 21 Statistical Reviewer's Geographic Region Subgroup Analysis Results for Primary and Secondary Efficacy Endpoints on Randomized Subjects Excluding Those Enrolled Prior to Study Re-start (Total=741)

	Placebo SC N=247	Ustekinumab 130 mg N=245	Ustekinumab 6 mg/kg N=249
Rest of World	N=220	N=218	N=220
Primary efficacy endpoint (clinical response at Week 6)			
Number (%)	47 (21.4%)	73 (33.5%)	75 (34.1%)
Difference from placebo		12.1%	12.7%
1. *Clinical remission at Week 8*			
Number (%)	16 (7.3%)	33 (15.1%)	45 (20.5%)
Difference from placebo		7.8%	13.2%
2. *Clinical response at Week 8*			
Number (%)	41 (18.6%)	73 (33.5%)	81 (36.8%)
Difference from placebo		14.9%	18.2%
3. *70-point response at Week 6*			
Number (%)	66 (30.0%)	100 (45.9%)	95 (43.2%)
Difference from placebo		15.9%	13.2%
4. *70-point response at Week 3*			
Number (%)	60 (27.3%)	81 (37.2%)	90 (40.9%)
Difference from placebo		9.9%	13.6%
Asia	N=19	N=19	N=21
Primary efficacy endpoint (clinical response at Week 6)			
Number (%)	5 (26.3%)	7 (36.8%)	6 (28.6%)
Difference from placebo		10.5%	2.3%
1. *Clinical remission at Week 8*			
Number (%)	2 (10.5%)	2 (10.5%)	5 (23.8%)
Difference from placebo		0.0%	13.3%
2. *Clinical response at Week 8*			
Number (%)	6 (31.6%)	4 (21.1%)	10 (47.6%)
Difference from placebo		-10.5%	15.0%
3. *70-point response at Week 6*			
Number (%)	8 (42.1%)	8 (42.1%)	10 (47.6%)
Difference from placebo		0.0%	5.5%
4. *70-point response at Week 3*			
Number (%)	5 (26.3%)	8 (42.1%)	8 (38.1%)
Difference from placebo		15.8%	11.8%
Eastern Europe	N=8	N=8	N=8
Primary efficacy endpoint (clinical response at Week 6)			
Number (%)	1 (12.5%)	4 (50.0%)	3 (37.5%)
Difference from placebo		37.5%	25.0%
1. *Clinical remission at Week 8*			
Number (%)	0 (0.0%)	4 (50.0%)	2 (25.0%)
Difference from placebo		50.0%	25.0%
2. *Clinical response at Week 8*			
Number (%)	3 (37.5%)	5 (62.5%)	3 (37.5%)
Difference from placebo		25.0%	0.0%
3. *70-point response at Week 6*			
Number (%)	1 (12.5%)	5 (62.5%)	4 (50.0%)

Difference from placebo		50.0%	37.5%
4. *70-point response at Week 3*			
Number (%)	2 (25.0%)	5 (62.5%)	3 (37.5%)
Difference from placebo		37.5%	12.5%

Table 22 Statistical Reviewer's Baseline CDAI Score Subgroup Analysis Results for Primary and Secondary Efficacy Endpoints on Randomized Subjects Excluding Those Enrolled Prior to Study Re-start (Total=741)

	Placebo SC N=247	**Ustekinumab 130 mg N=245**	**Ustekinumab 6 mg/kg N=249**
Baseline CDAI >300 (N)	N=134	N=135	N=135
Primary efficacy endpoint (clinical response at Week 6)			
Number (%)	33 (24.6%)	49 (36.3%)	45 (33.3%)
Difference from placebo		11.7%	8.7%
1. *Clinical remission at Week 8*			
Number (%)	5 (3.7%)	11 (8.2%)	15 (11.1%)
Difference from placebo		4.5%	7.4%
2. *Clinical response at Week 8*			
Number (%)	26 (19.4%)	49 (36.3%)	46 (34.1%)
Difference from placebo		16.9%	14.7%
3. *70-point response at Week 6*			
Number (%)	43 (32.1%)	67 (49.6%)	56 (41.5%)
Difference from placebo		17.5%	9.4%
4. *70-point response at Week 3*			
Number (%)	47 (35.1%)	59 (43.7%)	60 (44.4%)
Difference from placebo		8.6%	9.3%
Baseline CDAI <=300 (N)	N=113	N=110	N=114
Primary efficacy endpoint (clinical response at Week 6)			
Number (%)	20 (17.7%)	35 (31.8%)	39 (34.2%)
Difference from placebo		14.1%	16.5%
1. *Clinical remission at Week 8*			
Number (%)	13 (11.5%)	28 (25.5%)	37 (32.5%)
Difference from placebo		14.0%	21.0%
2. *Clinical response at Week 8*			
Number (%)	24 (21.2%)	33 (30.0%)	48 (42.1%)
Difference from placebo		8.8%	20.9%
3. *70-point response at Week 6*			
Number (%)	32 (28.3%)	46 (41.8%)	53 (46.5%)
Difference from placebo		13.5%	18.2%
4. *70-point response at Week 3*			
Number (%)	20 (17.7%)	35 (31.8%)	41 (36.0%)
Difference from placebo		14.1%	18.3%

4.1.2 For Study CNTO1275CRD3002

The following Tables 23 to 27 present the reviewers' subgroup analysis results for the primary and four major secondary efficacy endpoints. Of note, the sponsor only provided

odds ratios of each ustekinumab dose group versus placebo and corresponding 95% confidence intervals for each subgroups.

Table 23 Statistical Reviewer's Gender Subgroup Analysis Results for Primary and Secondary Efficacy Endpoints on Randomized Subjects Excluding Those Enrolled Prior to Study Re-start and Site 1127 (Total=627)

	Placebo SC N=209	Ustekinumab 130 mg N=209	Ustekinumab 6 mg/kg N=209
Female (N)	N=111	N=105	N=119
Primary efficacy endpoint (clinical response at Week 6)			
Number (%)	34 (30.6%)	52 (49.5%)	65 (54.6%)
Difference from placebo		18.9%	24.0%
1. *Clinical remission at Week 8*			
Number (%)	24 (21.6%)	29 (27.6%)	48 (40.3%)
Difference from placebo		6.0%	18.7%
2. *Clinical response at Week 8*			
Number (%)	36 (32.4%)	47 (44.8%)	66 (55.5%)
Difference from placebo		12.4%	23.1%
3. *70-point response at Week 6*			
Number (%)	45 (40.5%)	62 (59.1%)	76 (63.9%)
Difference from placebo		18.6%	23.4%
4. *70-point response at Week 3*			
Number (%)	37 (33.3%)	48 (45.7%)	60 (50.4%)
Difference from placebo		12.4%	17.1%
Male (N)	N=98	N=104	N=90
Primary efficacy endpoint (clinical response at Week 6)			
Number (%)	26 (26.5%)	56 (53.9%)	51 (56.7%)
Difference from placebo		27.4%	30.2%
1. *Clinical remission at Week 8*			
Number (%)	17 (17.4%)	35 (33.7%)	36 (40.0%)
Difference from placebo		16.3%	22.6%
2. *Clinical response at Week 8*			
Number (%)	31 (31.6%)	52 (50.0%)	55 (61.1%)
Difference from placebo		18.4%	29.5%
3. *70-point response at Week 6*			
Number (%)	36 (36.7%)	61	59 (65.6%)
Difference from placebo		22.0%	28.9%
4. *70-point response at Week 3*			
Number (%)	29 (29.6%)	55	46 (51.1%)
Difference from placebo		23.3%	21.5%

Table 24 Statistical Reviewer's Age Subgroup Analysis Results for Primary and Secondary Efficacy Endpoints on Randomized Subjects Excluding Those Enrolled Prior to Study Re-start and Site 1127 (Total=627)

	Placebo SC N=209	Ustekinumab 130 mg N=209	Ustekinumab 6 mg/kg N=209
Age ≤ median age (37)	N=96	N=108	N=115
Primary efficacy endpoint (clinical response at Week 6)			
Number (%)	29 (30.2%)	62 (57.4%)	68 (59.1%)
Difference from placebo		27.2%	28.9%
1. *Clinical remission at Week 8*			
Number (%)	21 (21.9%)	35 (32.4%)	49 (42.6%)
Difference from placebo		10.5%	20.7%
2. *Clinical response at Week 8*			
Number (%)	34 (35.4%)	55 (50.9%)	69 (60.0%)
Difference from placebo		15.5%	24.6%
3. *70-point response at Week 6*			
Number (%)	37 (38.5%)	70 (64.8%)	77 (67.0%)
Difference from placebo		26.3%	28.5%
4. *70-point response at Week 3*			
Number (%)	31 (32.3%)	61 (56.5%)	62 (53.9%)
Difference from placebo		24.2%	21.6%
Age > median age (37)	N=113	N=101	N=94
Primary efficacy endpoint (clinical response at Week 6)			
Number (%)	31 (27.4%)	46 (45.5%)	48 (51.1%)
Difference from placebo		18.1%	23.7%
1. *Clinical remission at Week 8*			
Number (%)	20 (17.7%)	29 (28.7%)	35 (37.2%)
Difference from placebo		11.0%	19.5%
2. *Clinical response at Week 8*			
Number (%)	33 (29.2%)	44 (43.6%)	52 (55.3%)
Difference from placebo		14.4%	26.1%
3. *70-point response at Week 6*			
Number (%)	44 (38.9%)	53 (52.5%)	58 (61.7%)
Difference from placebo		13.6%	22.8%
4. *70-point response at Week 3*			
Number (%)	35 (31.0%)	42 (41.6%)	44 (46.8%)
Difference from placebo		10.6%	15.8%

Table 25 Statistical Reviewer's Race Subgroup Analysis Results for Primary and Secondary Efficacy Endpoints on Randomized Subjects Excluding Those Enrolled Prior to Study Re-start and Site 1127 (Total=627)

	Placebo SC N=209	Ustekinumab 130 mg N=209	Ustekinumab 6 mg/kg N=209
White	N=176	N=175	N=174
Primary efficacy endpoint (clinical response at Week 6)			
Number (%)	55 (31.3%)	87 (49.7%)	96 (55.2%)
Difference from placebo		18.4%	23.9%
1. *Clinical remission at Week 8*			
Number (%)	35 (19.9%)	53 (30.3%)	73 (42.0%)
Difference from placebo		10.4%	22.1%
2. *Clinical response at Week 8*			
Number (%)	57 (32.4%)	83 (47.4%)	101 (58.1%)
Difference from placebo		15.0%	25.7%
3. *70-point response at Week 6*			
Number (%)	70 (39.8%)	100 (57.1%)	111 (63.8%)
Difference from placebo		17.3%	24.0%
4. *70-point response at Week 3*			
Number (%)	60 (34.1%)	84 (48.0%)	92 (52.9%)
Difference from placebo		13.9%	18.8%
Non-white	N=33	N=34	N=35
Primary efficacy endpoint (clinical response at Week 6)			
Number (%)	5 (15.2%)	21 (61.8%)	20 (57.1%)
Difference from placebo		46.6%	41.9%
1. *Clinical remission at Week 8*			
Number (%)	6 (18.2%)	11 (32.4%)	11 (31.4%)
Difference from placebo		14.2%	13.2%
2. *Clinical response at Week 8*			
Number (%)	10 (30.3%)	16 (47.1%)	20 (57.1%)
Difference from placebo		16.8%	26.8%
3. *70-point response at Week 6*			
Number (%)	11 (33.3%)	23 (67.7%)	24 (68.6%)
Difference from placebo		34.4%	35.3%
4. *70-point response at Week 3*			
Number (%)	6 (18.2%)	19 (55.9%)	14 (40.0%)
Difference from placebo		37.7%	21.8%

Table 26 Statistical Reviewer's Geographic Region Subgroup Analysis Results for Primary and Secondary Efficacy Endpoints on Randomized Subjects Excluding Those Enrolled Prior to Study Re-start and Site 1127 (Total=627)

	Placebo SC N=209	Ustekinumab 130 mg N=209	Ustekinumab 6 mg/kg N=209
Rest of World	N=143	N=145	N=146
Primary efficacy endpoint (clinical response at Week 6)			
Number (%)	36 (25.2%)	69 (47.6%)	79 (54.1%)
Difference from placebo		22.4%	28.9%
1. *Clinical remission at Week 8*			
Number (%)	25 (17.5%)	37 (25.5%)	62 (42.5%)
Difference from placebo		8.0%	25.0%
2. *Clinical response at Week 8*			
Number (%)	42 (29.4%)	56 (38.6%)	85 (58.2%)
Difference from placebo		9.2%	28.8%
3. *70-point response at Week 6*			
Number (%)	50 (35.0%)	77 (53.1%)	89 (61.0%)
Difference from placebo		18.1%	26.0%
4. *70-point response at Week 3*			
Number (%)	43 (30.1%)	71 (49.0%)	73 (50.0%)
Difference from placebo		18.9%	19.9%
Asia	N=16	N=15	N=15
Primary efficacy endpoint (clinical response at Week 6)			
Number (%)	1 (6.3%)	8 (53.3%)	8 (53.3%)
Difference from placebo		47.0%	47.0%
1. *Clinical remission at Week 8*			
Number (%)	2 (12.5%)	5 (33.3%)	5 (33.3%)
Difference from placebo		20.8%	20.8%
2. *Clinical response at Week 8*			
Number (%)	3 (18.8%)	8 (53.3%)	9 (60.0%)
Difference from placebo		34.5%	41.2%
3. *70-point response at Week 6*			
Number (%)	4 (25.0%)	9 (60.0%)	11 (73.3%)
Difference from placebo		35.0%	48.3%
4. *70-point response at Week 3*			
Number (%)	2 (12.5%)	7 (46.7%)	6 (40.0%)
Difference from placebo		34.2%	27.5%
Eastern Europe	N=50	N=49	N=48
Primary efficacy endpoint (clinical response at Week 6)			
Number (%)	23 (46.0%)	31 (63.3%)	29 (60.4%)
Difference from placebo		17.3%	14.4%
1. *Clinical remission at Week 8*			
Number (%)	14 (28.0%)	22 (44.9%)	17 (35.4%)
Difference from placebo		16.9%	7.4%
2. *Clinical response at Week 8*			
Number (%)	22 (44.0%)	35 (71.4%)	27 (56.3%)
Difference from placebo		27.4%	12.3%
3. *70-point response at Week 6*			

Number (%)	27 (54.0%)	37 (75.5%)	35 (72.9%)
Difference from placebo		21.5%	18.9%
4. *70-point response at Week 3*			
Number (%)	21 (42.0%)	25 (51.0%)	27 (56.3%)
Difference from placebo		9.0%	14.3%

Table 27 Statistical Reviewer's Baseline CDAI Score Subgroup Analysis Results for Primary and Secondary Efficacy Endpoints on Randomized Subjects Excluding Those Enrolled Prior to Study Re-start and Site 1127 (Total=627)

	Placebo SC N=209	Ustekinumab 130 mg N=209	Ustekinumab 6 mg/kg N=209
Baseline CDAI >300 (N)	N=88	N=87	N=87
Primary efficacy endpoint (clinical response at Week 6)			
Number (%)	30 (34.1%)	58 (66.7%)	52 (59.8%)
Difference from placebo		32.6%	25.7%
1. *Clinical remission at Week 8*			
Number (%)	14 (15.9%)	22 (25.3%)	24 (27.6%)
Difference from placebo		9.4%	11.7%
2. *Clinical response at Week 8*			
Number (%)	32 (36.4%)	48 (55.2%)	55 (63.2%)
Difference from placebo		18.8%	26.8%
3. *70-point response at Week 6*			
Number (%)	40 (45.5%)	64 (73.6%)	60 (69.0%)
Difference from placebo		28.1%	23.5%
4. *70-point response at Week 3*			
Number (%)	34 (38.6%)	51 (58.6%)	53 (60.9%)
Difference from placebo		20.0%	22.3%
Baseline CDAI <=300 (N)	N=121	N=122	N=122
Primary efficacy endpoint (clinical response at Week 6)			
Number (%)	30 (24.8%)	50 (41.0%)	64 (52.5%)
Difference from placebo		16.2%	27.7%
1. *Clinical remission at Week 8*			
Number (%)	27 (22.3%)	42 (34.4%)	60 (49.2%)
Difference from placebo		12.1%	26.9%
2. *Clinical response at Week 8*			
Number (%)	35 (28.9%)	51 (41.8%)	66 (54.1%)
Difference from placebo		12.9%	25.2%
3. *70-point response at Week 6*			
Number (%)	41 (33.9%)	59 (48.4%)	75 (61.5%)
Difference from placebo		14.5%	27.6%
4. *70-point response at Week 3*			
Number (%)	32 (26.5%)	52 (42.6%)	53 (43.4%)
Difference from placebo		16.1%	16.9%

4.1.3 For Study CNTO1275CRD3003

The following Tables 28 to 33 present the reviewers' subgroup analysis results for the primary and four major secondary efficacy endpoints. Of note, the sponsor only provided

odds ratios of each ustekinumab dose group versus placebo and corresponding 95% confidence intervals for each subgroups.

Table 28 Reviewer's Gender Subgroup Analysis Results for Primary and Secondary Efficacy Endpoints on Randomized Subjects (Week 8 Ustekinumab responders) Excluding Those Enrolled Prior to Study Re-start (Total=388)

	Placebo SC (N=131)	Ustekinumab 90 mg SC q12w (N=129)	Ustekinumab 90 mg SC q8w (N=128)
Female (N)	N=72	N=73	N=75
Primary efficacy endpoint (clinical remission at Week 44)			
Number (%)	23 (31.9%)	36 (49.3%)	41 (54.7%)
Difference from placebo		17.4%	22.8%
Four ranked key secondary efficacy endpoints			
1. *Clinical response at Week 44*			
Number (%)	31 (43.1%)	42 (57.5%)	46 (61.3%)
Difference from placebo		14.4%	18.2%
2. *Clinical remission at Week 44 among Week 8 remitters (133)*			
Number (%)	17 (41.5%)	28 (65.1%)	33 (67.4%)
Difference from placebo		23.6%	25.9%
3. *Corticosteroid-free remission at Week 44*			
Number (%)	34 (47.2%)	39 (53.4%)	45 (60.0%)
Difference from placebo		6.2%	12.8%
4. *Clinical remission at Week 44 in the subset of subjects who were refractory or intolerant to TNF antagonist therapy (109)*			
Number (%)	8 (24.2%)	13 (33.3%)	18 (48.7%)
Difference from placebo		9.1%	24.5%
Male (N)	N=59	N=56	N=53
Primary efficacy endpoint (clinical remission at Week 44)			
Number (%)	24 (40.7%)	27 (48.2%)	27 (50.9%)
Difference from placebo		7.5%	10.2%
Four ranked key secondary efficacy endpoints			
1. *Clinical response at Week 44*			
Number (%)	27 (45.8%)	33 (58.9%)	30 (56.6%)
Difference from placebo		13.1%	10.8%
2. *Clinical remission at Week 44 among Week 8 remitters (102)*			
Number (%)	19 (50.0%)	16 (45.7%)	19 (65.5%)
Difference from placebo		-4.3%	15.5%
3. *Corticosteroid-free remission at Week 44*			
Number (%)	27 (45.8%)	33 (58.9%)	29 (54.7%)
Difference from placebo		13.1%	8.9%
4. *Clinical remission at Week 44 in the subset of subjects who were refractory or intolerant to TNF antagonist therapy (65)*			
Number (%)	8 (28.6%)	9 (50.0%)	5 (26.3%)
Difference from placebo		21.4%	-2.3%

Table 29 Reviewer's Age Subgroup Analysis Results for Primary and Secondary Efficacy Endpoints on Randomized Subjects (Week 8 Ustekinumab responders) Excluding Those Enrolled Prior to Study Re-start (Total=388)

	Placebo SC (N=131)	Ustekinumab 90 mg SC q12w (N=129)	Ustekinumab 90 mg SC q8w (N=128)
Age <=median (36)	N=63	N=66	N=72
Primary efficacy endpoint (clinical remission at Week 44)			
Number (%)	23 (36.5%)	32 (48.5%)	43 (59.7%)
Difference from placebo		12.0%	23.2%
Four ranked key secondary efficacy endpoints			
1. *Clinical response at Week 44*			
Number (%)	26 (41.3%)	36 (54.6%)	45 (62.5%)
Difference from placebo		13.3%	21.2%
2. *Clinical remission at Week 44 among Week 8 remitters (127)*			
Number (%)	18 (45.0%)	23 (56.1%)	31 (67.4%)
Difference from placebo		11.1%	22.4%
3. *Corticosteroid-free remission at Week 44*			
Number (%)	31 (49.2%)	38 (57.6%)	44 (61.1%)
Difference from placebo		9.4%	11.9%
4. *Clinical remission at Week 44 in the subset of subjects who were refractory or intolerant to TNF antagonist therapy (87)*			
Number (%)	6 (22.2%)	10 (37.0%)	16 (48.5%)
Difference from placebo		14.8%	26.3%
Age > median (36)	N=68	N=63	N=56
Primary efficacy endpoint (clinical remission at Week 44)			
Number (%)	24 (35.3%)	31 (49.2%)	25 (44.6%)
Difference from placebo		13.9%	11.3%
Four ranked key secondary efficacy endpoints			
1. *Clinical response at Week 44*			
Number (%)	32 (47.1%)	39 (61.9%)	31 (55.4%)
Difference from placebo		14.8%	8.3%
2. *Clinical remission at Week 44 among Week 8 remitters (108)*			
Number (%)	18 (46.2%)	21 (56.8%)	21 (65.6%)
Difference from placebo		10.6%	19.4%
3. *Corticosteroid-free remission at Week 44*			
Number (%)	30 (44.1%)	34 (54.0%)	30 (53.6%)
Difference from placebo		9.9%	9.5%
4. *Clinical remission at Week 44 in the subset of subjects who were refractory or intolerant to TNF antagonist therapy (87)*			
Number (%)	10 (29.4%)	12 (40.0%)	7 (30.4%)
Difference from placebo		10.6%	1%

Table 30 Reviewer's Race Subgroup Analysis Results for Primary and Secondary Efficacy Endpoints on Randomized Subjects (Week 8 Ustekinumab responders) Excluding Those Enrolled Prior to Study Re-start (Total=388)

	Placebo SC (N=131)	Ustekinumab 90 mg SC q12w (N=129)	Ustekinumab 90 mg SC q8w (N=128)
White	N=113	N=108	N=107
Primary efficacy endpoint (clinical remission at Week 44)			
Number (%)	40 (35.4%)	52 (48.2%)	58 (54.2%)
Difference from placebo		12.8%	18.8%
Four ranked key secondary efficacy endpoints			
1. Clinical response at Week 44			
Number (%)	51 (45.1%)	62 (57.4%)	65 (60.8%)
Difference from placebo		12.3%	15.7%
2. Clinical remission at Week 44 among Week 8 remitters (201)			
Number (%)	30 (42.9%)	38 (58.5%)	44 (66.7%)
Difference from placebo		15.6%	23.8%
3. Corticosteroid-free remission at Week 44			
Number (%)	51 (45.1%)	59 (54.6%)	63 (58.9%)
Difference from placebo		9.5%	13.8%
4. Clinical remission at Week 44 in the subset of subjects who were refractory or intolerant to TNF antagonist therapy (146)			
Number (%)	15 (27.8%)	17 (37.0%)	19 (41.3%)
Difference from placebo		9.2%	13.5%
Non white	N=18	N=21	N=21
Primary efficacy endpoint (clinical remission at Week 44)			
Number (%)	7 (38.9%)	11 (52.4%)	10 (47.6%)
Difference from placebo		13.5%	8.7%
Four ranked key secondary efficacy endpoints			
1. Clinical response at Week 44			
Number (%)	7 (38.9%)	13 (61.9%)	11 (52.4%)
Difference from placebo		23.0%	13.5%
2. Clinical remission at Week 44 among Week 8 remitters (34)			
Number (%) of Patients	6 (66.7%)	6 (46.2%)	8 (66.7%)
Difference from placebo		-20.5%	0.0%
3. Corticosteroid-free remission at Week 44			
Number (%)	10 (55.6%)	13 (61.9%)	11 (52.4%)
Difference from placebo		6.3%	-3.2%
4. Clinical remission at Week 44 in the subset of subjects who were refractory or intolerant to TNF antagonist therapy (28)			
Number (%)	1 (14.3%)	5 (45.5%)	4 (40.0%)
Difference from placebo		31.2%	25.7%

Table 31 Reviewer's Region Subgroup Analysis Results for Primary and Secondary Efficacy Endpoints on Randomized Subjects (Week 8 Ustekinumab responders) Excluding Those Enrolled Prior to Study Re-start (Total=388)

	Placebo SC (N=131)	Ustekinumab 90 mg SC q12w (N=129)	Ustekinumab 90 mg SC q8w (N=128)
Rest of world (N=286)	N=100	N=93	N=93
Primary efficacy endpoint (clinical remission at Week 44)			
Number (%)	32 (32.0%)	37 (39.8%)	41 (44.1%)
Difference from placebo		7.8%	12.1%
Four ranked key secondary efficacy endpoints			
1. *Clinical response at Week 44*			
Number (%)	40 (40.0%)	46 (49.5%)	46 (49.5%)
Difference from placebo		9.5%	9.5%
2. *Clinical remission at Week 44 among Week 8 remitters (171)*			
Number (%)	25 (41.7%)	28 (49.1%)	31 (57.4%)
Difference from placebo		7.4%	15.7%
3. *Corticosteroid-free remission at Week 44*			
Number (%)	43 (43.0%)	46 (49.5%)	46 (49.5%)
Difference from placebo		6.5%	6.5%
4. *Clinical remission at Week 44 in the subset of subjects who were refractory or intolerant to TNF antagonist therapy (153)*			
Number (%)	16 (28.6%)	18 (36.7%)	17 (35.4%)
Difference from placebo		8.1%	6.8%
Asia (N=29)	N=7	N=11	N=11
Primary efficacy endpoint (clinical remission at Week 44)			
Number (%)	3 (42.9%)	6 (54.6%)	7 (63.6%)
Difference from placebo		11.7%	20.7%
Four ranked key secondary efficacy endpoints			
1. *Clinical response at Week 44*			
Number (%)	3 (42.9%)	8 (72.7%)	8 (72.7%)
Difference from placebo		29.8%	29.8%
2. *Clinical remission at Week 44 among Week 8 remitters (16)*			
Number (%)	3 (75.0%)	3 (60.0%)	6 (85.7%)
Difference from placebo		-15.0%	10.7%
3. *Corticosteroid-free remission at Week 44*			
Number (%)	4 (57.1%)	8 (72.7%)	9 (81.8%)
Difference from placebo		15.6%	24.7%
4. *Clinical remission at Week 44 in the subset of subjects who were refractory or intolerant to TNF antagonist therapy (13)*			
Number (%)	0 (0.0%)	2 (33.3%)	3 (50.0%)
Difference from placebo		33.3%	50.0%
Eastern Europe (N=73)	N=24	N=25	N=24
Primary efficacy endpoint (clinical remission at Week 44)			
Number (%)	12 (50.0%)	20 (80.0%)	20 (83.3%)
Difference from placebo		30.0%	33.3%
Four ranked key secondary efficacy endpoints			
1. *Clinical response at Week 44*			
Number (%)	15 (62.5%)	21 (84.0%)	22 (91.7%)
Difference from placebo		21.5%	29.2%
2. *Clinical remission at Week 44 among Week 8 remitters (49)*			
Number (%)	8 (53.3%)	13 (81.3%)	15 (88.2%)

Difference from placebo		28.0%	34.9%
3. *Corticosteroid-free remission at Week 44*			
Number (%)	14 (58.3%)	18 (72.0%)	19 (79.2%)
Difference from placebo		13.7%	20.9%
4. *Clinical remission at Week 44 in the subset of subjects who were refractory or intolerant to TNF antagonist therapy (8)*			
Number (%)	0 (0.0%)	2 (100.0%)	4 (100.0%)
Difference from placebo		100.0%	100.0%

Table 32 Reviewer's Baseline CDAI Score Subgroup Analysis Results for Primary and Secondary Efficacy Endpoints on Randomized Subjects (Week 8 Ustekinumab responders) Excluding Those Enrolled Prior to Study Re-start (Total=388)

	Placebo SC (N=131)	**Ustekinumab 90 mg SC q12w (N=129)**	**Ustekinumab 90 mg SC q8w (N=128)**
Baseline CDAI > 300 (N)	N=71	N=65	N=60
Primary efficacy endpoint (clinical remission at Week 44)			
Number (%)	13 (18.3%)	26 (40.0%)	28 (46.7%)
Difference from placebo		21.7%	28.4%
Four ranked key secondary efficacy endpoints			
1. *Clinical response at Week 44*			
Number (%)	24 (33.8%)	37 (56.9%)	32 (53.3%)
Difference from placebo		23.1%	19.5%
2. *Clinical remission at Week 44 among Week 8 remitters (75)*			
Number (%)	6 (21.4%)	12 (50.0%)	14 (60.9%)
Difference from placebo		28.6%	39.5%
3. *Corticosteroid-free remission at Week 44*			
Number (%)	24 (33.8%)	35 (53.9%)	29 (48.3%)
Difference from placebo		20.1%	14.5%
4. *Clinical remission at Week 44 in the subset of subjects who were refractory or intolerant to TNF antagonist therapy (96)*			
Number (%)	5 (13.2%)	6 (20.7%)	7 (24.1%)
Difference from placebo		7.5%	10.9%
Baseline CDAI ≤ 300 (N)	N=60	N=64	N=68
Primary efficacy endpoint (clinical remission at Week 44)			
Number (%)	34 (56.7%)	37 (57.8%)	40 (58.8%)
Difference from placebo		1.1%	2.1%
Four ranked key secondary efficacy endpoints			
1. *Clinical response at Week 44*			
Number (%)	34 (56.7%)	38 (59.4%)	44 (64.7%)
Difference from placebo		2.7%	8.0%
2. *Clinical remission at Week 44 among Week 8 remitters (160)*			
Number (%)	30 (58.8%)	32 (59.3%)	38 (69.1%)
Difference from placebo		0.5%	10.3%
3. *Corticosteroid-free remission at Week 44*			
Number (%)	37 (61.7%)	37 (57.8%)	45 (66.2%)
Difference from placebo		-3.9%	4.5%
4. *Clinical remission at Week 44 in the subset of subjects who were refractory or intolerant to TNF antagonist therapy (78)*			
Number (%)	11 (47.8%)	16 (57.1%)	16 (59.3%)
Difference from placebo		9.3%	11.5%

Table 33 Reviewer's Study Subgroup Descriptive Statistics for Primary and Secondary Efficacy Endpoints on Randomized Subjects (Week 8 Ustekinumab responders) Excluding Those Enrolled Prior to Study Re-start (Total=388)

	Placebo SC (N=131)	Ustekinumab 90 mg SC q12w (N=129)	Ustekinumab 90 mg SC q8w (N=128)
Study 3001 (N=174)	N=61	N=57	N=56
Primary efficacy endpoint (clinical remission at Week 44) same as the 4th key secondary endpoint			
Number (%)	16 (26.2%)	22 (38.6%)	23 (41.1%)
Difference from placebo		12.4%	14.9%
Four ranked key secondary efficacy endpoints			
1. *Clinical response at Week 44*			
Number (%)	23 (37.7%)	27 (47.4%)	27 (48.2%)
Difference from placebo		9.7%	10.5%
2. *Clinical remission at Week 44 among Week 8 remitters (89)*			
Number (%	12 (40.0%)	16 (55.2%)	17 (56.7%)
Difference from placebo		15.2%	16.7%
3. *Corticosteroid-free remission at Week 44*			
Number (%)	21 (34.4%)	26 (45.6%)	22 (39.3%)
Difference from placebo		11.2%	4.9%
Study 3002 (N=214)	N=70	N=72	N=72
Primary efficacy endpoint (clinical remission at Week 44)			
Number (%)	31 (44.3%)	41 (56.9%)	45 (62.5%)
Difference from placebo		12.6%	18.2%
Four ranked key secondary efficacy endpoints			
1. *Clinical response at Week 44*			
Number (%)	35 (50.0%)	48 (66.7%)	49 (68.1%)
Difference from placebo		16.7%	18.1%
2. *Clinical remission at Week 44 among Week 8 remitters (146)*			
Number (%)	24 (49.0%)	28 (57.1%)	35 (72.9%)
Difference from placebo (p-value)		8.1%	23.9%
3. *Corticosteroid-free remission at Week 44*			
Number (%)	40 (57.1%)	46 (63.9%)	52 (72.2%)
Difference from placebo		6.8%	15.1%

5 SUMMARY AND CONCLUSIONS

5.1. Statistical Issues and Collective Evidence

The sponsor submitted three efficacy studies (two induction studies: CNTO1275CRD3001 and CNTO1275CRD3002 and one maintenance study: CNTO1275CRD3003) to support the use of ustekinumab for the treatment of adult patients (18 years or older) with moderately to severely active Crohn's disease who have:

- failed or were intolerant to immunomodulators or corticosteroids, but never failed [redacted] (b) (4) or;
- failed or were intolerant to [redacted] (b) (4)

In addition to those three studies, an endoscopy substudy was also conducted in the purpose of demonstrating and quantifying endoscopic healing of the mucosa in the Phase 3 development program for ustekinumab in Crohn's disease.

During a meeting with the FDA on the clinical development of this product when planning the Phase 3 program, the sponsor was notified that the pre-specified clinical remission as primary endpoint for Crohn Disease is preferred and "maintenance of remission" claim should be based on a population that was induced into remission, remission at Week 44 in the subset of induction responders who are also in remission was made the second major secondary endpoint of the CNTO1275CRD3003 study. However, based on the pre-specified testing procedure, the low dose (90mg q12w) failed to demonstrate ustekinumab's maintenance effect of remission with p-value of 0.189.

Regarding the efficacy studies of induction phase, study data support the superiority of ustekinumab over placebo was demonstrated for all primary and four major secondary efficacy endpoints. However, for efficacy study of maintenance phase, the superiority of ustekinumab over placebo was only demonstrated for primary efficacy endpoint (clinical remission at Week 44), first secondary efficacy endpoint (clinical response at Week 44) and high dose group (90 mg q8w) for the second secondary efficacy endpoint (clinical remission at Week 44 among Week 8 remitters).

Before this BLA was submitted, the FDA also informed the sponsor that the data of the endoscopic sub-study from the two induction studies needs to be analyzed separately first, before any statistical inference can be made from the pooled data. Moreover, in order to control the overall Type I error rate, the sponsor was recommended to perform a sequential test dealing with different populations and induction doses. Nevertheless, no detailed information for multiplicity adjustment procedure was included in the protocol and SAP.

Additional analyses regarding alternative clinical remission and/or response for the three efficacy studies were conducted. All the analyses provide the supportive evidence of efficacy. There were issues about inclusion criteria violation and misclassifications. The reviewer conducted sensitivity analyses excluding those patients and the results are similar to the sponsor's analysis results without excluding those patients. Furthermore, for endoscopic substudy, analyses were done for both separate induction studies and the combined. The reviewer's conclusions are different from the sponsor's. However, it should be noted that all these analyses are either post-hoc or exploratory.

5.2. Conclusions and Recommendations

Of three submitted efficacy studies in this BLA, two induction studies (CNTO1275CRD3001 and CNTO1275CRD3002) are positive and support the indication of induction; Study CNTO1275CRD3003 supports the use of ustekinumab (90 mg q8w) for the maintenance of remission.

Although based on the sponsor's results of endoscopic substudy, they concluded that the ustekinumab endoscopy substudy was a positive study and provided compelling evidence for the efficacy of ustekinumab in inducing endoscopic healing of the mucosa, this conclusion would be changed simply when we analyzed two induction studies (CNTO1275CRD3001 and CNTO1275CRD3002) separately first before any statistical inference is made for the

pooled data from both studies as the FDA recommended. [redacted] (b) (4)

To further assess the study drug's efficacy by exploring the extent of the efficacy, the statistical reviewer performed different types of exploratory re-analyses by using alternative clinical remission and/or response efficacy endpoints. Those analysis results are supportive of the efficacy of the study drug.

6 APPENDIX

To further investigate impact of drop outs on the primary efficacy assessments for Study CNTO1275CRD3003, the sponsor performed four sensitivity analyses and the results are shown in Table 34.

Table 34 Sponsor's Sensitivity Analysis Results for Primary Efficacy Endpoint on Randomized Subjects (Week 8 Ustekinumab responders) Excluding Those Enrolled Prior to Study Re-start (Total=388)

	Placebo SC (N=131)	**Ustekinumab 90 mg SC q12w (N=129)**	**Ustekinumab 90 mg SC q8w (N=128)**
Sensitivity analysis 1: Observed case			
	Placebo SC (N=123)	**Ustekinumab 90 mg SC q12w (N=127)**	**Ustekinumab 90 mg SC q8w (N=118)**
Number (%)	47 (38.2)	63 (49.5)	68 (57.6)
p-value by CMH test**		0.079	0.002
Sensitivity analysis 2: LOCF			
Number (%)	53 (40.5)	65 (50.4)	75 (58.6)
p-value by CMH test**		0.119	0.003
Sensitivity analysis 3: Multiple Imputation			
Odds ratio of clinical response	1.7	2.2	1.9
95% CI		(1.0, 2.9)	(1.3, 3.9)
p-value by CMH test**		0.056	0.005
Sensitivity analysis 4: Worst case			
Number (%)	55 (42.0)	63 (48.8)	68 (53.1)
p-value by CMH test**		0.304	0.077
Sensitivity analysis 5: excluding subjects who were randomized but never treated			
	Placebo SC (N=131)	**Ustekinumab 90 mg SC q12w (N=129)**	**Ustekinumab 90 mg SC q8w (N=127)**
Number (%)	47 (35.9)	63 (48.8)	68 (53.5)
p-value by CMH test**		0.040	0.004

Source: Sponsor's Tables TEFCREM01B, TEFCREM01C, TEFCREM01D, TEFCREM01E and TEFCREM01F in cnto1275crd3003-study-report.pdf (Pages 218, 219, 220, 221 and 222) **stratified by clinical remission status at Week 0 (yes or no), ustekinumab induction dose (130 mg or tiered dosing approximating ustekinumab 6 mg/kg), and the induction study (CNTO1275CRD3001 or CNTO1275CRD3002).

Table 35 Reviewer's Region (US vs Non-US) Subgroup Analysis Results for Primary and Secondary Efficacy Endpoints on Randomized Subjects (Week 8 Ustekinumab responders) Excluding Those Enrolled Prior to Study Re-start (Total=388)

	Placebo SC (N=131)	**Ustekinumab 90 mg SC q12w (N=129)**	**Ustekinumab 90 mg SC q8w (N=128)**
US (N)	N=39	N=39	N=36
Primary efficacy endpoint (clinical remission at Week 44)			
Number (%)	11 (28.2%)	13 (33.3%)	14 (38.9%)
Difference from placebo		5.1%	10.7%
Four ranked key secondary efficacy endpoints			
1. *Clinical response at Week 44*			
Number (%)	15 (38.5%)	15 (38.5%)	15 (41.7%)
Difference from placebo		0.0%	3.2%
2. *Clinical remission at Week 44 among Week 8 remitters (62)*			
Number (%)	6 (30.0%)	7 (36.8%)	12 (52.2%)
Difference from placebo		6.8%	22.2%
3. *Corticosteroid-free remission at Week 44*			
Number (%)	14 (35.9%)	16 (41.0%)	19 (52.8%)
Difference from placebo		5.1%	16.9%
4. *Clinical remission at Week 44 in the subset of subjects who were refractory or intolerant to TNF antagonist therapy (55)*			
Number (%)	9 (37.5%)	6 (31.6%)	4 (33.3%)
		-2.9%	-4.2%
Non US (N)	N=92	N=90	N=92
Primary efficacy endpoint (clinical remission at Week 44)			
Number (%) of Patients	36 (39.1%)	50 (55.6%)	54 (58.7%)
Difference from placebo		16.5%	19.6%
Four ranked key secondary efficacy endpoints			
1. *Clinical response at Week 44*			
Number (%)	43 (46.7%)	60 (66.7%)	61 (66.3%)
Difference from placebo		20.0%	19.6%
2. *Clinical remission at Week 44 among Week 8 remitters (173)*			
Number (%)	30 (50.9%)	37 (62.7%)	40 (72.7%)
Difference from placebo		11.8%	21.8%
3. *Corticosteroid-free remission at Week 44*			
Number (%)	47 (51.1%)	56 (62.2%)	55 (59.8%)
Difference from placebo		11.1%	8.7%
4. *Clinical remission at Week 44 in the subset of subjects who were refractory or intolerant to TNF antagonist therapy (119)*			
Number (%)	12 (32.4%)	20 (52.6%)	18 (40.9%)
Difference from placebo		20.2%	8.5%

Table 36 Reviewer's Post-hoc Analysis Results for Clinical Remission in at least 10 out of 12 Maintenance Visits, including Week 44, based on Randomized Subjects (Week 8 Ustekinumab responders) Excluding Those Enrolled Prior to Study Re-start (Total=388)

	Placebo SC (N=131)	**Ustekinumab 90 mg SC q12w (N=129)**	**Ustekinumab 90 mg SC q8w (N=128)**
Clinical remission in at least 10 out of 12 maintenance visits (Week 44 included)			
Number (%)	36 (27.5%)	48 (37.2%)	54 (42.2%)
Difference from placebo and p-value by CMH test**		9.7% (0.1147)	14.7% (0.0134)

CMH test**: CMH test was adjusted for study and induction doses

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/s/

MIN MIN
08/31/2016

YEH FONG CHEN
08/31/2016