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APPLICATION NUMBER:

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CLINICAL REVIEW(S)

Clinical Review
Kerry Jo Lee, MD
BLA 761044
Stelara (ustekinumab)

CLINICAL REVIEW

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Division/Office	CDER/ODE III/DGIEP
Reviewer Name(s)	Kerry Jo Lee, MD, Medical Officer
Review Completion Date	August 27, 2016
Established Name	ustekinumab
(Proposed) Trade Name	Stelara
Applicant	Janssen Biotech, Inc.
Formulation(s)	Intravenous infusion and subcutaneous injection
Dosing Regimen	Initial Dose: A single intravenous (IV) infusion dose using weight-based tiers. Maintenance Dosing: A subcutaneous 90 mg dose 8 weeks after the initial IV dose, then every 8 weeks thereafter.
Applicant Proposed Indication(s)/Population(s)	Treatment of moderate to severe Crohn's disease in patients who have failed/were tolerant to immunomodulators or corticosteroids but never failed (b) (4) or have failed or were intolerant to (b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Moderate to severe Crohn's disease

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Glossary

AC	advisory committee
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
LOR	loss of response
LTE	long term extension
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application

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NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Ustekinumab (STELARA®) inhibits IL-12 and IL-23 and associated inflammatory pathways via blockade of the shared IL-12 p40 subunit. There is evidence to support that Crohn's disease is mediated by Th1 or Th17 cells, with strong contributions from the pro-inflammatory cytokines IL-12 and IL-23.^{1,2,3} Genome-wide studies have found associations between Crohn's disease and genetic polymorphisms in the IL-23 receptor gene,^{4,5,6} indicating a possible role for IL-23 (a heterodimer of IL-12 p40 and IL-23 p19) as a regulator in Crohn's disease.⁷

Ustekinumab (STELARA®) is human interleukin-12 and -23 antagonist that was approved in 2009 for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis (Ps) who are candidates for phototherapy or systemic therapy and in 2013 active psoriatic arthritis (PsA), alone or in combination with methotrexate. In this BLA submission, the Applicant proposes ustekinumab for the treatment of moderately to severely active Crohn's disease (CD) in patients who have failed or were intolerant to immunomodulators or corticosteroids but never failed (b) (4) or patients who failed or were intolerant to (b) (4) (b) (4)

The Applicant proposes the following dosage and administration for the treatment of adult patients with moderately to severely active Crohn's disease (CD):

- Initial Dose: A single intravenous (IV) infusion dose using weight-based tiers (approximately 6 mg/kg) specified below:
 - ≤ 55 kg = 260 mg
 - > 55 kg to ≤ 85 kg = 390 mg

¹Berrebi D, Besnard M, Fromont-Hankard G, et al. Interleukin-12 expression is focally enhanced in the gastric mucosa of pediatric patients with Crohn's disease. *Am J Pathol.* 1998; 152(3):667-672.

²Monteleone G, Biancone L, Marasco R, et al. Interleukin 12 is expressed and actively released by Crohn's disease intestinal lamina propria mononuclear cells. *Gastroenterology.* 1997; 112(4):1169-1178.

³Parrello T, Monteleone G, Cucchiara S, et al. Up-regulation of the IL-12 receptor beta 2 chain in Crohn's disease. *J Immunol.* 2000; 165(12):7234-7239.

⁴Duerr RH, Taylor KD, Brant SR, et al. A genome-wide association study identifies IL23R as an inflammatory bowel disease gene. *Science.* 2006; 314(5804):1403-1405.

⁵Umeno J, Asano K, Matsushita T, et al. Meta-analysis of published studies identified eight additional common susceptibility loci for Crohn's disease and ulcerative colitis. *Inflamm Bowel Dis.* 2011; 17(12):2407-2415.

⁶Wang K, Zhang H, Kugathasan S, et al. Diverse genome-wide association studies associate the IL12/IL23 pathway with Crohn disease. *Am J Hum Genet.* 2009; 84(3):399-405.

⁷Neurath MF. IL-23: a master regulator in Crohn disease. *Nat Med.* 2007; 13(1):26-28.

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- > 85 kg = 520 mg
- Maintenance Dosing: A subcutaneous 90 mg dose 8 weeks after the initial IV dose, then every 8 weeks thereafter. (b) (4)

While ustekinumab is not a new molecular entity, the IV dosage form is new and specific to the CD indication.

1.2. Conclusions on the Substantial Evidence of Effectiveness

This reviewer considers BLA 761044 acceptable to recommend approval of STELARA (ustekinumab) for the treatment of patients with moderately to severely active Crohn's disease who have failed or were intolerant to immunomodulators or corticosteroids but never failed (b) (4) or failed or were intolerant to (b) (4). This reviewer recommends approval of the following dosage and administration.

Initial Dose: A single intravenous (IV) infusion dose of STELARA[®] using weight-based tiers (approximately 6 mg/kg) as specified below.

Body Weight of Patient at the time of dosing	Dose	Number of 130 mg STELARA [®] vials
≤ 55 kg	260 mg	2
> 55 kg to ≤ 85 kg	390 mg	3
> 85 kg	520 mg	4

Maintenance Dosing: A subcutaneous 90 mg dose 8 weeks after the initial IV dose, then every 8 weeks thereafter.

(b) (4)
The maintenance dose of 90mg SC q12w weeks appears to offer inferior clinical benefit as compared to 90mg SC q8w dose. The q12w dosing did not achieve statistical significance for the clinically important endpoint of clinical remission achieved at the end of induction and continued through the end of maintenance. Additionally, the proportion of

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patients discontinuing the study for adverse events was double in the q12w dosing arm than the q8w dosing arm, most of which were Crohn's related, thus further supporting concerns of inferior clinical benefit.

Additionally, this reviewer recommends approval of ustekinumab with the requirement for a post-marketing requirement for a long-term observational study to further evaluate the long-term risk of ustekinumab on the development of malignancies and serious infections in the CD population.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Ustekinumab is intended for the treatment of patients with moderately to severely active Crohn's disease (CD) who have 1) failed or were intolerant to immunomodulators or corticosteroids but never failed (b) (4) or 2) failed or were intolerant to (b) (4)

(b) (4) This reviewer recommends approval of BLA 761044 for the weight tiered IV induction dose of approximately 6 mg/kg and the 90mg SC every 8 week maintenance dose for the treatment of moderately to severely active CD with a post-marketing requirement for an observations long-term study to follow evaluate the development of malignancy and serious infections in adult patients with Crohn's disease who received long-term treatment with ustekinumab.

Crohn's disease (CD) is a chronic immune-mediated inflammatory bowel disease (IBD) characterized as a relapsing, remitting disease occurring most commonly at the distal end of the small intestine (terminal ileum) and the proximal (right side) colon, with a prevalence of 201 per 100,000 adults and annual incidence rates ranging from 3.1 to 14.6 cases per 100,000 persons per year and in the United States. Peak age-specific incidence occurs between ages 15 and 30 years, and a second, smaller peak occurs in the sixth and seventh decades of life. Crohn's disease is associated with significant morbidity and mortality. Clinical manifestations include abdominal pain and diarrhea as well as systemic features such as cachexia, fever, anemia, and weight loss. Extraintestinal manifestations include pyoderma gangrenosum, uveitis, and arthritis. Complications include bowel fistulas, abscesses, and luminal strictures, which can require multiple surgeries. Given the potential for complications and morbidity, patients with IBD can suffer from reduced quality of life and are at increased risk for clinical depression. Current anti-inflammatory treatment options include 5-aminosalicylic acid (5-ASA) compounds, corticosteroids, immunomodulators including azathioprine (AZA) or its active metabolite 6-mercaptopurine (6-MP) and methotrexate (MTX). Biologic therapies include tumor necrosis factor (TNF α) antagonist therapies and anti-integrin therapies. Of these, only

the biologic agents and the corticosteroid, budesonide, are currently approved for the treatment of Crohn's disease. Moderately to severely active CD often requires biologic treatment; however, antibody development to biologic treatment can reduce the effectiveness of biologic therapies and the primary failure of response rates for TNF antagonists can range from 20-40%. Therefore, there is a need for additional safe and efficacious treatments for moderate to severe CD.

Ustekinumab is an IL 12/23 antagonist that binds with high affinity and specificity to a p40 subunit common to both cytokines. Both cytokines stimulate TNF production via the Th1 and Th17 pathways, which result in intestinal inflammation and epithelial cell injury seen in Crohn's disease. In the clinical trials, ustekinumab was administered as an intravenous injection given as a single, initial dose in two 8-week induction trials, and administered subcutaneously as a maintenance dose for long term management of CD in one 44-week maintenance trial. Two initial single dose regimens were evaluated in the 8-week induction trials, 130 mg IV and 6 mg/kg IV as weight-tied dosing. The primary endpoint of the induction trials was clinical response, as measured by reduction of the Crohn's Disease Activity Index (CDAI) score of ≥ 100 points, at week 6. The proportion of patients achieving clinical response ranged from 34% (84/245) for the ustekinumab 130 mg dose to 56% (116/209) for the ustekinumab 6 mg/kg dose depending on the study population (previously failed TNF antagonists or previously failed conventional therapy of corticosteroids or immunomodulators). When the primary endpoint was analyzed by patient population (prior therapy), both achieved statistical significance over placebo; however, the proportion of patients achieving the clinically important endpoint remission by week were numerically greater each week in the 6 mg/kg dose arm. Therefore this reviewer concludes the 6 mg/kg dose is the appropriate initial dose of ustekinumab. Patients who achieved clinical response at week 6 of the two induction trials were eligible to be randomized into the 44-week maintenance study, where two maintenance dose regimens were evaluated, 90 mg SC every 8 weeks and every 12 weeks. The primary endpoint was clinical remission, as defined a CDAI score < 150 points. At week 44, the proportion of patients who achieved clinical remission in the every 8 week dosing regimen was 53% (68/128) vs 36% (47/131) in the placebo arm which was statistically significant. In the every 12 week dosing regimen, 49% (63/129) patients also achieved statistical significance over placebo; however, the every 12 week dosing regimen failed to meet statistical significance for a clinically important endpoint of sustaining clinical remission in patients who had achieved remission by the end of the induction study. In addition, the incidence of serious adverse events resulting in withdrawal from the study was twice as great as compared to the every 8 week dosing regimen. These adverse events were largely related to the underlying CD, suggesting inferior clinical benefit when compared to the every 8 week dosing regimen. Therefore, the every 12 week maintenance dosing regimen does not appear to offer clinical benefit as compared to the every 8 week dose regimen (b) (4)

No new or unexpected safety issues were identified in this review as the safety profile

appeared overall similar to the adverse reactions known to be associated with ustekinumab, as per the approved label. Biologic products, in general, carry an increased risk of malignancy and serious infection and these events occurred in patients during the ustekinumab studies. The frequency was generally similar to placebo for malignancy, however this event may take more time to develop than the study window in CD and the currently approved label notes malignancy as a warning and precaution for ustekinumab. Serious infections were higher than placebo in certain dosing arms and patients with CD have compromised immune systems that place them and increased risk for serious infection to begin with. Those events that did occur at a higher rate in the ustekinumab population can be adequately addressed in labeling. The safety and efficacy of ustekinumab in pediatric patients with CD has not been established; however, there is an agreed initial Pediatric Study Plan (iPSP) for pediatric studies.

Approval of ustekinumab for use in the treatment of adult patients with moderately to severely active Crohn’s disease (CD) who have failed or were intolerant to prior therapy is supported by the available evidence of efficacy and safety. Ustekinumab will be the first drug in the class of IL-12/23 inhibitors for the treatment of CD.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Analysis of Condition</u>	• Crohn’s disease (CD) is an idiopathic inflammatory bowel disease (IBD) that can affect any portion of the intestinal tract with focal, asymmetric, transmural, and granulomatous inflammation and is characterized by transmural infiltration of lymphocytes and macrophages, granulomas, fissuring ulceration, and submucosal fibrosis. • The cause of CD is considered to be multifactorial, including environmental changes, genetic risk factors, gut microbiota, and immune defense mechanisms. • In the U.S, the prevalence of CD is 201 per 100,000 adults. It is estimated that the incidence is 3.1 to 14.6 cases per 100,000 persons per year. • Clinical manifestations of Crohn’s disease include abdominal pain, diarrhea, cachexia, fever, anemia, lower right quadrant mass, and perianal fistulae. Extraintestinal manifestations	If not well controlled, CD can result in significant morbidity and mortality. Patients can experience symptoms that are severe, debilitating, and may lead to major complications or require surgical intervention. CD is a significant public health concern.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	include pyoderma gangrenosum, uveitis, and arthritis. Complications include bowel fistulas, abscesses, and luminal strictures, which can require surgery. Seventy percent of CD patients will require major abdominal surgery within the first 15 years of disease diagnosis	
<u>Current Treatment Options</u>	- The current standard of care for CD utilizes anti-inflammatory therapies (i.e., 5-aminosalicylic acid [5-ASA] compounds, corticosteroids, and immunomodulators including azathioprine [AZA] or its active metabolite 6-mercaptopurine [6-MP] and methotrexate [MTX]), and biologic agents including tumor necrosis factor (TNFα) antagonist therapies and anti-integrin therapies. These therapies block inflammation pathways that contribute to the release of cytokines and/or pro-inflammatory cells and cellular pathways. These drugs may be combined with diet, and/or antibiotics in clinical practice and the regimen utilized depends on the severity of disease presentation and previous treatment history failure and immunogenicity. Of these therapies, only the biologic agents and the corticosteroid, budesonide, are approved for the treatment of CD. Ustekinumab would be the first IL-12/23 antagonist approved for the treatment of CD. - Biologics have decreased the morbidity and mortality associated with CD, particularly in severe disease. However, primary response failure and antibody development to biologic treatment can reduce the effectiveness of biologics and patients with moderate to severe CD benefit from a wider range of effective medications available.	Patients with moderate to severe CD disease may benefit from new therapeutic options that are safe and efficacious, and provide options for patients that have experienced primary failure or loss of response to other therapies. There is a specific unmet medical need: - For patients who have lost response to other biologic therapies. - For patients who have had serious adverse reactions to other approved CD therapies.

Dimension	Evidence and Uncertainties	Conclusions and Reasons								
<u>Benefit</u>	• Ustekinumab is indicated for both patients who have failed TNF-α therapy and patients who have failed conventional therapy (immunomodulators or steroids) • The efficacy of ustekinumab was established in three phase 3 clinical studies that enrolled a total of 1367 CD patients. The studies varied in terms of the treatment regimen (initial single dose vs maintenance, chronic dosing), dosage form (IV vs SC), and patient population prior treatment exposure (previously failed TNF antagonist or conventional therapy). • The primary efficacy endpoint of the two induction studies was clinical response, defined as reduction in the Crohn’s Disease Activity Index (CDAI) >100 points. The primary efficacy endpoint of the maintenance study was clinical remission, defined as CDAI <150. • Other important endpoints included the sustaining of clinical remission (i.e., patients in remission at the end of both the induction study and at the end of the maintenance study), and endoscopic improvement defined by changes in the Simplified Endoscopic Disease Severity Score for Crohn’s Disease (SES-CD) score and detection of presence/absence of mucosal ulceration supported by exploratory histologic evaluation; specifically, mucosal healing was defined as the complete absence of any mucosal ulcerations among patients who presented with ulceration in at least 1 ileocolonic segment at induction baseline <u>Study 3001: Clinical response at Week 6, defined as a reduction from baseline in the CDAI score of ≥ 100 points in patients who failed TNFα therapy</u> <table border="1" data-bbox="383 1780 1143 1894"> <thead> <tr> <th data-bbox="383 1780 553 1894">STUDY 3001 (failed)</th> <th data-bbox="553 1780 696 1894">Placebo N=247 n (%)</th> <th data-bbox="696 1780 922 1894">Ustekinumab 130 mg (N=245)</th> <th data-bbox="922 1780 1143 1894">Ustekinumab 6 mg/kg (N=249)</th> </tr> </thead> <tbody> <tr> <td></td> <td></td> <td></td> <td></td> </tr> </tbody> </table>	STUDY 3001 (failed)	Placebo N=247 n (%)	Ustekinumab 130 mg (N=245)	Ustekinumab 6 mg/kg (N=249)					Ustekinumab treatment was successful in achieving statistical significance over placebo on the primary endpoints of clinical response (induction studies) and clinical remission (maintenance study) in treatment of CD. The studies were adequate and well-controlled and demonstrated meaningful effects in CD based on the proportion of patients achieving clinical response at week 6 in the induction studies in both patients who had previously failed TNF-α and in patients to who had previously failed conventional therapy, but not failed a TNF α medication. In the maintenance study, both doses achieved statistical significance over placebo on the endpoint of clinical
STUDY 3001 (failed)	Placebo N=247 n (%)	Ustekinumab 130 mg (N=245)	Ustekinumab 6 mg/kg (N=249)							

Dimension	Evidence and Uncertainties				Conclusions and Reasons
	TNF α)		n (%)	n (%)	remission at week 44; however, the every 12 week dosing regimen failed to achieve statistical significance on the clinically important key secondary endpoint of sustaining clinical remission at week 44 in patients who achieved remission at the end of the induction.
	Clinical Response at Week 6	53 (21.5)	84 (34.3) p=0.002	84 (33.7) p=0.003	
	<u>Study 3002: Clinical response at Week 6, defined as a reduction from baseline in the CDAI score of ≥ 100 points in patients who failed conventional therapy</u>				
	STUDY 3002 (failed corticosteroids/Immunomodulators)	Placebo (N=209) n (%)	Ustekinumab 130 mg N=209 n (%)	Ustekinumab 6 mg/kg (N=209) n (%)	
	Clinical Response at Week 6	60 (28.7)	108 (51.7) p<0.001	116 (55.5) p<0.001	
	<u>Study 3003: Primary and Key Secondary Clinical Remission Endpoints at Week 44, defined as CDAI score <150</u>				
	STUDY 3003 Maintenance	Placebo N=131 n (%)	Ustekinumab 90mg q 12 N=129 n (%)	Ustekinumab 90mg q 8 N=128 n (%)	
	Primary Endpoint: Clinical Remission at Week 44	47 (35.9)	63 (48.8) p=0.040	68 (53.1) p=0.005	
	Key Secondary Endpoint: Clinical remission Week 44 in patients in clinical remission to Week 0 of Maintenance*	36/79 (45.6)	44/78 (56.4) P=0.189	52/78 (66.7) P=0.007	
	*N for this endpoint differs from overall N in dosing arm				

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Risk</u>	- The safety database for ustekinumab includes all randomized patients (N=1367) from the three phase 3 clinical studies; the drug exposure data are considered adequate to assess safety. - The safety profile demonstrated for ustekinumab was consistent with the known safety profile reported in approved labeling for the other approved indications. Ustekinumab is currently approved for psoriasis and psoriatic arthritis, however, there is no IV formulation for these indications and the SC dosing is lower than proposed for CD. The safety profile for ustekinumab also appears generally consistent with the safety profile for other biologics used to treat CD. - During the CD induction trials, there was a $\geq 3\%$ of the patient population and higher incidence than placebo of abdominal pain, nasopharyngitis, and vomiting reported for patients treated with the initial IV 6 mg/kg dose as compared to placebo. During the maintenance trial, patients treated with the subcutaneous dose regimen reported a $\geq 3\%$ of the patient population and higher incidence than placebo of headache, nasopharyngitis, rash, gastroenteritis, cough, injection site erythema, bronchitis, vulvovaginal mycotic infection, pruritus, migraine, pain in extremity, sinusitis and urinary tract infection in the 90mg SC every 8 week dosing regimen as compared to placebo. - Ustekinumab was originally approved in 2009 with a REMS to evaluate and mitigate the potential risks of serious infections and malignancy, and reversible posterior leukoencephalopathy syndrome (RPLS) associated with ustekinumab by alerting and warning healthcare providers about the risks. No cases of RPLS were identified in the CD studies.	No new or unexpected safety were identified during the CD trials and the safety profile was generally consistent with the known adverse reactions already described in the label for other approved indications. No cases of reverse posterior leukoencephalopathy syndrome (RPLS) were reported in CD studies. There appeared to be a favorable safety and tolerability profile for the maintenance dosing regimen of every 8 weeks compared to every 12 week dosing.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	The safety profile between maintenance dosing arms was remarkable for double the number of patients discontinuing the study for adverse events in the every 12 week dosing arm than in the every 8 week dosing regimen. The majority of these events were CD related, indicating inadequate treatment effect of the every 12 week dosing regimen as compared to the every 8 week dosing.	
<u>Risk Management</u>	- The majority of the adverse events reported during the CD studies are already noted in the approved labeling. - Biologic therapies, often used in the treatment of CD, are associated with increase in risks of serious infection and malignancy; therefore, long-term observational postmarketing studies are often recommended to evaluate the long-term risk of developing serious adverse events that may have a longer latency period. - The safety and efficacy of ustekinumab in pediatric patients with CD has not been studied. The Applicant does have an agreed initial Pediatric Study Plan in place.	The clinical trials evaluating safety and efficacy in CD were conducted in an adult patient population and will be labeled for adult patients. There is an agreed initial pediatric study plan for ustekinumab for the treatment of CD in pediatric patients. This application will also be patient to PREA requirements for post-marketing pediatric studies. Given the associated increased risk of serious infection and malignancy with the use of ustekinumab, a postmarketing

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
		requirement for a long-term observational study is recommended to further evaluate the risk of serious infection and malignancy in patients with CD, given that the introduction of the IV formulation and higher maintenance dosing, which differ from the previously approved indications.

2 Therapeutic Context

Analysis of Condition

Moderately to severely active Crohn's disease (CD) is a serious chronic disease which has a substantial impact on patients' quality of life. CD involves chronic inflammation of all layers of the bowel and may affect any segment of the gastrointestinal (GI) tract. The prevalence of Crohn's disease is 201 per 100,000 adults and annual incidence rates ranging from 3.1 to 14.6 cases per 100,000 persons per year and in the United States.⁸

For CD, the most common patterns of GI involvement are in descending order, (1) the distal small intestine and colon, (2) the small intestine alone, and (3) the colon alone. Diagnosis and surveillance of disease course includes endoscopy of the upper and lower GI tract with biopsies. However, computer tomography (CT), magnetic resonance imaging (MRI), laboratory tests (particularly of inflammation and bleeding), physical exam and patient reported symptoms are also included in the diagnostic workup and management according to the American Gastroenterology's algorithmic guidelines.⁹

CD typically has a chronic relapsing course with acute clinical episodes. Common symptoms of CD are diarrhea, abdominal pain, weight loss, fever, and rectal bleeding. The inflammation can extend beyond the mucosa and involve the wall of the bowel, leading to the development of strictures (narrowing), fistulae between diseased parts of the bowel and adjacent structures (i.e., bladder, other bowel segments and skin) and abscesses. Perianal manifestations are common. Extraintestinal tissues (skin, eyes and joints) may also be inflamed. In addition, there may be sequelae due to malabsorption (e.g., anemia, vitamin deficiency, cholelithiasis, nephrolithiasis or metabolic bone disease). Some patients, however, have chronic poor health due to active bowel inflammation, fistulae, or other disease-related events. Morbidity may be considerable, particularly for patients whose disease is not controlled by currently available agents. An increased risk of mortality has been reported.¹⁰

Overall, the addition biologic therapy in the treatment of Crohn's disease appears to be associated with a consistent decline in disease-related surgery and colectomy rates, improving

⁸ Loftus EV, Jr. 2004 Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. *Gastroenterology* 126:1504-17

⁹ Sandborn W et al. 2014. Crohn's Disease Evaluation and Treatment: Clinical Decision Tool. *Gastroenterology* 147:702-705.

¹⁰ Wolters et al. 2006. Crohn's disease: increased mortality 10 years after diagnosis in a Europe-wide population based cohort. *Gut* 2006 Apr; 55(4):510-8. Epub 2005 Sep 8

the morbidity associated with CD. The immunosuppression associated with these agents as compared to other therapies (steroids, immunomodulators) does not appear to increase mortality.¹¹

2.2. Analysis of Current Treatment Options

The current standard of care for CD utilizes anti-inflammatory therapeutics (i.e. 5-aminosalicylic acid [5-ASA] compounds, corticosteroids, and immunomodulators including azathioprine [AZA] or its active metabolite 6-mercaptopurine [6-MP] and methotrexate [MTX]), and biologic agents, including tumor necrosis factor (TNF α) antagonist therapies and anti-integrin therapies to block inflammation pathways that contribute to the release of cytokines and/or pro-inflammatory cells and cellular pathways. These drugs may be combined with diet, and/or antibiotics in clinical practice and the regimen utilized depends on the severity of disease presentation and previous treatment history failure and immunogenicity. Of these therapies, only the biologic agents and the corticosteroid budesonide are approved for the treatment of CD. Despite the currently approved therapies, new therapies are still needed for moderate to severe CD as primary failure of a therapy or loss of response over time can develop. The latter is not uncommon over potentially decades of therapy. Patients may also develop antibodies to an existing therapy with subsequent decrease in therapeutic effect, which requires a change to a new therapy with an alternate mechanism of action. Additionally, while current biological therapies can be successful, they can also produce serious side effects (see Table 1 below).¹²

The following table focuses on the adult indications for the purposes of comparison against ustekinumab, currently proposed only for an adult indication in moderate to severe Crohn's disease.

Table 1: Summary of Biologic Treatment Armamentarium Relevant to Proposed Indication

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Important Safety and Tolerability Issues
Remicade® <i>Infliximab</i> Anti-TNF α	- reducing signs and symptoms and inducing and maintaining clinical remission in adult and pediatric patients with	1998	-Adults: 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. Some adult patients	Serious infections, malignancy, anaphylaxis, lupus like syndrome, heart failure, demyelinating disease

¹¹ Annese et al. 2015. European Evidence-based Consensus: Inflammatory Bowel Disease and Malignancies. *J Crohns Colitis* 9(11): 945-65.

¹² Armuzzi et al. 2016. Expert Consensus Paper on the use of Vedolizumab for the Management of Patients with Moderate-to-Severe Inflammatory Bowel Disease. *Digestive and Liver Disease* 48 (4).

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	moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. -reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing Crohn's Disease (adults only)		who initially respond to treatment may benefit from increasing the dose to 10 mg/kg if they later lose their response	
Humira® <i>adalimumab</i> Anti-TNFα	-reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. -reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.	2007	-Initial dose (Day 1): 160 mg (four 40 mg injections in one day or two 40 mg injections per day for two consecutive days) -Second dose two weeks later (Day 15): 80 mg Two weeks later (Day 29): Begin a maintenance dose of 40 mg every other week.	Serious infections, malignancy, anaphylaxis, lupus like syndrome, heart failure, demyelinating disease
Cimzia® <i>certolizumab</i> Anti-TNFα	-reducing signs and symptoms of Crohn's disease and maintaining clinical response in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy.	2008	-400 mg initially and at Weeks 2 and 4. If response occurs, follow with 400 mg every four weeks	Serious infection, malignancy, heart failure, anaphylaxis, lupus like syndrome, demyelinating disease, cytopenias
Tysabri® <i>natalizumab</i> Integrin receptor antagonist	inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of TNF-α.	2007	-300 mg infused intravenously over one hour, every four weeks -In CD, discontinue in patients that have not experienced therapeutic benefit by 12 weeks of	REMS: Progressive multifocal leukoencephalopathy (PML) Serious infections, hepatotoxicity, anaphylaxis Other: TYSABRI should not be used in combination with immunosuppressants (e.g.,

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			induction therapy, and in patients that cannot discontinue chronic concomitant steroids within six months of starting therapy.	6-mercaptopurine, azathioprine, cyclosporine, or methotrexate) or inhibitors of TNF- α
Entyvio <i>vedolizumab</i> integrin receptor antagonist	Adult patients with moderately to severely active CD who have had an inadequate response with, lost response to, or were intolerant to a TNF blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids: - achieving clinical response - achieving clinical remission - achieving corticosteroid-free remission	2014	-Recommended dosage in UC and CD: 300 mg infused intravenously over approximately 30 minutes at zero, two and six weeks, then every eight weeks thereafter. -Discontinue ENTYVIO in patients who do not show evidence of therapeutic benefit by Week 14.	Serious infections, hypersensitivity, PML

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Stelara is a human interleukin (IL) 12/23 inhibitor that is currently approved for the indications of psoriasis and psoriatic arthritis. Stelara received its initial approval in 2009 for moderate to severe plaque psoriasis and a subsequent approval in 2013 for in the treatment of active psoriatic arthritis. The initial approval included a REMS to evaluate and mitigate the potential risks of serious infections and malignancy, and reversible posterior leukoencephalopathy syndrome (RPLS) associated with Stelara. These indications utilize a subcutaneous formulation of Stelara. The phase 3 studies submitted in this BLA to support approval and labeling for the Crohn’s indication also use a subcutaneous formulation for maintenance treatment, but additionally introduce a new intravenous formulation for the initiation of treatment. While

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Stelara does not have any clinical holds associated with its program, there was an interruption of clinical studies in 2011 to address a CMC issue of instability in the intravenous formulation new for this indication. The intravenous formulation was replaced with a stable version and clinical studies resumed.

3.2. Summary of Presubmission/Submission Regulatory Activity

Under IND 11632, the Applicant initiated the Crohn's disease clinical program on May 1, 2004. Key regulatory events in the clinical development program consist of a phase 2a proof-of-concept study, a phase 2b induction and maintenance study, and three phase 3 studies (2 induction and 1 maintenance). The phase 3 clinical studies were conducted with the currently approved 90 mg/mL subcutaneous formulation used to treat psoriasis and psoriatic arthritis. Therefore, a PK comparability study bridging the 90 mg/mL IV formulation used in the clinical program to the intended to-be-marketed 5 mg/mL IV formulation was also conducted. The PK exposure was found to be comparable between the 90 mg/mL LIV and the 5 mg/mL LIV formulation. C_{max} and AUC were similar between the two formulations based on the standard bioequivalence interval of 0.80 to 1.25. Refer to the Clinical Pharmacology review by Dr. Christine Hon for further details.

Key Regulatory History

15 Jan 2004, Pre-IND Meeting: The Applicant met with the Division to discuss clinical development of ustekinumab for the treatment of patients with moderately to severely active Crohn's disease. The Applicant proposed a phase 2a proof-of-concept study (C0379T07) to demonstrate safety and efficacy and determine if SC or IV formulations were necessary for induction of remission in the moderate to severe Crohn's population.

Two populations were proposed for this study, which remain in the currently proposed indication, patients who failed conventional therapy and patients who failed commercial infliximab (only approved biologic at the time).

The Division agreed with the proposed study design but recommended the Applicant add dose ranging at this phase of development.

18 July 2007, End of Phase 2 Meeting: After completion of a phase 2a proof-of-concept study, phase 3 development was discussed consisting of 2 identical induction studies based on study populations of only those who failed or were intolerant of anti-TNF therapy, feeding into a single maintenance study. The proposed induction studies included 2 parts: IV dose ranging (3 different IV doses) and dose confirming where one dose would be selected for further study. The maintenance study would include 90 mg every 8 weeks or every 12 weeks dosing. The Division had the following key recommendations regarding the proposed clinical development program:

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- Consider also studying a broader population, including those who failed conventional therapy as the therapy may be used in this population as well as a population with inadequate response to TNF antagonist therapies. (This suggestion is currently included in the present application in the phase 3 studies.)
- Perform an additional phase 2 study to help estimate the optimal IV induction dose and the dose and regimen for use in a phase 3 maintenance study. (This was done: phase 2b study (C0743T26))
- Response at Week 6 should be the primary endpoint for both parts of the induction studies. (Reflected in currently submitted study)

17 Feb 2011, Type C Meeting: After completion of the phase 2b study (C0743T26), key design elements of the phase 3 program were discussed. The proposed phase 3 program incorporated a new 5 mg/mL formulation (130 mg/26 mL) to facilitate the preparation of the IV dose, which was intended to be dosed in increments of 130 mg. The clinical development program consisted of 2 IV induction studies and a single, large SC maintenance study. The 2 induction studies proposed were identical in design, but differed in patient population (anti-TNF refractory patients vs those who failed conventional therapy):

- Study 1 (CNT01275CRD3001) to include patients who had an inadequate response or were intolerant to anti-TNF α therapy.
- Study 2 (CNT01275CRD3002) was initially to include a broad population of patients with moderate to severe Crohn's disease, including: those who are immunomodulator-naive, or immunomodulator experienced (including inadequate responders or intolerants), or those who have previously been treated with TNF antagonist therapy.

The Agency had concerns about the broadness of the Study 2 population and the definition of response that would justify a clinically meaningful endpoint in this broad population. The Division recommended that the Applicant select a more narrow population, and the Applicant proposed with the patient population that is in the currently submitted Study 2 for marketing: a population who failed conventional therapy excluding TNF antagonist-refractory patients as well as immunomodulator-naive patients.

23 August 2011, FDA Notification of Stability Issue: The Agency identified a potential stability issue with the IV formulation and notified the Applicant of this issue regarding the rate of degradation with the proposed 5 mg/mL formulation.

21 and 23 December 2011, Notification of Suspension of Dosing of the IV Formulation: In December 2011, the Applicant reported that their own CMC investigation yielded data that indicated the IV formulation was likely to fall outside of specifications at the 12 month time point. The Applicant informed the FDA that the 5 mg/mL clinical supplies has been quarantined, and that IV dosing was suspended in the ongoing phase 3 studies. Actions to replace this

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formulation were required by the FDA in order to resume dosing in the clinical studies. In February 2012, the Applicant revised the protocols and study documents replacing the 5 mg/mL (IV) formulation with the marketed 90 mg/mL vial formulation and studies were allowed to resume. The root cause of the instability with the 5 mg/mL formulation was identified and resolved. A new formulation was ultimately developed, the to-be-marketed 130 mg/26 mL (5 mg/mL) formulation.

26 June 2013, 7 August 2013, 02 June 2014, and 16 March 2015, Response to FDA IRs Concerning the Statistical Analysis Plans (SAP) for the Phase 3 Studies: The Applicant submitted modifications to the SAPs to address the Division's IRs received on 5 April 2013, 28 May 2013, and 19 July 2013. The responses included justification of clinical response at Week 6, meaningfulness of clinical response, treatment of missing data, and control of Type 1 error. Additionally, the Applicant provided a rationale for excluding the first 28 patients, who were dosed with the 5 mg/mL IV formulation, from the analysis in study CNTO1275CRD3001, and specified that analyses with all randomized patients would be included in the Summary of Clinical Efficacy (SCE) in the BLA submission.

18 December 2013, Type C Meeting: The Agency granted written responses in lieu of a Type C meeting regarding the following topics:

- The Applicant proposed exchanging a current secondary endpoint (clinical remission at week 8) and the primary endpoint (clinical response, defined by reduction of CDAI of 100 points) for the primary endpoint for the induction study, CNTO1275CRD3002. The Agency agreed that clinical remission is a preferable primary endpoint, however, concluded that the study was too far ongoing to change the primary endpoint at such a late stage. The Agency recommended to collect key signs and symptoms in addition to the CDAI to evaluate efficacy.
- The Agency agreed the Applicant's proposed CMC biophysical, biochemical, and biological comparability data package between the to-be-marketed 5 mg/mL IV and the 90 mg/mL formulations appeared reasonable in conjunction with the proposed design of a PK comparability study to be conducted in healthy patients comparing the to-be-marketed 5 mg/mL (IV), with the 90 mg/mL formulations used in the phase 3 IV induction studies.

12 May 2015, Type C Meeting: The Agency met with the Applicant regarding the endoscopic substudy where the Agency clarified the following:

- Mucosal healing would be limited to endoscopic appearance. Claims (b) (6) would remain a review issue.
- The Applicant was requested to provide a separate analysis of patients who discontinued corticosteroids and remained steroid free throughout the maintenance study. (The Applicant performed this analysis.)

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- The Applicant agreed to analyze key signs and symptoms of abdominal pain and stool frequency and proposed their scoring plan. (The Applicant submitted their analysis.)
- It was agreed that no Integrated Summary of Efficacy need be submitted with the submission.

19 November 2015: The Agency issued an agreement on the initial Pediatric Study Plan proposed by the Applicant. Key issues discussed prior to agreement were:

- Lowering the partial waiver age from 6 to 2 years of age. (The Applicant agreed.)
- Considering adding a placebo arm based on their exposure response data between adults and pediatrics. The Applicants European proposal contains a placebo arm. (The Applicant agreed.)

3.3. Foreign Regulatory Actions and Marketing History

In the United States, Stelara is approved for psoriatic arthritis (2013) and psoriasis (2009). It currently has a REMS to evaluate and mitigate the potential risks of serious infections and malignancy, and reversible posterior leukoencephalopathy syndrome (RPLS) associated with STELARA. Stelara is also approved in Europe for the same two indications and under development for Crohn's disease.

There is an agreed initial pediatric study plan (iPSP) in the US as of 2015 and a pediatric investigational plan in place in Europe as of 2014.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The OSI inspections identified two issues regarding the studies conducted for BLA 761044.

- During the inspection, it was noted that the line listings did not always match the calculated Crohn's Disease Activity Index (CDAI) scores documented in source records. This was attributed to the sponsor calculating the CDAI score reported in the line listings using the hematocrit value obtained from the patient's blood sample drawn at the time of the visit, whereas the clinical site used the hematocrit value obtained from the patient's blood sample drawn at the time of the previous visit as per the protocol.

In an IR dated May 10, 2016, the Applicant was asked to clarify whether local site
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hematocrit values from a previous visit were used for the CDAI calculation that determined eligibility for randomization into the maintenance study 3003 (i.e., Week 6 values used for Week 8 randomization). Given that the endpoint analyses utilized hematocrit values from the actual time point (i.e., Week 6 value for Week 6 analysis), the Applicant was asked to clarify whether there are any patients whose eligibility status would have changed (i.e., would or would not have been randomized) if hematocrit values from Week 8 had been used to calculate the CDAI values that determined randomization into the maintenance study. The Applicant identified 31 patients (11 of 388 patients [2.8%]) in the primary (randomized population) that would have been classified as ustekinumab nonresponders instead of responders. A re-analysis of the primary and key secondary endpoints was performed by FDA statisticians excluding these patients and it did not change the significance of any of the endpoints.

- Inspection of [REDACTED] (b) (4), the CRO responsible for the readings of the histology samples, confirmed that the histology study was designed as an exploratory study. The results of the study were not used in calculation of the primary efficacy outcome. The procedures agreed upon by the CRO and the sponsor were adhered to; however security controls do not appear adequate to meet standards to ensure data reliability and cannot be assured for data integrity. Of note, the clinical data investigated at the clinical sites and at [REDACTED] (b) (4) CRO responsible for the reading of the video endoscopies, appear to have been conducted adequately, and the data generated by these studies appear acceptable [REDACTED] (b) (4).

Additionally, during site selection for OSI inspections, efficacy analyses were performed excluding sites with large effect sizes for each Study (3001, 3002 and 3003) As well as sites that had investigators that had received large financial investments (>\$25,000) that were *also* high enrollers. None of these sites had any effect on the significance of the primary endpoint achieved in the induction studies of 3001 or 3002, or the q8w dosing regimen of the maintenance study. However, 3 sites (5104, 4803, and 3415) did affect the primary endpoint for the q12w dosing regimen of the maintenance study (e.g. rendering it not significant in achieving the primary endpoint of clinical remission). Two of these three sites were inspected (5104 in Serbia and 4803 in Poland) and the study was found to have been conducted adequately according to the OSI inspections.

4.2. Product Quality

Ustekinumab is a fully human immunoglobulin G1 kappa (IgG1k) monoclonal antibody to human interleukin (IL)-12/23p40 that binds with high affinity to human interleukin (IL)-12 and IL-23. Ustekinumab modulates IL-12 and IL-23 bioactivity by preventing interaction of IL-12 and

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IL-23 with the cell surface IL-12R β 1 receptor protein. Through this mechanism of action, ustekinumab neutralizes IL-12 (Th1)- and IL-23 (Th17)-mediated cellular responses.

The drug product used in the phase 3 developmental program (intravenous) is of a different formulation [REDACTED] (b) (4) as the to be marketed FVP (IV) drug product; however, the products are comparable from the analytical perspective. The Applicant also conducted a PK comparability study that supported comparability between the phase 3 product and the to be marketed product.

The CMC reviewers (Zhenzhen Liu, Maria Gutierrez-Lugo) find that the data submitted in this application support the conclusion that the manufacture of ustekinumab final vial product for intravenous injection [FVP (IV)] is well controlled, and leads to a product that is pure and potent. The product is free from endogenous or adventitious infectious agents, sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product is produced from the multiple production runs presented. It is recommended that this product be approved for human use under conditions specified in the package insert. Therefore, the CMC reviewers recommend that the intravenous dosage forms of ustekinumab be approved for human use under conditions specified in the package insert. The subcutaneous form of ustekinumab has been approved previously under BLA 125261. The ustekinumab solution is colorless to slightly yellow in appearance and has a pH of 5.7- 6.3. Ustekinumab does not contain preservatives.

Refer to CMC review by Dr. Zhenzhen Liu for the complete CMC review.

4.3. Clinical Microbiology

The ustekinumab drug product is a sterile, preservative-free 130 mg of ustekinumab in 26 mL, supplied as a single-use 30 mL Type I glass vial with a coated stopper for intravenous infusion or a 45 mg of ustekinumab in 0.5 mL and 90 mg of ustekinumab in 1 mL for subcutaneous injection.

The clinical microbiology team has determined that process validation studies confirm that the proposed drug product manufacturing process is under adequate microbial control and capable of consistently producing drug product that meets microbial specifications. In addition, media fill studies demonstrate that the drug product facility (Cilag AG) can consistently produce sterile drug product. Microbial in-process and release testing methods (bioburden, endotoxin, sterility, [REDACTED] (b) (4) and container closure integrity) were adequately validated and found to be adequate for use with ustekinumab drug product. Therefore, BLA 761044 is recommended for approval from a microbiology product quality perspective. See clinical microbiology review by Dr. Candace Gomez-Broughton for further details.

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4.4. **Nonclinical Pharmacology/Toxicology**

The nonclinical team (Drs. Jackye Peretz and Sushanta Chakder) did not find any approvability issues with this application. The Applicant did not conduct any new nonclinical studies to support the current biologics licensing application. The Applicant is cross-referencing all nonclinical information previously submitted under BLA 125261 that is supportive of the proposed indication and new intravenous formulation of ustekinumab. These studies were previously reviewed for BLA 125261 dated November 28, 2008 (J. Yao, Ph.D.; Dermatology and Dental Products). Please see nonclinical review by Dr. Jackye Peretz.

4.5. **Clinical Pharmacology**

Overall

The clinical pharmacology and pharmacometrics team recommend this BLA is acceptable to support approval for the induction dose of 6 mg/kg using weight tiered dosing and the maintenance dosing regimen of 90mg SC q8w. (b) (4)

The clinical pharmacology team did recommend a post-marketing commitment (PMC) for the following study: Conduct a clinical trial to assess whether ustekinumab alters the metabolism or pharmacokinetics of cytochrome P450 (CYP) substrates in CD patients treated with ustekinumab (e.g., using a cocktail of relevant CYP probe drugs). This recommendation is based on the current understanding that CD patients have elevated levels of proinflammatory cytokines which can suppress the expression of some CYP enzymes and the CYP enzyme expression could be normalized upon the disease improvement following the ustekinumab treatment.

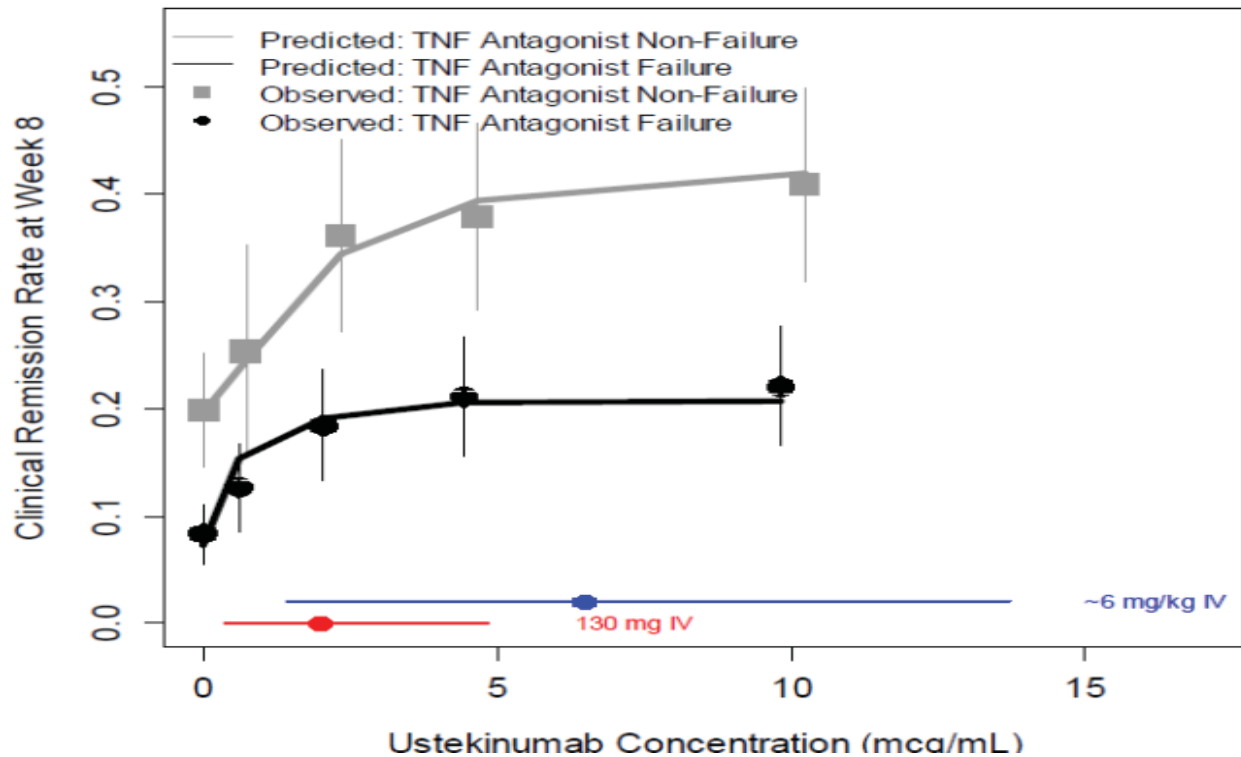
Dose Response

There were dose-dependent and concentration-dependent increases in clinical efficacy of ustekinumab for both the induction dose and the maintenance dosing regimen. Although both were significant, there were higher proportions of patient who achieved the clinically important endpoint of clinical remission at Week 8 in the 6 mg/kg IV dose group than in the 130 mg IV dose group (See Section 6.1.2 Study Results). Additionally, for the maintenance dosing regimen, the proportion of patients who achieved clinical remission at Week 44 was higher in the 90 mg/kg SC q8w dosing regimen than the 90 mg SC q12w group. Results from exposure response (E-R) analysis showed that clinical remission rate at Week 8 during induction was near plateau at ustekinumab concentrations of 5 – 10 µg/mL in patients who have or have not failed TNFα

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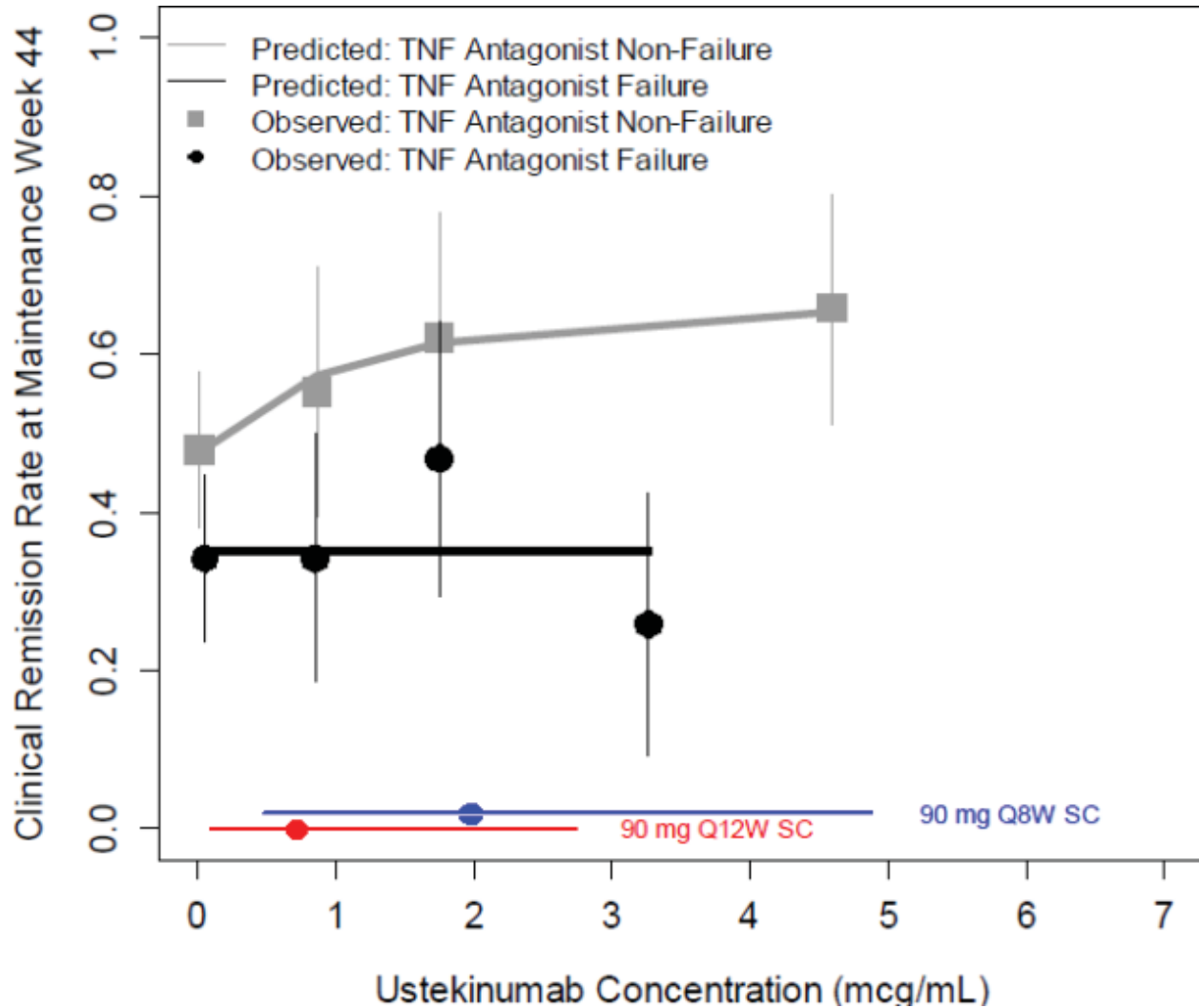
antagonist (Figure 1 below), whereas for maintenance phase a plateau was reached at ustekinumab concentrations of 2 – 5 µg/mL in patients who have not failed TNFα antagonist (Figure 2 below). There was no E-R relationship for maintenance therapy in patients who have failed TNFα antagonist.

Figure 1: Ustekinumab Concentration vs Clinical Remission at Week 8



Source: BLA 761044 Clinical Pharmacology Review by Dr. Christine Hon entitled Figure 5. Goodness-of-fit plot for E-R model in induction phase p. 20/84.

Figure 2: Ustekinumab Concentration vs Clinical Remission at Week 44



Source: BLA 761044 Clinical Pharmacology Review by Dr. Christine Hon entitled Figure 5: Goodness-of-fit plot for E-R model in maintenance phase p. 20/84.

Among patients who were randomized to ustekinumab 90 mg SC q12w dosing regimen, met loss of response (LOR) criteria and had a dose adjustment to 90 mg SC q8w dosing regimen, approximately 40% achieved clinical remission 16 weeks later, compared with 32% remission rate in patients in the ustekinumab 90mg SC q8w dosing regimen who met LOR criteria and remained on the 90 mg SC q8w regimen. The 8% improvement in clinical remission by increasing dosing frequency from q12w to q8w in patients who lost response over patients without dose adjustment suggested that the 90 mg SC q8w dosing regimen was more effective in achieving clinical remission than the 90 mg SC q12w dosing regimen. Additionally, serious infections had a higher incidence in the q12w dosing regimen than in the q8w regimen.

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Drug Drug Interactions

There were no formal drug-drug interaction studies or drug-disease interaction studies conducted. However looking at the concomitant use of immunomodulators (i.e. 6 mercaptopurine, azathioprine or methotrexate) did not appear to affect efficacy, PK or safety over the induction and maintenance dose trials.

Immunogenicity

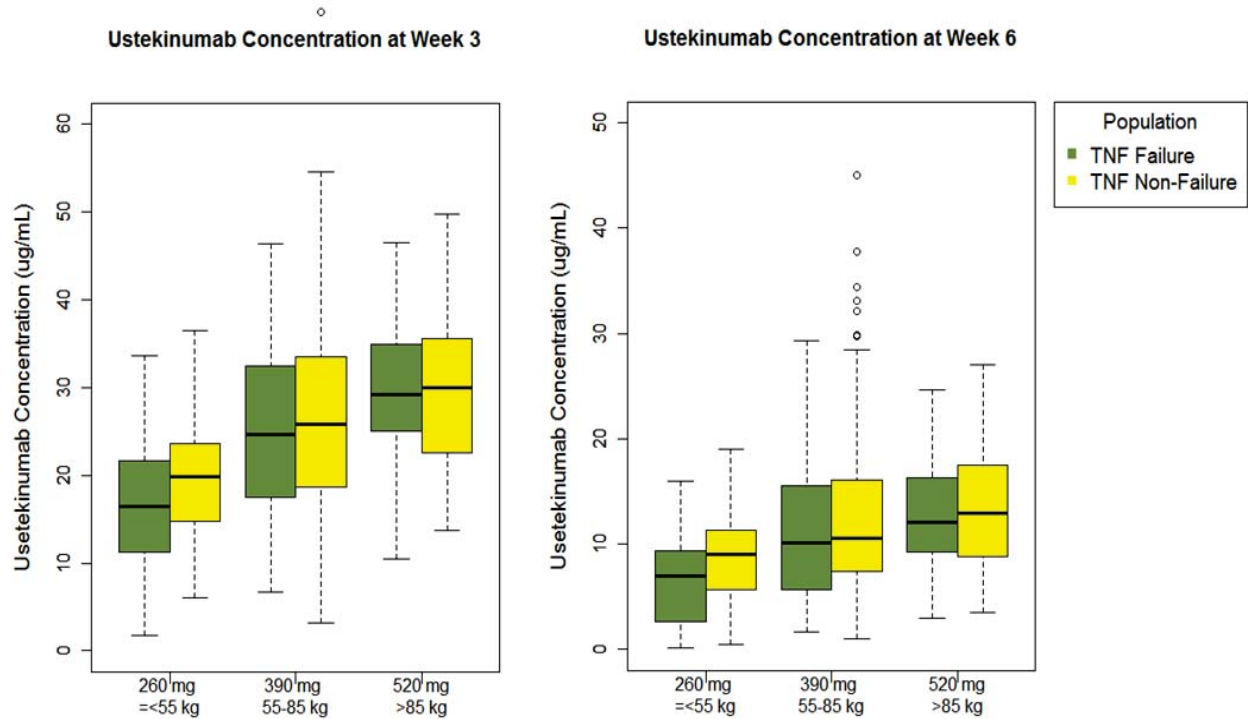
Twenty-seven of 1154 (2.3%) treated patients who received at least one dose of ustekinumab during induction or maintenance were positive for antidrug antibodies (ADA) in the phase 3 trials. Seventeen of the 27 (63%) patients were positive for neutralizing antibodies (NAb). The concomitant use 6-MP, AZA, and MTX had an impact on immunogenicity. The proportion of ADA+ patients was lower among those who received immunomodulators (7/375 patients, 1.9%) compared with those who did not receive immunomodulators (20/779 patients, 2.6%). However, immunogenicity did not appear to affect efficacy or safety, although these analyses were limited by the small number of patients who were ADA+. Immunogenicity did, however, have a negative effect on PK. The median observed serum ustekinumab concentrations were approximately two to three-fold lower in patients who were ADA+ than in patients who were ADA-. However as previously stated, this did not appear to have an effect on efficacy or safety.

Other Pertinent Issues

Body Weight

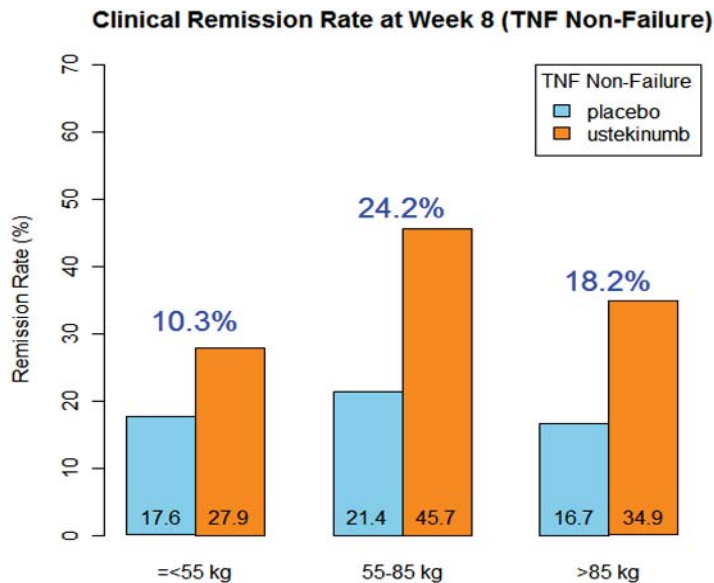
A Discipline Review letter was sent to the Applicant to request further datasets for analyses concerning the median ustekinumab concentrations by body weight, which despite being higher for the 6 mg/kg dose compared to 130 mg dose across all three body weight tiers (with up to two-fold or greater differences in median concentration), the remission rates across the body weight tiers were not consistently higher in the 6 mg/kg group than in the 130 mg group (See Figure 4 below). The lowers weight tier, <55kg, particularly did not appear to have the same levels of ustekinumab concentration after receiving the 6 mg/kg dosing as the other two higher weight tiers (See **Figure 3** below). After reviewing the datasets, the clinical pharmacology team determined that although the data indicated that the differences in ustekinumab concentrations within the same body weight tier across two dose regimens and across body weight tiers within the same regimen did not translate into differences in the clinical remission rates, when the combined data from all three body weight tiers are compared across two regimens, the 6 mg/kg dose showed a greater remission rate than the 130 mg dose and therefore should be the preferred IV dose for initial therapy.

Figure 3: Effect of weight-tiered induction dosing regimen on Week 3 and Week 6 ustekinumab concentrations



Source: Source: Discipline Review Letter dated July 21, 2016. Figures from clinical pharmacology reviewer Dr. Christine Hon and pharmacometrics reviewer Dr. Jee Eun Lee.

Figure 4: Clinical Remission By Weight Tier at Week 8 in Non TNF-failure Patients



Source: Source: Discipline Review Letter dated July 21, 2016. Figure from clinical pharmacology reviewer Dr. Christine Hon and pharmacometrics reviewer Dr. Jee Eun Lee.

See Clinical Pharmacology/Pharmacometric Review by Drs. Christine Hon, Jee Eun Lee, and Anuradha Ramamoorthy for further details.

4.5.1. Mechanism of Action

Ustekinumab is a fully human immunoglobulin G1 kappa (IgG1k) monoclonal antibody to human IL-12/23p40 that binds with high affinity to human interleukin IL-12 and IL-23. Ustekinumab modulates IL-12 and IL-23 bioactivity by preventing their interaction with their cell surface IL-12R β 1 receptor protein. Through this mechanism of action, ustekinumab blocks IL-12 (Th1)- and IL-23 (Th17)-mediated cellular responses. Abnormal regulation of IL-12 and IL-23 has been associated with multiple immune-mediated diseases, including IBD, as intestinal antigen-presenting cells secrete increased levels of IL-12 and IL-23 in CD.^{13,14} Therefore, binding

¹³ Liu Z, Yadav PK, Xu X, et al. The increased expression of IL-23 in inflammatory bowel disease promotes intraepithelial and lamina propria lymphocyte inflammatory responses and cytotoxicity. J Leukoc Biol. 2011;

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the IL-12/23 p40 subunit may provide effective therapy in CD. In CD, the Th1 and Th17 pathway stimulate TNF production, which results in intestinal inflammation and epithelial cell injury typical of CD.

Evidence for the role of IL-12/23p40 in CD was first supported by the results of Study C0379T07, a phase 2a study of ustekinumab administered intravenously (IV) or subcutaneously (SC) in patients who had failed conventional CD therapy¹⁵ and in study C0743T26 (CERTIFI), a positive phase 2b study of ustekinumab in CD patients who had failed or were intolerant to TNF antagonist therapy.¹⁶

4.5.2. Pharmacodynamics

Clinical Pharmacology and Pharmacometrics worked together for this review, please see Section 4.5, Clinical Pharmacology above.

4.5.3. Pharmacokinetics

Please see Section 4.5, Clinical Pharmacology, above.

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

At the time of this review, the Division of Medication Error Prevention and Analysis (DMEPA) had not yet provided their review.

89:597-606.

¹⁴ Monteleone G, Biancone L, Marasco R, et al. Interleukin 12 is expressed and actively released by Crohn's disease intestinal lamina propria mononuclear cells. *Gastroenterology*. 1997; 112(4):1169-1178.

¹⁵ Sandborn WJ, Feagan BG, Fedorak RN, et al. A randomized trial of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with moderate to severe Crohn's disease. *Gastroenterology*. 2008; 135(4):1130-1141.

¹⁶ Sandborn WJ, Gasink C, Gao LL, et al. Ustekinumab induction and maintenance therapy in refractory Crohn's disease. *N Engl J Med*. 2012;367(16):1519-1528.

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 2: Listing of Clinical Studies Relevant to this BLA 761044

Trial Identity	Trial Design	Regimen/schedule/route	Study Endpoints	Treatment Duration/Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
C0379T0 7 Phase 2a	Randomized, multicenter, blinded, placebo-controlled study in patients with Crohn's disease despite treatment with 5-ASA compounds, antibiotics, corticosteroids, and/or immunomodulators (Population 1), and an open-label study in patients who failed to respond to infliximab at the maximum approved dose and treatment regimen for Crohn's disease as defined in US package insert (Population 2)	Population 1 Placebo: SC dose at Weeks 0, 1, 2, and 3. At Weeks 8, 9, 10, and 11, patients were to receive CNTO1275 90 mg SC (n=26) Population 1 CNTO 1275 90 mg SC at Weeks 0, 1, 2, and 3. At Weeks 8, 9, 10, and 11, patients were to receive placebo SC (n=25) Population 1 Placebo IV at Week 0 and CNTO 1275 4.5 mg/kg IV at Week 8 (n=27)	Primary Endpoint: Clinical response at Week 8 defined as a reduction from baseline in the CDAI score of $\geq 25\%$ and ≥ 70 points at Week 8. Key Secondary Endpoints: 1. To assess which route of administration was more efficacious, the proportion of patients in clinical response following treatment with SC CNTO 1275 (SC Placebo → SC CNTO 1275 group at Week 16 and SC CNTO 1275 → SC Placebo group at Week	54 weeks	131	Men and women 18 years of age or older with moderately to severely active Crohn's disease or fistulizing Crohn's disease of at least 6 weeks duration.	3 countries: BEL, CAN, USA 62 centers

		Population 1 CNTO 1275 4.5 mg/kg IV at Week 0 and placebo IV at Week 8 (n=26) Population 2 CNTO 1275 90 mg SC at Weeks 0, 1, 2, and 3 (n=14) Population 2 CNTO1275 4.5 mg/kg IV at Week 0 (n=13)	8) was compared with the proportion of patients in clinical response following treatment with IV CNTO 1275 (IV Placebo → IV CNTO 1275 group at Week 16 and IV CNTO 1275 → IV Placebo group at Week 8) for the primary population (<i>Population 1</i>). 2. The efficacy of CNTO 1275 in Population 2 was assessed by summarizing the proportion of patients in clinical response at Week 8 among patients who received CNTO 1275 IV or SC in this population. 3. The PK profile of CNTO 1275 in patients with Crohn's disease was evaluated by summarizing separately the serum				

			concentrations and PK parameters following a single 4.5 mg/kg IV infusion and following 4 weekly 90-mg SC doses of CNTO 1275. 4. To assess whether CNTO 1275 is superior to placebo at inducing clinical remission, the proportion of patients in clinical remission at Week 8 following treatment with CNTO 1275 (SC CNTO 1275 → SC Placebo group and IV CNTO 1275 → IV Placebo group combined) was compared with the proportion of patients in clinical remission at Week 8 following treatment with placebo (SC Placebo → SC CNTO 1275 group and IV Placebo → IV CNTO 1275			

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			group combined) in the primary population (Population 1).				
C0743T2 6 Phase 2b	Multicenter, randomized, double-blind, placebo-controlled, parallel group, dose-ranging study	Study drug Administration (IV): Placebo (n=132) Ustekinumab 1 mg/kg (n=130) Ustekinumab 3 mg/kg (n=133) at Weeks 0, 8, and 16; and follow-up at Week 36	Primary Endpoint: The proportion of patients in clinical response at Week 6 Key Secondary Endpoints: 1) clinical remission at Week 6 2) clinical response at Week 4 3) clinical remission at Week 22 Among patients randomized as responders to ustekinumab induction.	36 weeks	395	Men and women 18 years of age or older with moderately to severely active Crohn's disease for at least 3 months, with colitis, ileitis, or ileocolitis as confirmed by radiography and/or endoscopy previously treated with TNF antagonist therapies (failures and non-failures)	12 countries: AUS, AUT, BEL, CAN, DEU, ESP, FRA, GBR, ISR, ITA, NLD, USA 153 centers

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			Clinical Response: CDAI decrease by ≤100 points Clinical Remission: CDAI <150				
CNT012 75CRD30 01 – Phase 3	Multicenter, randomized, double-blind, placebo-controlled, parallel group study	One time dose Group 1: Placebo (n=245) Group 2: Ustekinumab 130 mg (n=246) Group 3: Ustekinumab 6 mg/kg Tiered by weight: 260 mg for weight ≤ 55 kg); 390 mg (weight >55 kg and ≤85 kg); 520 mg (weight >85 kg) (n=249)	Primary Endpoint: Clinical response at Week 6, defined as a reduction from baseline in the CDAI score of ≥100 points Key Secondary Endpoints: 1) Clinical Remission at Week 8 2) Clinical Response at Week 8 defined as reduction from baseline in CDAI score of ≥100 points 3) 70 point CDAI Reduction at Week 6 Response 4) 70 point CDAI Reduction at Week 3 Response	20 weeks	741	Men or women 18 years of age or older with moderately to severely active Crohn's disease who have failed or are intolerant to TNF antagonist therapies	AUS, AUT, BEL, BRA, CAN, CZE, DEU, DNK, 22 countries: ESP, FRA, GBR, HUN, IRL, ISR, ITA, JPN, KOR, NLD, NZL, POL, USA, ZAF 178 centers
CNT012 75CRD30 02 Phase 3	Multicenter, randomized, double-blind, placebo-controlled, parallel group study	One time dose Group 1: Placebo (n=208)	Primary Endpoint: Clinical response at Week 6,	20 weeks	640	Men or women 18 years of age or older with moderately	22 countries; AUS, BEL, BGR, BRA, CAN, DEU, ESP, FRA, GBR, HRV,

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		Group 2: Ustekinumab 130 mg (n=212) Group 3: Ustekinumab 6 mg/kg Tiered by weight: 260 mg for weight ≤ 55 kg); 390 mg (weight >55 kg and ≤85 kg); 520 mg (weight >85 kg) (n=207)	defined as a reduction from baseline in the CDAI score of ≥100 points Key Secondary Endpoints: 1) Clinical Remission at Week 8 2) Clinical Response at Week 8 defined as reduction from baseline in CDAI score of ≥100 points 3) 70 point CDAI Reduction at Week 6 Response 4) 70 point CDAI Reduction at Week 3 Response			to severely active Crohn's disease who previously failed conventional therapy (i.e. corticosteroids and immunomodulators); had evidence of active inflammation (i.e., elevated C-reactive protein [CRP] or elevated fecal calprotectin or endoscopic/histologic or radiologic evidence of active Crohn's disease); had not previously demonstrated inadequate response or intolerance to 1 or more TNF antagonists	HUN, ISL, ISR, ITA, JPN, KOR, NLD, NZL, POL, RUS, USA, ZAF 175 centers
CNT012 75CRD30 03 Phase 3	Multicenter, randomized, double-blind, placebo-controlled, parallel group study	Group 1 Placebo (n=133) Group 2	Primary Endpoint: Clinical remission at Week 44, defined as	44 weeks	397	397 patients who responded (i.e. were in clinical response) to	22 countries: AUS, BEL, BGR, BRA, CAN, DEU, ESP, FRA, GBR, HRV,

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		ustekinumab 90 mg q12w (n=132) Group 3 ustekinumab 90 mg q8w (n=132)	CDAI <150 Key Secondary Endpoints: 1) Clinical Response at Week 44 (based on CDAI reduction from beginning of Study 3001/3002) 2) Clinical Remission Week 44 in patients in clinical remission at week 0 of maintenance 3) Corticosteroid free remission at Week 44 4) Clinical remission at Week 44 in TNF refractory/intolerant patients (i.e. from Study 3002)			the IV dose by week 8 (31.0%) from studies 3001 and 3002 were randomized into the primary population <i>Non-randomized population: 884 patients (69.0%) were enrolled but not randomized</i> <i>- 123 placebo induction responders who continued to receive placebo</i> <i>- 285 placebo induction nonresponders who received an ustekinumab 130 mg IV infusion at Week 0. Patients who achieved clinical response by Week 8 of maintenance continued to receive</i>	HUN, ISL, ISR, ITA, JPN, KOR, NLD, NZL, POL, RUS, USA, ZAF 260 centers

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					<i>ustekinumab 90 mg q12w (subsequent induction responders).</i> <i>- 476 ustekinumab induction nonresponders who received ustekinumab 90 mg at Week 0. Patients who achieved clinical response by Week 8 of maintenance continued to receive ustekinumab 90 mg q8w (delayed responders).</i>	

5.2. Review Strategy

Studies CNTO1275CRD3001 (study 3001), CNTO1275CRD3002 (study 3002), and CNTO1275CRD3003 (study 3003) are the primary sources of data that are reviewed in this document. Studies 3001 and 3002 provided the main sources of data to support the efficacy and safety of a single, initial intravenous (IV) induction regimen of ustekinumab in patients with moderately to severely active Crohn's disease. The main difference between these two induction studies was the patient population of study 3001 included patients who have failed or are intolerant to 1 or more tumor necrosis factor (TNF) antagonist therapies, whereas the population of study 3002 was required to have failed conventional therapy (i.e., 5-ASAs or immunomodulators) and must *not* have failed or been intolerant to anti-TNF therapy in the past. Therefore, these two induction studies will be presented together in this document and any differences between them will be noted.

Study 3003 provides the main source of data to support longer-term efficacy and safety for the 2 subcutaneous (SC) maintenance regimens of ustekinumab in patients with moderately to severely active Crohn's disease induced into clinical response with ustekinumab in induction studies 3001 and 3002. All studies conducted by the Applicant in patients with CD are summarized above in Section 5.1, Table of Clinical Studies.

6 Review of Relevant Individual Trials Used to Support Efficacy

Studies: Induction Protocols CNTO1275CRD3001 (study 3001): Patients Who Have Failed or Are Intolerant to TNF Antagonist Therapy and CNTO1275CRD3002 (study 3002): Patients Who Have Failed Conventional Therapy and Maintenance Protocol CNTO1275CRD3003 (study 3003): Combined Maintenance Protocol

6.1.1. Study Design

Overview and Objective

The following two induction studies will be reviewed together in this section as the study design was similar between the two studies, and any differences will be noted:

- Protocol CNTO1275CRD3001: A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Induction Therapy in Patients with Moderately to Severely Active Crohn's Disease Who

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Have Failed or Are Intolerant to TNF Antagonist Therapy (this study will be referred to as study 3001)

- Protocol CNTO1275CRD3002: A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Induction Therapy in Patients with Moderately to Severely Active Crohn's Disease (this study will be referred to as study 3002).

The primary objective of studies 3001 and 3002 was to evaluate the efficacy and safety of 2 different intravenous (IV) induction regimens of ustekinumab over 8 weeks for inducing clinical response in patients with moderately to severely active Crohn's disease. Study 3001 enrolled a patient population who have failed or were intolerant to 1 or more tumor necrosis factor (TNF α) antagonist therapies. The patient population of study 3002 differed in that the patient population must have failed conventional therapy (i.e., immunomodulators, 5-ASAs) and must *not* have previously demonstrated inadequate response or intolerance to 1 or more tumor necrosis factor (TNF) antagonist therapies.

Secondary objectives of studies 3001 and 3002 were:

- to evaluate the efficacy of IV induction regimens of ustekinumab in inducing clinical remission;
 - to evaluate the efficacy of IV induction regimens of ustekinumab in improving disease-specific health-related quality of life;
 - to evaluate the pharmacokinetics and pharmacodynamics of ustekinumab therapy, including changes in C-reactive protein (CRP), fecal calprotectin, fecal lactoferrin, and other pharmacodynamic biomarkers;
 - to provide the target study population to be evaluated in the maintenance study CNTO1275CRD3003
-

Maintenance Study 3003

The following maintenance study will be reviewed in this section:

- Protocol CNTO1275CRD3003: A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Maintenance Therapy in Patients with Moderately to Severely Active Crohn's Disease (this study will be referred to as study 3003)

The primary objective of study 3003 was to evaluate clinical remission of 2 subcutaneous (SC) maintenance regimens of ustekinumab in patients with moderately to severely active Crohn's disease induced into clinical response with ustekinumab in the induction studies, 3001 and 3002, and to evaluate the safety of 2 SC maintenance regimens of ustekinumab in patients with moderately to severely active Crohn's disease.

Secondary objectives of study 3003 were:

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- to evaluate the efficacy of ustekinumab in maintaining clinical response in patients induced into clinical response;
- to evaluate the efficacy of ustekinumab in maintaining clinical remission in patients induced into clinical remission;
- to evaluate the efficacy of ustekinumab in achieving corticosteroid free remission;
- to evaluate the pharmacokinetics (PK), immunogenicity, and pharmacodynamics (PD) of ustekinumab therapy, including changes in C-reactive protein (CRP), fecal calprotectin, fecal lactoferrin, and other PD biomarkers;
- to evaluate the effect of ustekinumab on health-related quality of life (QOL).

Trial Design

Study Design: Induction Trials 3001 and 3002

Study Design

Studies 3001 and 3002 were both 8 week, multicenter, randomized, parallel-group, placebo controlled studies to evaluate the efficacy and safety of 2 different IV induction regimens of ustekinumab in inducing clinical response in:

- patients with moderately to severely active Crohn's disease who have failed or are intolerant to 1 or more TNF antagonist therapies (study 3001), and
- patients must have failed conventional therapy (i.e. immunomodulators or 5-ASAs) and must not have previously demonstrated inadequate response or intolerance to 1 or more TNF antagonist therapies (i.e., infliximab, adalimumab, or certolizumab pegol) (study 3002).

Patients were randomized in a 1:1:1 ratio at Week 0 to receive a single IV dose of the one following:

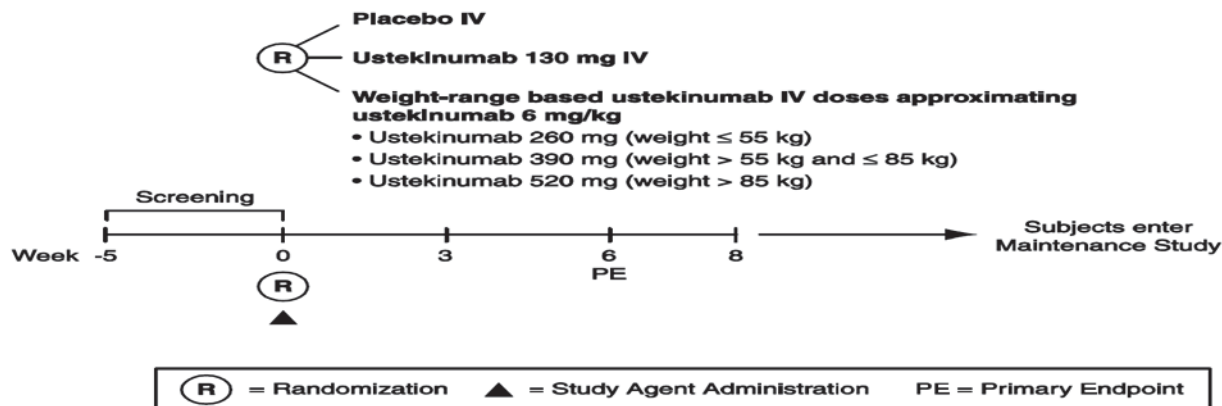
- Placebo
- 130 mg IV ustekinumab
- One of 3 tiered weight-based doses of approximately 6 mg/kg IV ustekinumab
 - 260 mg for weight ≤ 55 kg
 - 390 mg for weight >55 kg and ≤ 85 kg
 - 520 mg for weight >85 kg

Patients were evaluated for the primary endpoint of clinical response, defined as a reduction from baseline in the CDAI score of ≥ 100 points, at week 6. Those who were in clinical response and received treatment with ustekinumab at week 8 were eligible to enter the maintenance study (study 3003) at week 8. Patients found not to be in clinical response and all patients who received placebo were eligible to enter study 3003 but were *not* included in the primary

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efficacy analyses for the maintenance study (study 3003). Patients who did not enter study 3003 at the end of studies 3001 and 3002 were scheduled for follow up safety visits 20 weeks after they initiated the induction study. Figure 5 below shows a study schematic for studies 3001 and 3002.

Figure 5: Schematic of Induction Studies 3001 and 3002



Source: From Applicant's Figure 1, entitled, in Clinical Protocol CNTO1275CRD3001 A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Induction Therapy in Patients with Moderately to Severely Active Crohn's Disease Who Have Failed or Are Intolerant to TNF Antagonist Therapy p. 23/116.

Colonoscopy was optional in this study but for patients who consented to undergo colonoscopy, the results were used to assess endoscopic improvement as measured by change from baseline by the Simple Endoscopic Score for Crohn's Disease (SES-CD). A video ileocolonoscopy examination was to be performed according to the study reference manual provided to each site to standardize the procedure, including biopsies, across sites, at screening (at least 8 days before or at the Week 0 visit), and at least 8 days before or at the Week 8 visit to determine the presence or absence of mucosal inflammation and ulceration. Video endoscopies were assessed by a central reader that was blinded to treatment group and visit. A complete video endoscopic examination did not require assessment of the terminal ileum if it could not be visualized. A histological assessment of disease and healing was performed as an additional component of the endoscopy substudy. Biopsies were taken at pre-specified locations in the colon and measured for change from baseline using a modified version of the Global Histology Activity Score (GHAS). Copies of the SES-CD and GHAS are provided in the Appendix, 12.3.

Study 3001 enrolled 703 patients and was conducted in 178 sites across North and South America, Europe, the Asia Pacific Region, Israel and South Africa. The study was initiated on June 23, 2011 and completed July 03, 2013 with a database lock date of August 16, 2013.

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Study 3002 enrolled 612 patients and was conducted in 175 sites across North and South America, Europe, the Asia Pacific Region and South Africa. The study was initiated on June 23, 2011 and completed October 28, 2014 with a database lock date of September 9, 2014.

The Applicant stated that the clinical studies were conducted in accordance with the Institutional Review Board (IRB) and/or Independent Ethics Committee (IEC), and in accordance with United States and international standards of Good Clinical Practice (GCP) as defined by the Food and Drug Administration [FDA] Title 21 part 312 and International Conference on Harmonization [ICH] guidelines.

Diagnostic Criteria

To enroll, patients had to be ≥ 18 years of age and have moderately to severely active Crohn's disease (of at least 3 months' duration), defined as a Crohn's Disease Activity Index [CDAI] score ≥ 220 but ≤ 450 . This reviewer finds this definition of moderately to severely active disease acceptable. Patients had to have colitis, ileitis, or ileocolitis previously confirmed at some time in the past by either radiography, histology, and/or endoscopy. At the time this study was designed and conducted this approach was acceptable; however, currently the Division requires a biopsy proven diagnosis of Crohn's disease at baseline to qualify for enrollment in the study in addition to a patient reported outcome measurement because the CDAI does not always correlate with underlying mucosal inflammation.¹⁷ For study 3001, a washout period of at least 8 weeks was required for patients who received prior TNF antagonist therapy with infliximab (REMICADE®), adalimumab (HUMIRA®), or certolizumab pegol (CIMZIA®) at a dose approved for the treatment of Crohn's disease, and have been documented to have not responded initially, responded initially but then lost response, or were intolerant¹⁸ to the medication. For study 3002 patients must have failed conventional therapy and must not have previously demonstrated inadequate response or intolerance to 1 or more TNF antagonist therapies (i.e., infliximab, adalimumab, or certolizumab pegol), and have active disease, as defined by one of the following in addition to CDAI:

- an abnormal CRP (>3.0 mg/L);
- fecal calprotectin >250 mg/kg at screening; or
- endoscopy (within 3 months prior to baseline) with evidence of active Crohn's disease during the current disease flare.

¹⁷ Regueiro et al. 2011. Crohn's disease activity index does not correlate with endoscopic recurrence one year after ileocolonic resection. *Inflammatory Bowel Disease* 17(1): 118-126.

¹⁸ Intolerance was defined as documented adverse reaction that meets 1 of the following 3 criteria: 1) significant acute infusion/administration reaction; 2) significant delayed infusion/administration reaction (for example, delayed hypersensitivity or serum-sickness like reaction); or 3) significant injection site reaction. Adverse reactions also must have followed at least 1 dose of infliximab, adalimumab, or certolizumab pegol and, in the treating physician's opinion, precluded continued use of the therapy.

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Inclusion/Exclusion Criteria

Key Inclusion Criteria

- Males and females ≥ 18 years of age.
- Diagnosis of active Crohn's disease or fistulizing Crohn's disease of at least 3 months duration, with colitis, ileitis, or ileocolitis, confirmed at any time in the past by radiography, histology, and/or endoscopy, and a baseline CDAI score of ≥ 220 and ≤ 450 .
- Adhere to the requirements for concomitant medication for the treatment of Crohn's disease. The following medications are permitted provided doses meet the requirements below are stable for or have been discontinued at least 3 weeks prior to baseline (Week 0), unless otherwise specified.
 - Oral 5-ASA compounds (dose not defined).
 - Oral corticosteroids (e.g., prednisone, budesonide) at a prednisone-equivalent dose of ≤ 40 mg/day or ≥ 9 mg/day of budesonide.
 - Antibiotics being used as a primary treatment of Crohn's disease.
 - Patients receiving conventional immunomodulators (i.e., AZA, 6-MP, or MTX) must have been taking them for ≥ 12 weeks, and on a stable dose for at least 4 weeks prior to baseline.
- Have baseline laboratory values within the defined ranges
 - Hemoglobin ≥ 8.5 g/dL
 - WBCs $\geq 3.5 \times 10^3/\mu\text{L}$
 - Neutrophils $\geq 1.5 \times 10^3/\mu\text{L}$
 - Platelets $\geq 100 \times 10^3/\mu\text{L}$
 - Serum creatinine < 1.7 mg/dL
 - AST and ALT concentrations must be within 2 times the ULN range for the laboratory conducting the test.
 - Direct (conjugated) bilirubin < 1.0 mg/dL.
- Have TB screening and history negative for latent or active TB (confirmed with QuantiFERON-TB gold and CXR)
- Unable to bear or take precautions to prevent childbearing
- Able to sign and understand informed consent and be able to adhere to the prohibitions and restrictions of the study.

STUDY 3001 ONLY

- Received infliximab, adalimumab, or certolizumab pegol at a dose approved for the treatment of Crohn's disease and
 - Did not respond initially (i.e., primary nonresponders);
 - Responded initially but then lost response with continued therapy (i.e., secondary nonresponders);
 - Were intolerant to the medication.

STUDY 3002 ONLY

- Active Crohn's disease, defined as at least one of the following:
 - An abnormal CRP (> 0.3 mg/dL or 3.0 mg/L) at screening; or
 - Calprotectin > 250 mg/kg at screening; or
 - Endoscopy with evidence of active Crohn's disease during the current disease flare (defined as ulcerations in the ileum and/or colon). The endoscopy must have occurred within 3 months prior to baseline.
- Meet the following requirements for prior or current medications for Crohn's disease:
 - Has failed conventional therapy:
 - Is currently receiving corticosteroids and/or immunomodulators (i.e., AZA, MTX, or 6-MP) at adequate therapeutic doses; or
 - Has a history of failure to respond to or tolerate an adequate course of corticosteroids and/or immunomodulators (i.e., AZA, MTX, or 6-MP); or
 - Is corticosteroid dependent or has had a history of corticosteroid dependency (defined by professional society guidelines¹⁹); and
 - Has not previously demonstrated inadequate response or intolerance to 1 or more TNF antagonist therapies (i.e., infliximab, adalimumab, or certolizumab pegol)

Exclusion Criteria

- Complications of Crohn's disease such as symptomatic strictures or stenosis, short gut syndrome, or any other manifestation that might be anticipated to require surgery, could preclude the use of the CDAI to assess response to therapy, or would possibly confound the ability to assess the effect of treatment with ustekinumab.
- Currently has or is suspected to have an abscess. Recent cutaneous and perianal abscesses are not exclusionary if drained and adequately treated at least 3 weeks prior to baseline, or 8 weeks prior to baseline for intra-abdominal abscesses, provided that there is no anticipated need for any further surgery. Patients with active fistulas may be included if there is no anticipation of a need for surgery and there are currently no abscesses identified.
- History of bowel resection within 6 months or any other intra-abdominal surgery within 3 months prior to baseline.
- Current draining (i.e., functioning) stoma or ostomy.
- Received any of the following prescribed medications or therapies within the specified period:
 - IV corticosteroids < 3 weeks prior to baseline.
 - Other oral immunomodulatory agents (e.g., 6-thioguanine [6-TG], cyclosporine,

¹⁹ van Assche G, Dignass A, Panes J, et al. 2010. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: definitions and diagnosis. *Journal of Crohn's and Colitis* 4(1):7-27.

- tacrolimus, sirolimus, or mycophenolate mofetil) < 6 weeks prior to baseline.
- Non-biologic experimental or investigational agents < 4 weeks or within 5 half-lives of agent prior to baseline, whichever is longer.
- Non-autologous stem cell therapy (e.g., Prochymal), natalizumab, efalizumab, or biologic agents that deplete B or T cells (e.g., rituximab, alemtuzumab, or visilizumab) < 12 months prior to baseline.
- Anti-TNF biologic agents (e.g., monoclonal antibody therapies) or other agents intended to suppress or eliminate TNF < 8 weeks prior to baseline.
- Other immunomodulatory biologic agents < 12 weeks or within 5 half-lives of agent prior to baseline, whichever is longer.
- Treatment with apheresis (e.g., Adacolumn apheresis) or total parenteral nutrition (TPN) as a treatment for Crohn's disease < 3 weeks prior to baseline.
- Positive stool culture or other examination positive for an enteric pathogen, including Clostridium difficile toxin, in the last 4 months unless a repeat examination is negative and there are no signs of ongoing infection with that pathogen.
- Previously received a biologic agent targeting IL-12 or IL-23, including but not limited to ustekinumab (CNTO 1275) or briakinumab (ABT-874).
- Received a Bacille Calmette-Guérin (BCG) vaccination within 12 months or any other live bacterial or live viral vaccination within 12 weeks of baseline.
- History of, or ongoing, chronic or recurrent infectious disease, including but not limited to, chronic renal infection, chronic chest infection, recurrent urinary tract infection (e.g., recurrent pyelonephritis or chronic nonremitting cystitis), or open, draining, or infected skin wounds or ulcers.
- Current signs or symptoms of infection. Established nonserious infections (e.g., acute upper respiratory tract infection, simple urinary tract infection) need not be considered exclusionary at the discretion of the investigator.
- History of serious infection (e.g., sepsis, pneumonia, or pyelonephritis), including any infection requiring hospitalization or IV antibiotics, for 8 weeks prior to baseline.
- Evidence of a herpes zoster infection < 8 weeks prior to baseline.
- History of latent or active granulomatous infection, including histoplasmosis or coccidioidomycosis, prior to screening. Refer to inclusion criteria for information regarding eligibility with a history of latent TB.
- Evidence of current active infection, including TB, or a nodule suspicious for lung malignancy on screening or any other available chest radiograph, unless definitively resolved surgically or by additional imaging and with source document confirmation.
- Current or history of a nontuberculous mycobacterial infection or serious opportunistic infection (e.g., cytomegalovirus colitis, Pneumocystis carinii, aspergillosis).
- Is known to be infected with HIV, hepatitis B, or hepatitis C.

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- Severe, progressive, or uncontrolled renal, hepatic, hematological, endocrine, pulmonary, cardiac, neurologic, cerebral, or psychiatric disease, or signs and symptoms thereof.
- History of transplanted organ (with exception of a corneal transplant > 12 weeks prior to screening).
- Known history of lymphoproliferative disease, including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy and/or splenomegaly.
- Known malignancy or has a history of malignancy (with the exception of basal cell carcinoma; squamous cell carcinoma in situ of the skin; or cervical carcinoma in situ that has been treated with no evidence of recurrence; or squamous cell carcinoma of the skin that has been treated with no evidence of recurrence within 5 years prior to screening).
- Previously undergone allergy immunotherapy for prevention of anaphylactic reactions.
- Is unable or unwilling to undergo multiple venipunctures because of poor tolerability or lack of easy access to veins.
- Is known to have had a substance abuse (drug or alcohol) problem within the previous 12 months prior to baseline.
- Has known allergies, hypersensitivity, or intolerance to ustekinumab or its excipients (refer to Investigator's Brochure).
- Currently or intending to participate in any other study using an investigational agent or procedure during participation in this study.
- Is a woman who is pregnant, or breast-feeding, or planning to become pregnant or is a man who plans to father a child while enrolled in this study or within 20 weeks after the last dose of study agent.
- Has any condition that, in the opinion of the investigator, would make participation not be in the best interest (e.g., compromise the well-being) of the patient or that could prevent, limit, or confound the protocol-specified assessments.

Dose Selection and Administration

Induction doses selected for studies 3001 and 3002 (i.e., ustekinumab 130 mg and tiered ustekinumab doses approximating 6 mg/kg ustekinumab) were based on the results of the phase 2 study C0743T26, in which a single IV infusion of 1 mg/kg, 3 mg/kg, or 6 mg/kg was administered to patients with Crohn's disease to induce clinical response, followed by maintenance doses of 90 mg SC injections at Weeks 8 and 16. In C0743T26, greater proportions of patients in the ustekinumab groups were in clinical response at Week 6 and at Week 8 compared with the placebo group for all doses; however, at the primary endpoint (clinical response at week 6) the 6 mg/kg group was statistically significant from placebo (39.7% vs 23.5%) with p value =0.005. Serum ustekinumab concentrations through Week 8 appeared lower in the 1 mg/kg group nonresponders compared with responders at Week 6. This

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difference was not observed in the 3 or 6 mg/kg groups. Additionally, when compared with Week 6, the proportions of patients in clinical response were higher at Week 8 in the 6 mg/kg group and lower in the 1 and 3 mg/kg groups. Therefore, the Applicant concluded that a dose response was demonstrated. Additionally, the 6 mg/kg dose showed the highest clinical response rates in study C0743T26 as exemplified by greatest reduction in CDAI, and the highest proportions of patients with normalization of CRP, improvement in IBDQ, and fistula response compared with the other induction doses. Therefore, a 130 mg IV fixed dose was chosen as an intermediate dose between the 1 and 3 mg/kg doses to be compared with a tiered dosing approach based on 6 mg/kg in phase 3 studies.

For dosing administration in induction studies 3001 and 3002, all patients were to receive a single IV administration of study agent (placebo or ustekinumab) at Week 0. Intravenous study agent was to be administered to each patient over a period of not less than 1 hour. The infusion was to be completed within 5 hours of preparation.

Treatment Compliance

Doses of IV study agent were administered by appropriately licensed and authorized health professionals according to the treatment groups assigned by an interactive voice response system (IVRS). Compliance with the treatment assignments was controlled by the study site personnel. Site personnel administered the study agent and recorded the amount of study agent given. A site monitor designated by the Applicant was to monitor all patient eCRFs. During these monitoring visits, all procedures were evaluated for compliance with the protocol. Missed study visits were recorded on the eCRF.

Blinded site monitors designated by the Applicant verified source documents, performed drug accountability, and ensured overall site compliance. Patient charts were reviewed and compared with data entries on the eCRFs to ensure consistency. Study agent was not to be used for any purpose other than that outlined in the protocol. Used vials of study agent were to be retained at the site until the study agent accountability forms had been checked by the site monitor.

Dose Modification, Rescue Therapy, Permission of Prior and Concomitant Therapy

Dose modification was allowed at a specific time point in the study between induction studies 3001 and 3002 and maintenance study 3003. This modification, described in the above section on study design, applied only to patients who had received placebo during induction studies 3001 and 3002 or had exhibited lack of clinical response during the induction study. This modification excluded the patient from entry as a randomized patient into maintenance Study 3003. See Section 6.1.1, Maintenance Study 3003 below for criteria defining randomized and non-randomized patients moving from the induction to the maintenance study. Patients were permitted to receive oral 5-ASA compounds, the immunomodulators AZA, 6-MP,

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and MTX, oral corticosteroids, and/or antibiotics for the treatment of Crohn's disease during the study, provided that the patient was on a stable dose for a specified period (described in the inclusion criteria above). Patients who received these medications at baseline were to maintain a stable dose throughout this study.

Patients were not to initiate treatment with any of the following concomitant Crohn's disease-specific medical therapies: oral or rectal 5-ASA compounds; immunomodulators (AZA, 6-MP, or MTX); oral, parenteral, or rectal corticosteroids; antibiotics as a treatment for Crohn's disease; or total parenteral nutrition as a treatment for Crohn's disease. Patients who initiated such medications or modified their doses/regimens were to complete all efficacy visits and the final safety visit in this study. Modifications in Crohn's disease therapies could exclude the patient from entry into the maintenance study 3003. If such medications were initiated or increased, due to medical necessity in the opinion of the investigator they were considered treatment failures for the final analysis.

The following medications were prohibited and considered deviations from the study protocol:

- Immunomodulatory agents other than 6-MP/AZA or MTX (including but not limited to 6-TG, cyclosporine, tacrolimus, sirolimus, mycophenolate mofetil).
- Immunomodulatory biologic agents (including but not limited to TNF antagonists, natalizumab, abatacept).
- Experimental Crohn's disease medications (including but not limited to thalidomide, briakinumab, vedolizumab, traficet, AMG 827).

Study Procedures and Timing of Events

For additional details and a complete list of the induction studies schedule of events, refer to Figure 6 below.

The following assessments were performed during the study:

- Pharmacokinetics (PK): Serum ustekinumab concentration.
 - at Week 0 (both before and approximately 1 hour after the completion of the infusion), and at Weeks 3, 6, and 8 (or at the early termination visit)
- Immunogenicity: Antibodies to ustekinumab.
 - collected at Week 0 (pre- and post-infusion) and Week 6 (and at an early termination visit if necessary) to determine the immune response to ustekinumab. A patient was considered to have developed a positive immune response if antibodies specifically binding to ustekinumab could be demonstrated in serum samples following study agent administration. Otherwise, the patient was classified as negative for antibodies to ustekinumab.
- Pharmacodynamics (PD)/biomarkers: Serum-based biomarkers, peripheral blood messenger ribonucleic acid (RNA) expression, RNA expression and histologic assessment of disease and healing in mucosal biopsies, analysis of whole blood DNA.

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- Blood samples for serum-based biomarker analyses were to be collected at Weeks 0, 3, and 6 (and at an early termination visit if necessary).
- Efficacy: Crohn's Disease Activity Index (CDAI) assessment, c-reactive protein (CRP) concentrations, fecal lactoferrin and fecal calprotectin concentrations (all measured at a central lab), fistula assessment, pyoderma gangrenosum assessment, ileocolonoscopy (in patients who consented to the procedure at targeted sites) measured at week 6.
 - CDAI was assessed at each visit by collecting information on 8 different Crohn's disease-related variables: extraintestinal manifestations, abdominal mass, weight, hematocrit, total number of liquid stools, abdominal pain/cramping, use of antidiarrheal drug(s) and/or opiates, and general well-being. The last 4 variables were obtained directly from the patient using daily diary cards over 7 days.
- Patient-reported outcomes: Inflammatory Bowel Disease Questionnaire (IBDQ), 36-item short form health survey (SF-36).
- Health economics: Resource utilization, productivity visual analog scale (VAS), Work Limitations Questionnaire (WLQ).
- Safety: Adverse events (AEs), serious adverse events (SAEs), vital signs, AEs that occurred during or within 1 hour of the administration of study agent (referred to as infusion reactions), hematology and chemistry parameters (abnormal values defined in the Appendix), physical examinations, 12-lead ECGs.
 - Safety data obtained during the study were reviewed on a routine basis by an unblinded, independent data monitoring committee (DMC).

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Figure 6: Time and Events Schedule Studies 3001 and 3002

TIME AND EVENTS SCHEDULE

Table 1 Protocol CNT01275CRD3001							
Study Procedures ^a	Screening ^a	Induction Period ^b					
	-5Weeks	Week 0	Week 3	Week 6	Week 8	Early Termination ^d	Safety Follow-up ^d
Screening/Administrative							
Informed consent	X						
Inclusion/exclusion criteria	X	X					
Medical history and demographics	X						
Chest radiograph ^c	X						
QuantiFERON-TB Gold In-Tube test ^f	X						
Stool studies to evaluate for enteric pathogens ^g	X						
Training on diary card completion	X						
Study Agent Administration							
Randomization		X					
Administer study agent		X					
Safety Assessments							
Detailed physical examination	X					X	X
Weight	X	X	X	X	X	X	
Height	X						
Vital signs ^h	X	X ⁱ				X	X
Baseline 12-lead ECG	X						
Serum pregnancy test	X						
Urine pregnancy test		X ^j				X	X
TB evaluation ^k /other infection assessment		X	X	X	X	X	X
Efficacy Assessments							
Collect and review diary cards		X	X	X	X	X	
CDAI assessments ^l		X	X	X	X	X	
Fistula exam		X	X	X	X	X	
Stool sample (fecal lactoferrin and calprotectin)	X			X		X	
C-reactive protein (CRP)	X	X	X	X	X	X	
Pyoderma gangrenosum assessment		X	X	X	X	X	
Video ileocolonoscopy ^m with biopsies for RNA analysis and histology	X				X		

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Study Procedures ^a	Screening ^a		Induction Period ^b				
	-5Weeks	Week 0	Week 3	Week 6	Week 8	Early Termination ^d	Safety Follow-up ^d
Inflammatory Bowel Disease Questionnaire (IBDQ)		X			X	X	
36-Item Short-form Health Survey (SF-36)		X			X	X	
Health economics							
Work Limitations Questionnaire (WLQ)		X			X	X	
Productivity Visual Analog Scale (VAS)		X			X	X	
Time Lost from Work		X			X	X	
Clinical Laboratory Assessments							
Hematology and chemistry	X	X ⁿ	X	X	X	X	
Pharmacokinetics/Immunogenicity							
Ustekinumab serum concentration		X ^o	X	X	X	X	X
Antibodies to ustekinumab		X		X		X	X
Pharmacodynamics							
Serum sample collection		X	X	X		X	
Whole blood sample collection for RNA analysis ^p		X ^q		X			
Pharmacogenomics							
Whole blood sample collection for DNA analysis ^r		X ^q					
Ongoing Subject Review							
Concomitant therapy	X	X	X	X	X	X	X
AEs	X	X	X	X	X	X	X
Crohn's disease-related hospitalizations and surgeries		X	X	X	X	X	X

Footnotes:

^a The screening period should be a minimum of 7 days to allow for collection of CDAI data. Subjects who are rescreened do not need to have a minimum of 7 days provided they have enough data to support CDAI calculation.

^b The visit windows will be ± 4 days for each visit.

^c All assessments are to be completed prior to study agent administration, unless otherwise specified. It is recommended that patient reported outcome (PRO) assessments be completed first.

^d If a subject ends study participation prior to Week 8, the Early Termination Visit should be completed. If a subject will not enter the maintenance study, but is still participating in the induction study, the subject should complete all scheduled visits and complete the final safety follow up visit approximately 20 weeks after study agent administration at Week 0.

^e May be taken within 3 months prior to the Week 0 visit.

^f In countries in which the QuantiFERON-TB Gold test is not considered approved/registered, a tuberculin skin test is additionally required. The QuantiFERON-TB Gold In-Tube test is not required at screening for subjects with a history of latent TB and appropriate treatment as described in Inclusion Criterion 7d.
^g Stool studies for enteric pathogens may be performed at either the central or local laboratory and must include a stool culture and <i>Clostridium difficile</i> toxin assay. These must have been performed during the current episode of disease exacerbation and within 4 months prior to Week 0. Additional testing, such as ova and parasite or <i>E. coli</i> O157:H7 assessments may be performed at the investigator's clinical discretion.
^h Temperature, pulse/heart rate, and blood pressure.
ⁱ At Week 0, vital signs obtained prior to infusion, approximately every 30 minutes during infusion, and twice (approximately 30-minute intervals) after the completion of infusion.
^j Must be performed prior to study agent administration at Week 0 in females of childbearing potential.
^k If TB is suspected at any time during the study, a chest x-ray, QuantiFERON-TB Gold In-Tube test, and/or a tuberculin skin test (in countries in which the QuantiFERON-TB Gold test is not considered approved/registered) should be performed.
^l For calculation of CDAI at Week 0, the hematocrit value obtained during screening will be used.
^m For sites selected to perform video ileocolonoscopy: Because these procedures must not interfere with the collection of CDAI data, the video ileocolonoscopy examination will be performed at least 8 days before or at the Week 0 visit and at least 8 days before or at the Week 8 visit. If performed on the day of these visits, the 7 days prior to the initiation of the colonoscopy preparation should be utilized to calculate CDAI scores for these visits.
ⁿ Laboratory tests at Week 0 are not required if screening laboratory tests were performed within 2 weeks before the Week 0 visit.
^o Blood should be drawn before the infusion begins and approximately 60 minutes after completion of the infusion.
^p Whole blood for RNA analysis will be collected from all subjects in the study.
^q Sample may be collected at another timepoint if not collected at Week 0.
^r Whole blood for DNA will be collected from subjects who consent to participate in pharmacogenomic assessments.

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Maintenance Study 3003

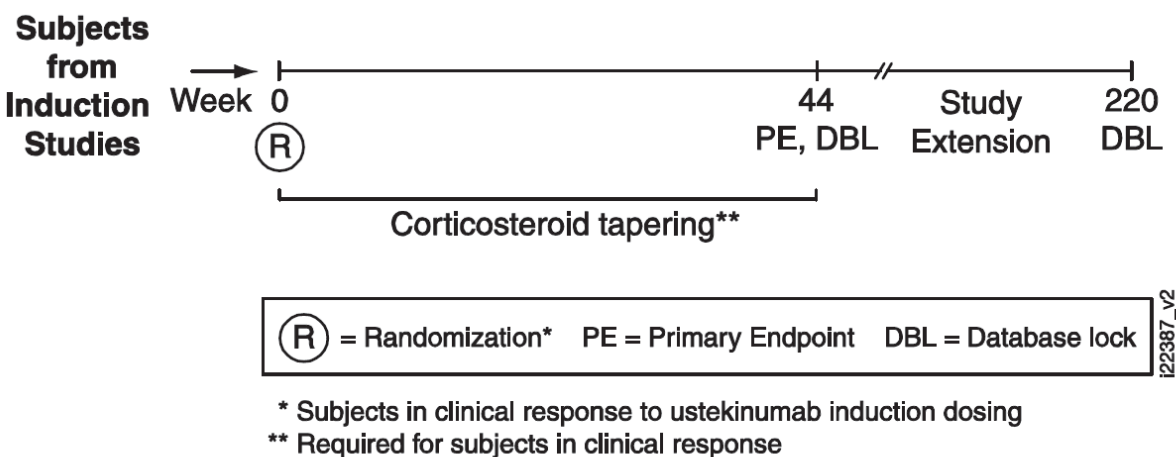
Study Design

Study 3003 was 44 week multicenter, randomized, parallel-group, placebo controlled study to evaluate the long-term efficacy and safety of ustekinumab in patients with moderately to severely active Crohn's disease who achieved clinical response in studies 3001 and 3002.

Study 3003 enrolled 1281 patients and was conducted in 260 sites across North and South America, Europe, the Asia Pacific Region, Israel, Australia, New Zealand and South Africa and was initiated on September 13, 2011 and completed June 10, 2015 with a database lock date of July 8, 2015.

All patients not discontinued from ustekinumab were provided a long term extension to continue up to week 272 to provide continued access to the study agent.

Figure 7: Schematic of Maintenance Study 3003



Source: From Applicant's Figure 1: Study Design, in Statistical Analysis Plan CNT01275CRD3003 6/36.

Randomized Population

There were 397 patients who met the definition of clinical response from studies 3001 and 3002 and were randomized in a 1:1:1 ratio at Week 0 to receive an SC administration dose of either placebo or one of two maintenance doses of ustekinumab:

- ustekinumab 90 mg every 12 weeks [q12w] through Week 36, or
- ustekinumab 90 mg every 8 weeks [q8w] through Week 40, or
- placebo.

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The primary endpoint was clinical remission at week 44. Patients who met criteria for loss of response (LOR), defined by defined a CDAI score ≥ 220 points AND a ≥ 100 point increase from the maintenance study Week 0 CDAI score (i.e., Week 8 in induction study 3001 or 3002), between weeks 8 and 32 of the maintenance study were eligible to have a single dose adjustment to the ustekinumab 90 mg q8 week dosing regimen. Patients who underwent dose adjustment were evaluated 16 weeks after the dose adjustment and were discontinued if not in clinical response. If response was attained, these patients were still treated as treatment failures in the analyses due to meeting LOR status.

Non-randomized population

In addition to the randomized population, included in the efficacy and safety analyses, the Applicant continued to follow all patients who did not meet the criteria for randomization into the maintenance study. This population is referred to as the “non-randomized” patient population. There were 884 patients who were not in clinical response at the completion of induction studies 3001 and 3002 or who received placebo in the induction studies and were eligible to enter Study 3003. These patients were not included in the primary randomized population, and were considered as the “non-randomized” patient population. Non-randomized patients were not included in the Applicant’s primary efficacy analyses and will not be included in the primary evaluations of efficacy and safety by this reviewer. However, results will be noted descriptively when they differ from those of the primary population. These non-randomized patients were stratified in the following manner:

- Patients who received placebo during the induction study and were in clinical response at the end of the induction study continued to receive SC placebo throughout the maintenance study
- Patients who received placebo but were not in clinical response at the end of induction study were administered ustekinumab 130 mg IV at week 0 of the maintenance study.
 - Patients who achieved clinical remission at week 8 of the maintenance study after the additional IV induction dose (responders), continued to receive ustekinumab 90mg SC at week 8 and q12 weeks until the end of the maintenance study
 - Patients who failed to achieve clinical response or remission after the additional IV induction dose (non-responders) were discontinued from receiving ustekinumab
- Patients who failed to achieve clinical response or remission after receiving ustekinumab in the induction study received ustekinumab 90mg SC at week 0 of the maintenance study
 - Patients who achieved clinical remission at week 8 of the maintenance study (responders) continued to receive ustekinumab 90mg SC at week 8 and q8 weeks until the end of the maintenance study
 - Patients who failed to achieve clinical response or remission (non-responders) were discontinued from receiving ustekinumab

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Diagnostic Criteria

Study 3003 was a 44-week study that enrolled patients who were treated during induction studies 3001 and 3002. Patients were eligible for enrollment in study 3003 if they 1) received study agent at Week 0 in study 3001 or 3002, 2) completed the Week 8 CDAI score evaluation, and 3) were able to complete the Week 0 visit in study 3003 within 4 days of the Week 8 visit of the induction studies. Patients were placed in the randomized or non-randomized study population as described above based on clinical response status at Week 8 of the previous induction studies. Detailed eligibility criteria are described below.

Inclusion/Exclusion Criteria

Key Inclusion Criteria

- Have received study agent at Week 0 in study 3001 or 3002
- Completed the Week 8 CDAI score evaluation and met clinical response criteria.
- Able to complete the Week 0 visit in study 3003 within 4 days of the Week 8 visit in study 3001 or 3002. At the discretion of the investigator, the window may be extended to 8 days to allow appropriate treatment of, ruling out, or recovery from nonserious infections (e.g., acute upper respiratory tract infection, simple urinary tract infection) or other conditions to ensure patient safety.
- Able to provide informed consent.
- Able and willing to adhere to the study visit schedule and comply with other protocol requirements.

Key Exclusion Criteria

- Had any of the following changes to their concomitant medications due to Crohn's disease (i.e., lack of efficacy) since Week 0 of studies 3001 and 3002
 - Increase in physician-prescribed daily dose of oral corticosteroids of more than 5 mg of prednisone (or equivalent increase in prednisone-equivalent dose of other corticosteroids),
 - Initiation of oral budesonide or increase in daily dose
 - Initiation of parenteral, and oral corticosteroids for Crohn's disease, except for dose equivalent substitutions among oral corticosteroids
 - Initiation or increased physician-prescribed daily dose of methotrexate (MTX), 6-MP, or azathioprine (AZA), except for dose equivalent substitutions.
- Initiated a protocol prohibited medication since Week 0 of studies 3001 and 3002:
 - Immune suppressing immunomodulatory agents other than 6-MP/AZA or MTX (including but not limited to 6-TG, cyclosporine, tacrolimus, sirolimus, mycophenolate mofetil, tofacitinib and other Janus kinase [JAK] inhibitors)

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- Immunosuppressant biologic agents (including but not limited to TNF-antagonists, natalizumab, abatacept, commercial ustekinumab)
- Experimental Crohn's disease medications (including but not limited to thalidomide, briakinumab, vedolizumab, traficet, AMG-827)
- Underwent a Crohn's disease related surgery since Week 0 of induction study 3001 or 3002. Seton placement and recent cutaneous and perianal abscesses which have been drained and adequately treated at least 3 weeks prior to receiving baseline study agent are not exclusionary provided that there is no anticipated need for any further surgery
- Patients from countries with high multidrug-resistant TB burden (e.g., South Africa, Bulgaria, and the Russian Federation) diagnosed with latent TB during induction study 3001 or 3002, or any patient who has discontinued or is noncompliant with appropriate therapy for the treatment of latent TB.
- Are diagnosed with any medical condition (or signs or symptoms thereof) which would have precluded enrollment in induction studies 3001 and 3002. This includes any lymphoproliferative disorder or malignancy (other than basal cell carcinoma of the skin), opportunistic or other significant infection, or other severe, progressive, or uncontrolled medical (e.g., renal, hepatic, hematological, endocrine, pulmonary, cardiac, neurologic, or autoimmune) or psychiatric disease, including recent significant instability in a previous condition.
- Have signs and symptoms of latent or active granulomatous infection, including TB, histoplasmosis, or coccidioidomycosis
- Is a woman who is pregnant, or breast-feeding, or planning to become pregnant or is a man who plans to father a child while enrolled in this study or within 20 weeks after the last dose of study agent.

Dose Selection and Administration

Maintenance doses were selected for study 3003 based on the results of the phase 2 study C0743T26, in which a single IV infusion of 1 mg/kg, 3 mg/kg, or 6 mg/kg was administered to patients with Crohn's disease to induce clinical response, followed by maintenance doses of 90 mg SC injections at Weeks 8 and 16. In study C0743T26, the primary endpoint was clinical response at Week 6; however, patients receiving ustekinumab induction were re-randomized at Week 8 in a 1:1 ratio to receive either placebo or ustekinumab 90 mg SC injections at Weeks 8 and 16 (2 separate randomizations for patients in clinical response and for those not in clinical response). Safety and efficacy evaluations were performed through Week 36.

In study C0743T26, the proportion of patients in clinical remission at measured at Week 22 was significantly greater in the ustekinumab 90 mg SC group (41.7%) than in the placebo SC group (27.4%, $p = 0.029$). The proportion of patients in clinical response also measured at Week 22 was also significantly greater in the ustekinumab 90 mg SC group (69.4%) than in the placebo SC

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BLA 761044
Stelara (ustekinumab)

group (42.5%, $p = 0.001$). The proportion of patients in sustained clinical response through Week 22 was significantly greater in the ustekinumab 90 mg SC group (55.6%) than in the placebo SC group (32.9%, $p = 0.005$). Among the limited number of patients who were in remission at Week 6, 78.6% remained in clinical remission at Week 22 in the ustekinumab 90 mg SC group compared with 53.3% in the placebo SC group ($p = 0.056$). Based on two doses of 90mg SC ustekinumab every 8 weeks in study C0743T26, the Applicant decided to investigate the every 8 week dosing and a longer interval of every 12 weeks in study 3003.

Dose Administration: Randomized Population

The 90 mg SC every 8 weeks or every 12 weeks dosing regimen was selected based on the results of the phase 2 study described above. In the phase 3 maintenance study (study 3003), all patients received a SC administration of study agent (either placebo or ustekinumab) every 4 weeks from Week 0 to Week 40 with the exception of Week 4 to preserve the double blind between administration every 8 or every 12 week dosing for investigators and patients.

Dose Administration: Non-Randomized Population

All patients who were not in clinical response after the single induction dose became part of the non-randomized population and received a single IV administration dose of ustekinumab at Week 0. Placebo administrations were given at dosing visits in which an active administration is not planned in order to maintain the blind.

For patients receiving an IV administration at Week 0, the study agent was administered over a period of not less than 1 hour. The infusion should be completed within 5 hours of preparation.

Treatment Compliance

Doses of SC study agent were administered by appropriately licensed and authorized health professionals according to the treatment groups assigned by the IVRS. Compliance with the treatment assignments was controlled by the study site personnel. Site personnel administered the study agent and recorded the amount of study agent given. A site monitor designated by the Sponsor was to monitor all patient eCRFs. During these monitoring visits, all procedures were evaluated for compliance with the protocol. Missed study visits were recorded on the eCRF.

Blinded site monitors designated by the Applicant verified source documents, performed drug accountability, and ensured overall site compliance. Patient charts were reviewed and compared with data entries on the eCRFs to ensure consistency. Study agent was not to be used for any purpose other than that outlined in the protocol. Used syringes and vials of study agent were to be retained at the site until the study agent accountability forms had been checked by the site monitor.

Dose Modification, Rescue Therapy, Permission of Prior and Concomitant Therapy

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Dose modification was only allowed at a specific timepoint in the study between induction studies 3001 and 3002 and maintenance study 3003. Dose modification, described in the above section on study design, applied only to patients who had received placebo during induction studies 3001 and 3002 or had exhibited lack of clinical response during the induction study. Patients who underwent dose modification were excluded from the randomized patient population in maintenance Study 3003. See Figure 7 and the text below Figure 7 for criteria defining randomized and non-randomized patients moving from the induction to the maintenance study.

Patients were permitted to maintain a stable dose of baseline concomitant therapy with oral 5-ASA compounds, the immunomodulators AZA, 6-MP, and MTX, oral corticosteroids, and/or antibiotics for the treatment of Crohn's disease during the study, provided that the patient was on a stable dose for a specified period (described in the inclusion criteria above).

Patients were not to initiate new treatment with any of the following concomitant Crohn's disease-specific medical therapies: oral or rectal 5-ASA compounds; immunomodulators (AZA, 6-MP, or MTX); oral, parenteral, or rectal corticosteroids; antibiotics as a treatment for Crohn's disease; or total parenteral nutrition as a treatment for Crohn's disease. Patients who initiated such medications or modified doses/regimens were to complete all efficacy visits and the final safety visit in this study but were discontinued from the study. If such medications were initiated or increased, due to medical necessity in the opinion of the investigator they were considered treatment failures for the final analysis.

The following medications were prohibited and considered deviations from the study protocol:

- Immunomodulatory agents other than 6-MP/AZA or MTX (including but not limited to 6-TG, cyclosporine, tacrolimus, sirolimus, mycophenolate mofetil).
- Immunomodulatory biologic agents (including but not limited to TNF antagonists, natalizumab, abatacept).
- Experimental Crohn's disease medications (including but not limited to thalidomide, briakinumab, vedolizumab, traficet, AMG 827).

Study Procedures and Timing of Events

For additional details and a complete list of the study schedule of events, refer to Figure 8 below.

The following assessments were performed during the study:

- Pharmacokinetics (PK): Serum ustekinumab concentration.
 - at Week 0 (both before and approximately 1 hour after the completion of the infusion), and every 4 weeks thereafter until Week 44, then Week 64 at the safety follow up visit)

- Immunogenicity: Antibodies to ustekinumab.
 - collected at Week 0 (pre- and post-infusion) and Weeks 12, 24, 36, 44 and 64 (and at an early termination visit if necessary) to determine the immune response to ustekinumab. A patient was considered to have developed a positive immune response if antibodies specifically binding to ustekinumab could be demonstrated in serum samples following study agent administration. Otherwise, the patient was classified as negative for antibodies to ustekinumab.
- Pharmacodynamics (PD)/biomarkers: Serum-based biomarkers, peripheral blood messenger ribonucleic acid (RNA) expression, RNA expression and histologic assessment of disease and healing in mucosal biopsies, analysis of whole blood DNA.
 - Blood samples for serum-based biomarker analyses were to be collected at Weeks 8, 16 (whole blood only), 24, and 44 (and at an early termination visit if necessary).
- Efficacy: Crohn's Disease Activity Index (CDAI) assessment, c-reactive protein (CRP) concentrations, fecal lactoferrin and fecal calprotectin concentrations (all measured at a central lab), fistula assessment, pyoderma gangrenosum assessment to be collected every 4 weeks from Week 0-Week 44 (and early termination visit, if necessary ileocolonoscopy (in patients who consented to the procedure at targeted sites) measured at week 44.
 - CDAI was assessed by collecting information on 8 different Crohn's disease-related variables at each visit: extraintestinal manifestations, abdominal mass, weight, hematocrit, total number of liquid stools, abdominal pain/cramping, use of antidiarrheal drug(s) and/or opiates, and general well-being. The last 4 variables were scored by the patient over 7 days on a daily diary card.
- Patient-reported outcomes: Inflammatory Bowel Disease Questionnaire (IBDQ), 36-item short form health survey (SF-36).
- Health economics: Resource utilization, productivity visual analog scale (VAS), Work Limitations Questionnaire (WLQ).
- Safety: Adverse events (AEs), serious adverse events (SAEs), vital signs, hematology and chemistry parameters (abnormal values defined in the Appendix), physical examinations, 12-lead ECGs.
 - Safety data obtained during the study were reviewed on a routine basis by an unblinded, independent data monitoring committee (DMC).

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Figure 8: Time and Events Schedule Maintenance Study 3003

TIME AND EVENTS SCHEDULE														
Table 1 Protocol CNO1275CRD3003 – Maintenance Treatment Phase														
	Week 0 ^e	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36 ^e	Week 40 ⁱ	Week 44 ^c	Early Term ^h	Safety F/U ^g
Study Procedures^{a, b}														
Screening/Administrative														
Informed consent	X													
Inclusion/exclusion criteria	X													
Study Agent Administration														
Randomization ⁱ	X													
Administer study agent	X ^g		X	X	X	X	X	X	X	X	X			
Safety Assessments														
Detailed physical examination														
Weight	X ^h	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs ⁱ	X ^j		X	X	X	X	X	X	X	X	X	X	X	X
Urine Pregnancy test ^k	X		X	X	X	X	X	X	X	X	X	X	X	X
TB evaluation ^l /other infection assessment	X ^h	X	X	X	X	X	X	X	X	X	X	X	X	X
Study agent injection-site evaluation	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy Assessments														
Collect and review diary cards	X ^h	X	X	X	X	X	X	X	X	X	X	X	X	X
CDAI assessments ^m	X ^h	X	X	X	X	X	X	X	X	X	X	X	X	X
Fistula exam	X ^h		X	X	X	X	X	X	X	X	X	X	X	X
Stool sample (fecal lactoferrin and calprotectin)	X ⁿ		X				X					X	X	
CRP	X ^h	X	X	X	X	X	X	X	X	X	X	X	X	X
Pyoderma gangrenosum assessment	X ^h	X	X	X	X	X	X	X	X	X	X	X	X	X
Video ileocolonoscopy ^o with biopsies for RNA analysis and histology	X ^h											X	X	
IBDQ	X ^h					X						X	X	
SF-36	X ^h					X						X	X	
Health Economics														
Productivity VAS	X ^h					X						X	X	
WLQ	X ^h					X						X	X	
Time Lost from Work	X ^h					X						X	X	
Clinical Laboratory Assessments														
Hematology and chemistry														
Pharmacokinetics/Immunogenicity														
Ustekinumab serum concentration ^p	X ^h	X	X	X	X	X	X	X	X	X	X	X	X	X
Antibodies to ustekinumab	X ^h			X			X			X		X	X	X

Table 1 Protocol CNT01275CRD3003 – Maintenance Treatment Phase

Study Procedures ^{a,b}	Week 0 ^c	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36 ^e	Week 40 ^f	Week 44 ^g	Early Term ^h	Safety F/U ⁱ
Pharmacodynamics														
Serum sample collection			X				X					X	X	
Whole blood sample collection for RNA analysis ^j			X		X		X					X		
Ongoing Subject Review														
Concomitant therapy	X ^h	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Crohn's disease related hospitalizations and surgeries	X ^h	X	X	X	X	X	X	X	X	X	X	X	X	X

Footnotes:
 a The visit windows will be ± 10 days for each visit.
 b All assessments are to be completed prior to study agent administration, unless otherwise specified. It is recommended that patient reported outcome (PRO) assessments be completed first.
 c Week 0 visit should be within 4 days of the Week 8 visit in study CNT01275CRD3001 or CNT01275CRD3002. At the discretion of the investigator, the window may be extended to 8 days to allow appropriate treatment and/or recovery of nonserious infections.
 d All subjects will be assessed at Week 44 to determine eligibility for entry into the long-term extension. Study agent administration at Week 44 will be considered part of the long-term extension and is captured in the Time and Events Schedule for the long-term extension (Table 2).
 e Subjects who discontinue study agent administration (but have not terminated study participation) or who do not enter the study extension will have a final follow-up safety visit approximately 20 weeks after the last administration of study agent.
 f Subjects in clinical response to ustekinumab induction dosing.
 g Subjects in clinical response following induction will receive SC study agent and subjects not in clinical response will receive both SC and IV study agent.
 h Data from study procedure performed at Week 8 of induction study CNT01275CRD3001 or CNT01275CRD3002 will be used for Week 0 of this study.
 i Temperature, pulse/heart rate, and blood pressure. Vital signs should be obtained prior to and approximately 30 minutes post study agent injections.
 j For subjects receiving IV infusion at Week 0, vital signs should be obtained prior to infusion, approximately every 30 minutes during the infusion, and twice (approximately 30 minute intervals) after the completion of the infusion.
 k Must be performed prior to each study agent administration in females of childbearing potential.
 l If TB is suspected at any time during the study, a chest x-ray, QuantiFERON-TB Gold In-Tube test and/or a tuberculin skin test (in countries in which the QuantiFERON-TB Gold test is not considered approved/registered) should be performed.
 m For calculation of CDAI at Week 0, the hematocrit value obtained during Week 6 of induction study CNT01275CRD3001 or CNT01275CRD3002 will be used.
 n Data from study procedure performed at Week 6 of induction study CNT01275CRD3001 or CNT01275CRD3002 will be used for Week 0 of this study.
 o For sites selected to perform video ileocolonoscopy: Because these procedures must not interfere with the collection of CDAI data, the video ileocolonoscopy evaluation will be performed at least 8 days before or at the Week 44 visit. If performed on the day of this visit, the 7 days prior to the initiation of the colonoscopy preparation should be utilized to calculate the CDAI score for this visit.
 p For subjects receiving IV infusion at Week 0, a sample should be drawn approximately 60 minutes after completion of the infusion. At all other study agent administration visits blood samples should be collected prior to study agent injection.
 q Whole blood for RNA analysis will be collected from all subjects in the study.
 r When early termination coincides with a scheduled visit, perform activities identified for early termination.
 s Subjects who discontinue study agent on or after Week 36 should complete the Week 44 visit (in addition to a final safety visit).

Study Endpoints

INDUCTION STUDIES: 3001 and 3002

Primary Endpoint

The primary endpoint for both induction studies 3001 and 3002, was clinical response at Week 6, defined as a reduction from baseline in the CDAI score of ≥100 points. Patients with a baseline CDAI score of ≥220 to ≤248 were considered to be in clinical response if a CDAI score of <150 was attained.

This reviewer notes that importantly, the Division is re-evaluating the appropriateness of the CDAI to define the primary efficacy endpoint for studies in Crohn's disease. The Division currently is moving towards a primary efficacy endpoint that includes both key signs and symptoms (e.g., abdominal pain and stool frequency) and an endoscopic evaluation of disease improvement. However, at the time of initiation of these studies, the CDAI was considered to

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be acceptable for use to define the primary efficacy endpoint in Crohn's disease clinical studies. Of note, the Applicant collected efficacy data using the new endpoints as exploratory endpoints during this trial to inform endpoint selection for future trials.

Key Secondary Endpoints (listed in the order in which they were tested):

- Clinical remission at Week 8, defined as a CDAI score of <150 points at Week 8
 - Subgroup analyses of clinical remission at Week 8 were performed to evaluate the consistency of efficacy over demographics, baseline disease characteristics, Crohn's disease medication history, concomitant Crohn's disease medication use at baseline, center location, and initial response to TNF antagonist therapy. The odds ratios of each ustekinumab dose group versus placebo and corresponding 95% confidence intervals were provided for each of the subgroups evaluated for the primary endpoint.
- Clinical response at Week 8, defined as a reduction from baseline in the CDAI score of ≥ 100 points at Week 8. Patients with a baseline CDAI score of ≥ 220 to ≤ 248 were considered in clinical response if a CDAI score of <150 was attained.
- 70-point response at Week 6, defined as a reduction from baseline in the CDAI score of ≥ 70 points at Week 6.
- 70-point response at Week 3, defined as a reduction from baseline in the CDAI score of ≥ 70 points at Week 3.

The major secondary endpoints were only tested if the primary endpoint was significant for both the high and low dose groups. Additionally, both high and low dose key secondary endpoints had to test positive at a level of $p < 0.05$ significance to proceed to the next major secondary endpoint.

Other Secondary Endpoints

Clinical

- The proportion of patients in clinical remission at Week 3 and the proportion of patients in clinical remission at Week 6 were summarized and compared between each of the ustekinumab treatment groups and the placebo group.
- The proportion of patients in clinical response at Week 3 was summarized and compared between each of the ustekinumab treatment groups and the placebo group.
- The proportion of patients in 70-point response at Week 8 was summarized and compared between each of the ustekinumab treatment groups and the placebo group.
- The change from baseline in the CDAI score at Weeks 3, 6, and 8 were summarized and compared between each of the ustekinumab treatment groups and the placebo group, respectively.
- The proportions of patients in fistula response at Weeks 3, 6, and 8 were summarized

and compared between each of the ustekinumab treatment groups and the placebo group, respectively, for patients with 1 or more fistulas at baseline. A fistula response was defined as a $\geq 50\%$ reduction in the number of draining fistulas. No treatment failure rules or missing data rules were applied to this endpoint; if the number of draining fistulas at baseline or at the visit of interest was missing, fistula response could not be derived.

- The total number of lesions, size of primary lesion, and resolution were listed by visit for patients with pyoderma gangrenosum at baseline. No treatment failure rules or missing data rules were applied to this endpoint; data were presented as observed.

CRP and Fecal Biomarkers

- The proportions of patients with normalized CRP at Week 3, 6, and 8 in patients with abnormal CRP at baseline were summarized and compared between each of the ustekinumab treatment groups and the placebo group. Abnormal CRP was defined as a CRP value >3 mg/L measured at the Applicant's central lab.
- The change from baseline in CRP concentration at Week 3, 6, and 8 were summarized and compared between each of the ustekinumab treatment groups and the placebo group.
- The change from baseline in fecal lactoferrin concentration at Week 6 was summarized and compared between each of the ustekinumab treatment groups and the placebo group.
- The proportion of patients with normalized fecal lactoferrin at Week 6 in patients with abnormal fecal lactoferrin at baseline was summarized and compared between each of the ustekinumab treatment groups and the placebo group.
- The change from baseline in fecal calprotectin concentration at Week 6 was summarized and compared between each of the ustekinumab treatment groups and the placebo group.
- The proportions of patients with fecal calprotectin ≤ 250 mg/kg, and ≤ 100 mg/kg at Week 6 in patients with fecal calprotectin >250 mg/kg at baseline were summarized and compared between each of the ustekinumab treatment groups and the placebo group.

Patient-Reported Outcomes

- The change from baseline in the IBDQ score at Week 8 was summarized and compared between each of the ustekinumab treatment groups and the placebo group.
- The change from baseline in the IBDQ dimension scores at Week 8 was summarized and compared between each of the ustekinumab treatment groups and the placebo group.

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- The proportion of patients with IBDQ score increased by ≥ 16 points at Week 8 was summarized and compared between each of the ustekinumab treatment groups and the placebo group.
- The change from baseline in the physical component score (PCS) and mental component summary (MCS) scores of the SF-36 at Week 8 were summarized and compared between each of the ustekinumab treatment groups and the placebo group.
- The change from baseline in the individual SF-36 scales at Week 8 was summarized and compared between each of the ustekinumab treatment groups and the placebo group.
- The proportions of patients with at least 5-point improvement from baseline in SF-36 PCS and MCS scores at Week 8 were summarized and compared between each of the ustekinumab treatment groups and the placebo group.

MAINTENANCE STUDY: 3003

Primary Endpoint

The primary endpoint for maintenance study 3003 was clinical remission at Week 44, defined as a CDAI < 150 points. Please refer to the discussion about the Division's current view on endpoints for IBD in the section above on the Primary Endpoint of the Induction studies 3001 and 3002.

Key Secondary Endpoints (listed in the order in which they were tested):

- Clinical response at Week 44.
 - Clinical response at Week 44 is defined as a reduction from Week 0 of induction study 3001 or 3002 in the CDAI score of ≥ 100 points at Week 44.
 - Patients with a CDAI score of ≥ 220 to ≤ 248 points at Week 0 of induction study 3001 or 3002 are considered to be in clinical response if a CDAI score of < 150 is attained at Week 44.
- Clinical remission at Week 44 among patients in clinical remission to ustekinumab at Week 0.
- Corticosteroid-free remission at Week 44.
 - Corticosteroid-free remission at Week 44 is defined as a CDAI score of < 150 points without receiving corticosteroids at Week 44. For patients without corticosteroid information at Week 44, the last available corticosteroid dose will be carried forward to Week 44.
- Clinical remission at Week 44 in the subset of patients who were refractory or intolerant to TNF-antagonist therapy (i.e., patients from induction study 3001).

The major secondary endpoints were only tested if the primary endpoint was significant for both the every 8 week and every 12 week groups. If one group failed, key secondary

endpoints that followed were considered exploratory. Both high and low dose key secondary endpoints had to test positive at a level of $p < 0.05$ significance to proceed to the next major secondary endpoint. In addition, for each of the major secondary endpoints, patients with a missing CDAI score at Week 44 were considered to not have achieved the endpoint.

Other Secondary Endpoints

Clinical

- The change from baseline in the CDAI score at each time point through Week 44 will be summarized by treatment group, and will be compared between each ustekinumab group and the placebo treatment group at Week 44.
- The proportion of patients in clinical remission at Week 44 and not receiving corticosteroids for at least 90 days prior to Week 44 will be summarized and compared between each ustekinumab group and the placebo treatment group.
- The proportion of patients in clinical remission at Week 44 and not receiving corticosteroids for at least 30 days prior to Week 44 will be summarized and compared between each ustekinumab group and the placebo treatment group.
- The proportion of patients in corticosteroid-free clinical response at Week 44 will be summarized and compared between each ustekinumab group and the placebo treatment group.
- The proportion of patients who were able to eliminate corticosteroids at Week 44 will be summarized and compared between each ustekinumab group and the placebo treatment group for patients who were receiving corticosteroids at baseline.
- The proportion of patients who were able to eliminate corticosteroids at Week 44 (not receiving corticosteroids for at least 90 days prior to Week 44) will be summarized and compared between each ustekinumab group and the placebo treatment group for patients who were receiving corticosteroids at baseline.
- The proportion of patients who were able to eliminate corticosteroids at Week 44 (not receiving corticosteroids for at least 30 days prior to Week 44) will be summarized and compared between each ustekinumab group and the placebo treatment group for patients who were receiving corticosteroids at baseline.
- The proportion of patients in corticosteroid-free clinical remission at Week 44 will be summarized and compared between each ustekinumab group and the placebo treatment group for patients who were receiving corticosteroids at baseline.
- The change from baseline in the oral prednisone-equivalent corticosteroid dose at each time point through Week 44 will be summarized by treatment group, and will be compared between each ustekinumab group and the placebo treatment group at Week 44 for patients who were receiving corticosteroids at baseline. Corticosteroid medication change treatment failure rules described in Section 6.1.1, Study Design will not apply to this analysis; in the case of treatment failure due to other reasons, the

highest dose in the two weeks prior to the treatment failure will be carried forward to subsequent visits.

- The number of days without corticosteroids prior to Week 44 will be summarized and compared between each ustekinumab group and the placebo treatment group for patients who were receiving corticosteroids at baseline. Corticosteroid medication change treatment failure rules described in Section 6.1.1 will not apply to this analysis; in the case of treatment failure due to other reasons, the number of days without corticosteroids is counted up to the time of treatment failure.
- The proportion of patients in fistula response at each time point through Week 44 will be summarized by treatment group, and will be compared between each ustekinumab group and the placebo treatment group at Week 44, for patients with 1 or more fistulas at baseline of the induction study. A fistula response is defined as a 50% reduction from baseline of the induction study in the number of draining fistulas. To calculate the percentage fistula response, the number of draining fistulas at baseline of the induction is used as the denominator, and the number of draining fistulas at baseline of the induction study subtracted from the number of currently draining fistulas (regardless of the time of fistula drainage onset) at a timepoint of interest is used as the numerator. There are no treatment failure rules and missing data rules for this endpoint. If the number of draining fistulas at baseline or the number of draining fistulas at the visit of interest is missing, fistula response cannot be calculated.
- The total number of lesions, and location, size and resolution of primary lesion will be listed by visit for patients with pyoderma gangrenosum at baseline. There are no treatment failure rules and missing data rules applied for this endpoint.
- The proportions of patients in sustained clinical remission (clinical remission at Week 36, Week 40, and Week 44) will be summarized and compared between each of the ustekinumab treatment groups and the placebo group.
- The proportion of patients in sustained clinical response (clinical response at Week 36, Week 40, and Week 44) will be summarized and compared between each of the ustekinumab treatment groups and the placebo group.
- The proportion of patients in clinical remission at each time point through Week 44 will be summarized by induction dose and treatment group, and will be compared between each ustekinumab group and the placebo treatment group at Week 44.
- The proportion of patients in clinical remission 16 weeks after dose adjustment will be summarized by treatment groups for patients who had a dose-adjustment due to loss of clinical response. There are no treatment failure rules for this analysis.
- The change from the time of dose adjustment in the CDAI score through 16 weeks after dose adjustment will be summarized by treatment group, and will be compared between each ustekinumab group and the placebo treatment group. There are no treatment failure rules for this analysis.

CRP and Fecal Biomarkers

- The change from baseline in CRP concentration at each time point through Week 44 will be summarized by treatment group, and will be compared between each ustekinumab group and the placebo treatment group at Week 44.
- The proportion of patients who with normalization of CRP at each time point through Week 44 will be summarized by treatment group, and will be compared between each ustekinumab group and the placebo treatment group at Week 44 for patients with abnormal CRP at baseline (of the induction study). CRP will be assayed using a validated, high sensitivity CRP assay. Abnormal CRP is defined as CRP value > 3 mg/L.
- The change from baseline in fecal lactoferrin concentration at Week 24 and Week 44 will be summarized by treatment group, and will be compared between each ustekinumab group and the placebo treatment group at Week 44.
- The proportion of patients with normalization of fecal lactoferrin at Week 24 and Week 44 will be summarized by treatment group, and will be compared between each ustekinumab group and the placebo treatment group at Week 44 for patients with abnormal fecal lactoferrin at baseline (of the induction study).
- The change from baseline in fecal calprotectin concentration at Week 24 and Week 44 will be summarized by treatment group, and will be compared between each ustekinumab group and the placebo treatment group at Week 44.
- The proportion of patients who have fecal calprotectin ≤ 250 (milligrams/kg), and ≤ 100 (milligram/kg) at Week 24 and Week 44 will be summarized by treatment group, and will be compared between each ustekinumab group and the placebo treatment group at Week 44 for patients with fecal calprotectin > 250 (milligrams/kg) at baseline (of the induction study).

Patient-Reported Outcomes

- The change from baseline in the IBDQ score and each of four dimension scores at Week 20 and Week 44 will be summarized by treatment group, and will be compared between each ustekinumab group and the placebo treatment group at Week 44. The IBDQ²⁰ is a 32-item questionnaire specifically designed for patients with IBD. The range of the IBDQ score is 32 to 224. Higher scores indicate better quality of life. The IBDQ has 4 dimension scores (bowel, systemic, social, and emotional). Each of the individual IBDQ dimensions will be calculated when ≤ 1 item is missing in the dimension. The missing

²⁰ Irvine et al. 1994. Quality of life: a valid and reliable measure of therapeutic efficacy in the treatment of inflammatory bowel disease. Canadian Crohn's Relapse Prevention Trial Study Group. *Gastroenterology*. 1994;106(2):287-296.

item will be estimated using the average value across the nonmissing items. If any one of the dimensions within the IBDQ cannot be calculated, then the total IBDQ score cannot be calculated.

- The proportion of patients with at least a 16-point improvement from baseline of the induction study in the IBDQ score at Week 20 and Week 44 will be summarized by treatment group, and will be compared between each ustekinumab group and the placebo treatment group at Week 44.
- The change from baseline in the physical and mental component summary scores and each of 8 individual subscales of the SF-36 at Week 20 and Week 44 will be summarized by treatment group, and will be compared between each ustekinumab group and the placebo treatment group at Week 44.²¹ The SF-36 was developed as part of the Rand Health Insurance Experiment and consists of 8 multi-item scales:
 - Limitations in physical functioning due to health problems
 - Limitations in usual role activities due to physical health problems
 - Bodily pain
 - General mental health (psychological distress and well-being)
 - Limitations in usual role activities due to personal or emotional problems
 - Limitations in social functioning due to physical or mental health problems
 - Vitality (energy and fatigue)
 - General health perception
- The proportion of patients with ≥ 5 points improvement from baseline (of the induction study) in the SF-36 physical and mental component summary scores at Week 20 and Week 44 will be summarized and compared between each of the ustekinumab treatment groups and the placebo group.

²¹ These scales are scored from 0 to 100 with higher scores indicating better health. Another algorithm yields 2 summary scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS). These summary scores are also scaled with higher scores indicating better health but are scored using a norm-based system where linear transformations are performed to transform scores to a mean of 50 and standard deviations of 10, based upon general US population norms. The concepts measured by the SF-36 are not specific to any age, disease, or treatment group, allowing comparison of relative burden of different diseases and the relative benefit of different treatments. Subscales are calculated whenever 50% of the items that comprise the subscale are available (nonmissing). Any missing items will be estimated using the average value across the nonmissing items for that subscale. If $< 50\%$ of the items that comprise the subscale is available, the subscale will not be calculated. If any of the individual subscales that comprise the physical component score or the mental component score are missing, then the physical or mental component summary scores cannot be calculated. (Ware JE, Kosinski M, Keller SD. *Interpretation: Norm-Based. In: SF-36 Physical and Mental Health Summary Scales: A User's Manual. Boston, MA: The Health Institute; 1994:8:1-8:42 and Ware JE Jr, Sherbourne CD. The MOS 36 item short form health survey (SF 36), I: conceptual framework and item selection. Med Care. 1992;30(6):473-483.*)

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Statistical Analysis Plan

Induction Studies 3001 and 3002

Planned Method of Analysis

Demographic and baseline disease characteristics were summarized; these analyses and the efficacy analyses were based on the 741 patients (Study 3001) or 628 patients (Study 3002) who were randomly assigned after the study was restarted following instability of the intravenous formulation discovered in study 3001 (see U.S. Regulatory Actions and Marketing History, Section 3.1 for details). Efficacy analyses for Study 3002 were based on 627 patients; data for 1 patient randomized after study restart were retrospectively excluded from the efficacy analyses because the Applicant was unable to make a determination of the accuracy and validity of the patient's data. The proportion of patients in clinical response at Week 6 (primary endpoint) was summarized and 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. The study was considered positive if the ustekinumab high-dose group was significantly different from the placebo group for the primary endpoint. Global and US-specific multiple testing procedures were prespecified to control the overall Type 1 error rate at the 0.05 level in this study.

A fixed-sequence testing procedure was used to control the overall Type 1 error rate at the 0.05 level of significance. Specifically, the ustekinumab high-dose group (dose approximating 6 mg/kg ustekinumab) was first compared with the placebo group at the 2-sided 0.05 level of significance. If the ustekinumab high-dose group was significantly different from the placebo group, then the ustekinumab low-dose group (130 mg ustekinumab) was compared with the placebo group at the 2-sided 0.05 level of significance.

The study was considered positive if the ustekinumab high-dose group was significantly different from the placebo group for the primary endpoint. The primary analysis was based on an intent-to-treat principle. Therefore, the efficacy data for each patient randomly assigned to a treatment group was analyzed according to the assigned treatment regardless of the actual treatment received. This did not affect the overall outcome of the analyses. Please refer to statistical review by Dr. Min Min.

The same data-handling rules specified for the primary endpoint analysis were used for each of the major secondary endpoints.

Sensitivity analyses:

Sensitivity analyses of the primary endpoint were conducted using the observed case, last

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observation carried forward, multiple imputation, and the worst case missing data methods. Treatment failure rules were to override the missing data rules, meaning that if a patient has both an event of treatment failure (i.e., a Crohn's disease-related surgery thought to be a result of lack of efficacy of study agent or specified changes in concomitant Crohn's disease medications) before Week 6 and has a missing CDAI score at Week 6 (i.e., <4 components of the CDAI available), the patient was considered as a nonresponder in the sensitivity analysis regardless of whether the CDAI data were present.

Safety Analysis

Safety analyses were based on the 740 patients in Study 3001 or 627 patients in Study 3002 who were randomly assigned (after the study was restarted) and received the Week 0 dose of study agent (1 patient in each of the studies placebo groups was randomized but did not receive study agent). Safety was assessed by summarizing the frequency and type of AEs and changes from baseline in clinical laboratory parameters for hematology and chemistry analyses.

Treatment-emergent AEs and laboratory values reported during the study were summarized. Treatment-emergent AEs were coded in accordance with the Medical Dictionary for Regulatory Activities (MedDRA), version 15.0, using the lower-level term (LLT) as the description most closely related to the investigator's terminology, a preferred term describing a group of closely related LLTs, and the system organ class (SOC), which is the broad category including related preferred terms.

The frequency of AEs through Week 8 was summarized by treatment group and MedDRA system-organ class and preferred term. All reported AEs with onset during the treatment phase (i.e., treatment-emergent AEs, and AEs that have worsened since baseline) were included in the analysis. For patients who did not enter into the maintenance study, a listing of patients with AEs occurring after Week 8 through the final safety follow-up visit was provided.

The proportion of patients with 1 or more of the following treatment-emergent AEs through Week 8 was summarized by treatment group:

- Any AEs.
- SAEs.
- Reasonably related AEs.
- AEs leading to discontinuation.
- Infections, serious infections, and infections requiring oral or parenteral antimicrobial treatment.
- Hypersensitivity Reactions

Maintenance Study 3003

Planned Method of Analysis

CDER Clinical Review Template 2015 Edition
Version date: November 5, 2015 for initial rollout (NME/original BLA reviews)

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Demographic and baseline disease characteristics were summarized; these analyses and the efficacy analyses were based on the 388 patients who were randomized into the maintenance study 3003 from inductions studies 3001 and 3002. Initially 397 patients were enrolled, excluding 9 patients who were randomized prior to study restart when the study was halted for instability noted in a batch of the intravenous dosing formulation in study 3001 (see U.S. Regulatory Actions and Marketing History, Section 3.1 for details). The proportion of patients in clinical remission at Week 44 (primary endpoint) was summarized and compared between each of the ustekinumab treatment groups and the placebo group using a 2-sided Cochran-Mantel-Haenszel chi-square test, stratified by clinical remission status at Week 0 (yes or no), ustekinumab induction dose (130 mg or weight-range based doses approximating ustekinumab 6 mg/kg), and the induction study (3001 or 3002) at a significance level of 0.05. US-specific multiple testing procedures were prespecified to control the overall Type 1 error rate at the 0.05 level in this study.

A fixed-sequence testing procedure was employed to control the Type 1 error rate within each of the major secondary endpoint analyses at the 0.05 (2-sided) significance level. Therefore, the low dose (ustekinumab 90 mg SC q12w) for a major secondary endpoint could not be tested unless the high dose tested positive for that endpoint. In addition, the low dose will not be tested for an endpoint unless the low dose tested positive for the previous endpoint in the hierarchy.

The study was considered positive if the ustekinumab high-dose group was significantly different from the placebo group for the primary endpoint. The primary analysis was based on an intent-to-treat principle. Therefore, the efficacy data for each patient randomly assigned to a treatment group was analyzed according to the assigned treatment regardless of the actual treatment received.

The same data-handling rules specified for the primary endpoint analysis were used for each of the major secondary endpoints.

Sensitivity analyses:

Sensitivity analyses of the primary endpoint were conducted using the observed case, last observation carried forward, multiple imputation, and the worst case missing data methods. Treatment failure rules were to override the missing data rules, meaning that if a patient has both an event of treatment failure (i.e., a Crohn's disease-related surgery thought to be a result of lack of efficacy of study agent or specified changes in concomitant Crohn's disease medications) before Week 44 and has a missing CDAI score at Week 44 (i.e., <4 components of the CDAI available), the patient was considered as a nonremitter in the sensitivity analysis regardless of whether the CDAI data were present.

Safety Analysis

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Safety analyses were based on the 397 randomized patients in who received the Week 0 dose of study agent. Safety was assessed by summarizing the frequency and type of AEs and changes from baseline in clinical laboratory parameters for hematology and chemistry analyses.

Treatment-emergent AEs and laboratory values reported during the study were summarized. Treatment-emergent AEs were coded in accordance with the Medical Dictionary for Regulatory Activities (MedDRA), version 15.0, using the lower-level term (LLT) as the description most closely related to the investigator's terminology, a preferred term describing a group of closely related LLTs, and the system organ class (SOC), which is the broad category including related preferred terms.

The frequency of AEs through Week 8 was summarized by treatment group and MedDRA system-organ class and preferred term. All reported AEs with onset during the treatment phase (i.e., treatment-emergent AEs, and AEs that have worsened since baseline) were included in the analysis.

The proportion of patients with 1 or more of the following treatment-emergent AEs through Week 44 was summarized by treatment group:

- Any AEs.
- SAEs.
- Reasonably related AEs.
- AEs leading to discontinuation.
- Infections, serious infections, and infections requiring oral or parenteral antimicrobial treatment.
- Hypersensitivity reactions

Protocol Amendments

Induction Study 3001

Amendment 1 (September 12, 2011): Included minor revisions of renumbering/clarification of inclusion and exclusion criteria, fixing incorrect attachments with the previous submission, and clarifying that all SAEs would be tracked for 20 weeks after the last dose of the study agent. These changes had no effect on the integrity of the trial or this reviewer's interpretation of the results.

Amendment 2 (December 12, 2011): This amendment described the potential problem and changes in the protocol to exclude patients who were affected by a drug stability issue identified for the IV drug batch (130 mg ustekinumab (b) (4)) that was allocated for use at some sites. This affected 28 patients who were later withdrawn from the Applicant's
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analyses as they were unblinded to identify who had received this dosing. This amendment did not have an effect on the integrity of the trial or this reviewer's interpretation of the results as they were removed from the Applicant analyses.

Amendment 3 (July 9, 2013): This amendment changed the protocol from two database locks (at weeks 8 and 20) to only one database lock after the final safety visit at week 20. This change had no effect on the integrity of the trial or this reviewer's interpretation of the results.

Induction Study 3002

Amendment 1 (December 12, 2011): These changes were the same for the Study 3002 Protocol as Study 3001 (please see above) except for the addition of a minor correction of units used to measure the C-reactive protein level. These changes had no effect on the integrity of the trial or this reviewer's interpretation of the results.

Amendment 2 (December 15, 2011): The same drug stability issue described in study 3001 above affected 12 patients in Study 3002 as well. These patients were also removed from the analyses and the protocol was revised accordingly. Therefore this did not have an effect on the integrity of the trial or this reviewer's interpretation of the results as they were removed from the Applicant analyses.

Amendment 3 (June 3, 2014): For Study 3002 this amendment included a number of clarifications regarding the time and events schedule, exclusion/restriction rules, and study withdrawal rules to clarify these patients should follow up with end of study visits but that they will be considered to have early termination from the study. Concomitant therapy rules were also amended to state changes to these medications may exclude the patient from continuing on into the maintenance study 3003 and if a patient used prohibited medications and did not complete final efficacy/safety visits they would be considered an early termination from the study. Prohibited medications were amended to add Janus kinase inhibitors and commercial ustekinumab. These changes made the protocol for 3002 consistent with that for 3001 had no effect on the integrity of the trial or this reviewer's interpretation of the results.

Maintenance Study 3003

Amendment 1 (December 12, 2011): This amendment was largely to clarify that the sponsor tracks all SAEs for 20 weeks following the last dose of study agent and to add description of the problem with instability of an IV induction dose (described in the induction study amendments above) and removal of these patients from key analyses. These patients were removed from the analyses and the protocol was revised accordingly. Therefore this did not have an effect on the integrity of the trial or this reviewer's interpretation of the results as they were removed from the Applicant analyses.

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Amendment 2 (June 24, 2014): The overall reasons for this amendment was to incorporate changes in the way SAEs attributed to the disease under study are reported, to update the description of prohibited medications based on newly approved therapies for Crohn's disease similar to the changes noted in Study 3002 above, and based on feedback from health authorities, the functionality of the system used to project the expected number of patients in the primary analysis population of this study. The changes to SAE reporting were as follows: Serious adverse events attributed to Crohn's disease or related symptoms or progression of the disease under study will not be unblinded for expedited reporting

Amendment 3 (August 6, 2015): The major change in this amendment extended the study for ustekinumab responders by one year (to week 272 for a total of 4 years) in the long term extension study after week 44 of the primary endpoint of the maintenance study. This was to allow for a 20 week safety follow up period to occur after the patient's last dose given at week 252. Other changes in this amendment were made to reflect the new time and events or follow up schedule proposed. This change had no effect on the integrity of the trial or this reviewer's interpretation of the results.

Data Quality and Integrity: Sponsor's Assurance

The study was monitored according to the Applicant's current standard operating procedures (SOPs) for the monitoring of clinical studies.

The accuracy and reliability of the data from Studies 3001, 3002, and 3003 were assured by the selection of qualified investigators and an appropriate study center, review of protocol procedures with the investigator and associated personnel before the study, and by periodic monitoring visits by the Applicant. Written instructions were provided for the collection, preparation, and shipment of plasma samples. Instruction booklets for completion of eCRFs were also provided and reviewed with study personnel before the start of the study. eCRFs were reviewed for accuracy and completeness by the Applicant during on site monitoring visits and after their return to the Applicant, and any discrepancies were resolved with the investigator or designees, as appropriate. The data were entered into the database and their accuracy verified using appropriate validation programs.

6.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant states these studies were conducted in compliance with Good Clinical Practice, including the archival of essential documents.

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Financial Disclosure

The applicant adequately disclosed financial arrangements with the clinical investigators. These arrangements do not raise concern over the integrity of the data or the approvability of the data. Refer to Section 13.2, Appendix: Financial Disclosure for further discussion and tables detailing the financial disclosures.

Patient Disposition

Induction Study 3001

Seven hundred sixty-nine patients were randomly assigned to receive study agent in induction study 3001. Of these patients, there were 28 patients that were excluded prior to the study restarting were evenly distributed between the 3 treatment groups with 10, 9, and 9 patients in the placebo, ustekinumab 130 mg, and ustekinumab 6 mg/kg dose, respectively. The disposition of these patients discussed here is based on the 741 patients who were randomized in a 1:1:1 ratio to receive a single IV administration of placebo (n=247) or 1 of 2 induction doses of ustekinumab at Week 0: ustekinumab 130 mg (n=245) or tiered ustekinumab doses approximating 6 mg/kg (n=249) after the study was restarted (see U.S. Regulatory Actions and Marketing History, Section 3.1). Patients were enrolled from 22 countries, 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. Three hundred and four patients (41.0%) were from the United States.

Of the patients who withdrew from the studies, 33/43 patients withdrew from the induction study 3001 prior to week 8, and 10/43 patients withdrew study after week 8 but prior to week 20, which was the safety follow up period. Of these patients, 13 patients were in the placebo dosing arm, 11 patients dropped out of the 130 mg arm and 19 in the 6 mg/kg weight tiered dosing arm. The majority (21/43 patients) withdrew consent, 5/43 patients were lost to follow up, and 7/33 patients were noted by the Applicant not to meet study criteria for enrollment.

Of the 71/741 (9.6%) patients that did not enter the maintenance study, a greater proportion of patients in the placebo group did not enter the maintenance study (33/247 [13.4%]) compared with patients in the ustekinumab groups (16/245 [6.5%] and 22/249 [8.8%] in the 130 mg and 6 mg/kg groups, respectively). The most common reasons for not continuing to receive study agent by entering the maintenance study were adverse events (25/741), the most common AE leading to withdrawal was AEs related to Crohn's disease (6/25), and lack of efficacy (19/741). Adverse events and lack of efficacy both occurred in a greater proportion of patients in the placebo group (AEs 15/247 [6.1%]; lack of efficacy 8/247 [3.2%]), as compared to the ustekinumab dose groups (130 mg: AEs 2/245 [0.8%]; lack of efficacy 7/245 [2.9%] and 6 mg/kg: AEs 8/249 (3.2%); lack of efficacy 4/249 [1.6%]). Of the active treatment dosing arms, AEs were

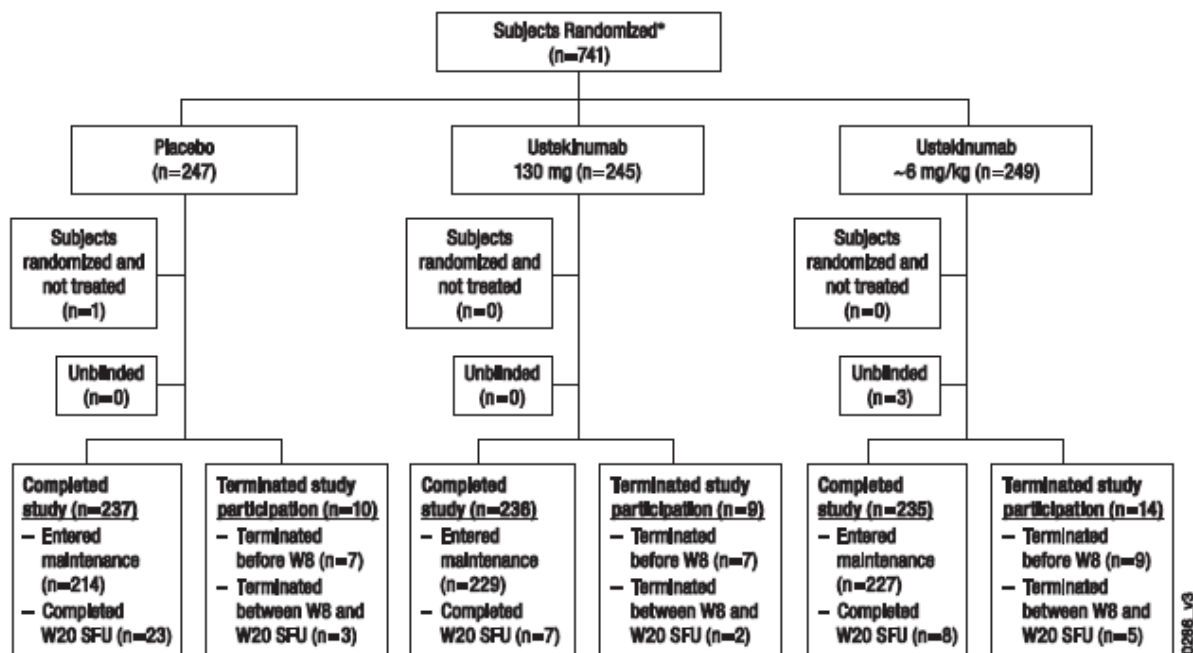
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more common in the 6 mg/kg higher dosed group, however lack of efficacy was more common in the 130 mg lower dosed group.

Of the 741 patients enrolled in study 3001, 737/741 (99.5%) patients received the study treatment to which they were assigned. Of the 4 patients who did not receive the assigned study treatment, 1 patient randomized to the placebo group never received study agent, another patient randomized to the placebo group received ustekinumab (39.6 mg) and was analyzed in the 130 mg ustekinumab group for PK and safety, 1 patient randomized to the 130 mg ustekinumab group actually received a dose more closely approximating the high dose (219.6 mg in a 63.5 kg patient, i.e., 3.5 mg/kg) and was therefore analyzed in the 6 mg/kg ustekinumab group for PK and safety. Lastly, a patient who was randomized to the 6 mg/kg ustekinumab group actually received a dose (3.1 mg) more closely approximating the 130 mg dose because his infusion was interrupted and the drug was withdrawn due to an AE during the infusion. This patient was therefore analyzed in the 130 mg ustekinumab group for PK and safety. This reviewer believes these patients should have been excluded from efficacy, but included in safety analyses. However, excluding them from the efficacy analysis does not change the overall results of the primary or key secondary endpoints.

All of these patients except one received at least 1 study drug infusion and were included in the modified patient population (MPP). The MPP was used for all efficacy and safety analyses. The efficacy analyses were repeated excluding patients with protocol violations and the results were not significantly different from the analyses conducted using the Applicant's MPP. Therefore, the conclusions were unchanged and the analyses conducted using the Applicant's will be presented in this document. See statistical review by Dr. Min Min for further details. The overall disposition for patients screened, enrolled, and randomized is shown below.

Figure 9: Disposition of Patients in Study 3001



Source: Applicant's submission, BLA 761044, clinical study report for study 3001, page 48/396

Finally, the 3 patients that were unblinded in the 6 mg/kg study arm were unblinded to follow the suspected unexpected serious adverse reactions (SUSARs) which were listeria meningitis, *E. coli* sepsis, and colonic fistula.

Induction Study 3002

Six hundred forty patients were randomly assigned to receive study agent in induction study 3002. Of these, there were 12 patients that were excluded prior to the study restarting were evenly distributed between the 3 treatment groups with 4 in each; however, these patients were excluded from the efficacy analyses. The disposition of patients discussed here is based on the 628 patients who were randomized in a 1:1:1 ratio to receive a single IV administration of placebo (n=210) or 1 of 2 induction doses of ustekinumab at Week 0: ustekinumab 130 mg (n=209) or tiered ustekinumab doses approximating 6 mg/kg (ustekinumab 6 mg/kg; n=209) after the study was restarted (see Section 3.1). Patients were enrolled from 22 countries, at 175 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. Two hundred and eight patients (33.1%) were from the United States.

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Of the 628 patients enrolled in study 3002, 605/628 (96.3%) patients completed the induction study and 585/628 patients continued into the maintenance study 3003. Of the patients who withdrew early, 14/23 patients withdrew from the induction study prior to week 8 and 9/23 patients withdrew from the study after week 8 but prior to week 20, which was the safety follow up period. Of the patients who withdrew early, 12 patients were in the placebo arm, 9 patients were in the 130 mg arm and 2 patients were in the 6 mg/kg weight tiered dosing arm. The majority of patients (15/23) withdrew consent, 7/23 patients were lost to follow up, and 1/23 patient was noted by the Applicant not to meet study criteria for enrollment.

Of the 43/628 (6.8%) patients that did not enter the maintenance study. A greater proportion of patients in the placebo group (24/210 [11.4%]) did not enter the maintenance study compared with patients in the ustekinumab groups (13/209 [6.2%] and 6/209 [2.9%] in the 130 mg and 6 mg/kg groups, respectively). The most common reasons for not entering into the maintenance study were patient ineligibility (9/210 [4.3%] patients in the placebo group; 1/209 [0.5%] and 2/209 [1.0%] patients the 130 mg and 6 mg/kg groups, respectively) and withdrawal of consent (6/210 [2.9%] patients in the placebo group; 5/209 [2.4%] and 1/209 [0.5%] patients in the 130 mg and 6 mg/kg groups, respectively). Five out of 210 (2.4%) patients in the placebo group, and 3/209 (1.4%) and 2/209 (1.0%) patients in the 130 mg and 6 mg/kg groups, respectively, did not enter the maintenance study due to an AE. The majority of these AEs were due to Crohn's disease.

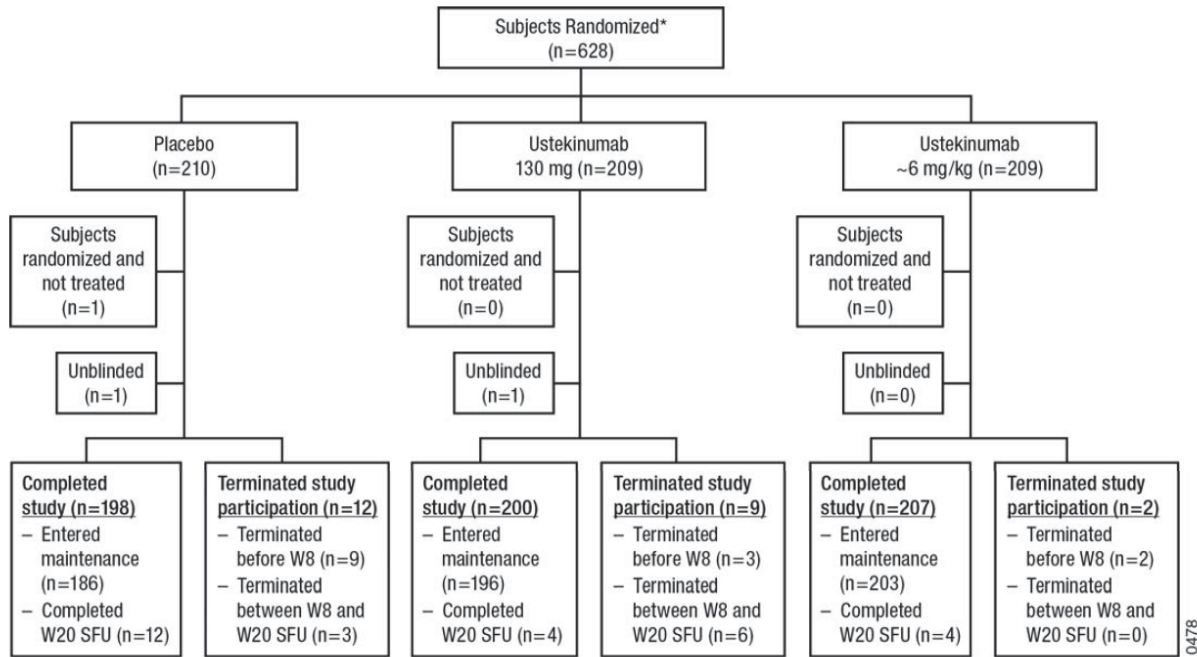
Of the 628 patients enrolled, 624/628 (99.4%) patients received the study treatment to which they were assigned. Of these 4 patients, one patient was randomized to the placebo group but never received study agent and another was randomized to the placebo group and received a ustekinumab dose approximating the low dose (130 mg). This patient was analyzed in the ustekinumab 130 mg group for PK and safety. In addition, 2 patients who were randomized to the ustekinumab 6 mg/kg group actually received doses more closely approximating the low dose (130 mg); those 2 patients were analyzed in the ustekinumab 130 mg group for PK and safety. All of these patients except one received at least 1 study drug infusion and were included in the modified patient population (MPP).

Of the patients enrolled in study 3002, 186/210 (88.6%) of patients in the placebo arm 196/209 (93.8%) of patients in the 130 mg dose arm and 203/209(97.1%) of patients in the 6 mg/kg weight tiered dose arm completed the induction study and entered maintenance. All of these patients except one received at least 1 study drug infusion and were included in the modified patient population (MPP). The MPP was used for all efficacy and safety analyses. The efficacy analyses were repeated excluding patients with protocol violations and the results were not significantly different from the analyses conducted using the Applicant's MPP. Therefore, the conclusions were unchanged and the analyses conducted by the Applicant will be presented in this document. See statistical review by Dr. Min Min for further details and verification of the

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Applicant's analyses. The overall disposition for patients screened, enrolled, and randomized is shown below.

Figure 10: Disposition of Patients in Study 3002



*Excludes subjects randomized before study restart; SFU=safety follow-up.

Source: Applicant's submission, BLA 761044, clinical study report for study 3002, page 51/366)

Finally, the 2 patients that were unblinded (1 in the placebo arm, one in the 130 mg study arm) were unblinded to follow the suspected unexpected serious adverse reactions (SUSARs) which were pancytopenia (placebo) and perianal abscess (130 mg dose).

Maintenance Study 3003

All patients who completed the induction studies (study 3001 and 3002) were eligible to enroll into the maintenance study (study 3003); however, only patients who met the criteria for clinical response were included in the randomized patient population for the efficacy and safety analyses. Patients who did not achieve clinical response or who received placebo during the induction studies were considered to be the non-randomized patient population. A total of 1,281 patients who completed the ustekinumab induction studies 3001 and 3002 were enrolled

in this study. Among these patients, 397 patients (31.0%) were in clinical response to ustekinumab induction and randomized in a 1:1:1 ratio to receive a SC administration of placebo (n=133) or 1 of 2 maintenance dosing regimens of ustekinumab 90 mg SC at Week 0: q12w (n=132) with final dose at Week 36 or q8w (n=132) with final dose at Week 40 into the primary population. Patients were enrolled from 22 countries and 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. Two hundred and eight patients (33.1%) were from the United States. An additional 884 (69.0%) patients who were not in clinical response to study agent or were in clinical response to placebo also enrolled into this maintenance study but were not part of the primary analysis population (i.e., were not randomized) coming from 221 sites in Asia (7.6%), Eastern Europe (10.5%), and other countries (81.9%) in North America and Western Europe, and countries including Israel, South Africa, Australia, New Zealand, and Brazil. This section will focus on the randomized population.

Nine patients that were excluded for randomization prior to the study restarting were evenly distributed between the 3 treatment groups. Additionally, 1/397 (0.3%) patient in the ustekinumab 90 mg SC q8w dose group who did not meet study entry criteria was enrolled. Removal of these patients does not affect the final conclusions of the primary or key secondary endpoints.

Of the 397 patients enrolled in study 3003, 361/397 (90.9%) patients completed the maintenance study (either to week 44 or by completing a final safety/efficacy visit if they withdrew early) and 298/397 (75.1%) patients continued into a long term extension study. Of the 397 randomized patients in the primary population, 90/397 (22.7%) patients discontinued study agent prior to Week 44. The proportions of patients 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 q12w, and q8w groups, respectively). The most common reasons for discontinuation of study agent among patients in the primary population were lack of efficacy (11.3% [15/133], 10.6% [14/132], and 11.4% [15/132] in the placebo, ustekinumab 90 mg SC q12w and q8w groups, respectively), or an AE (6.8% [9 /133], 9.1% [12], and 4.5% [6] in the placebo, ustekinumab 90 mg SC q12w and q8w groups, respectively). AEs causing discontinuation were largely related to Crohn's disease and the number of these in the q12 week dosing group is double that of the q8 week dosing group, which could indicate inferior treatment effect of the q12 week dose.

A total of 27.5% (109/397 patients) of the primary population had a dose adjustment if they met LOR criteria (described above in Study Design, Section 6.1.1) as follows:

- 38.3% (51/133) patients in placebo had a dose adjustment to an ustekinumab 90 mg SC q8w dose regimen
- 22.0% (29/132) patients in the 90mg SC q12w regimen had a dose adjustment to an ustekinumab 90 mg SC q8w regimen

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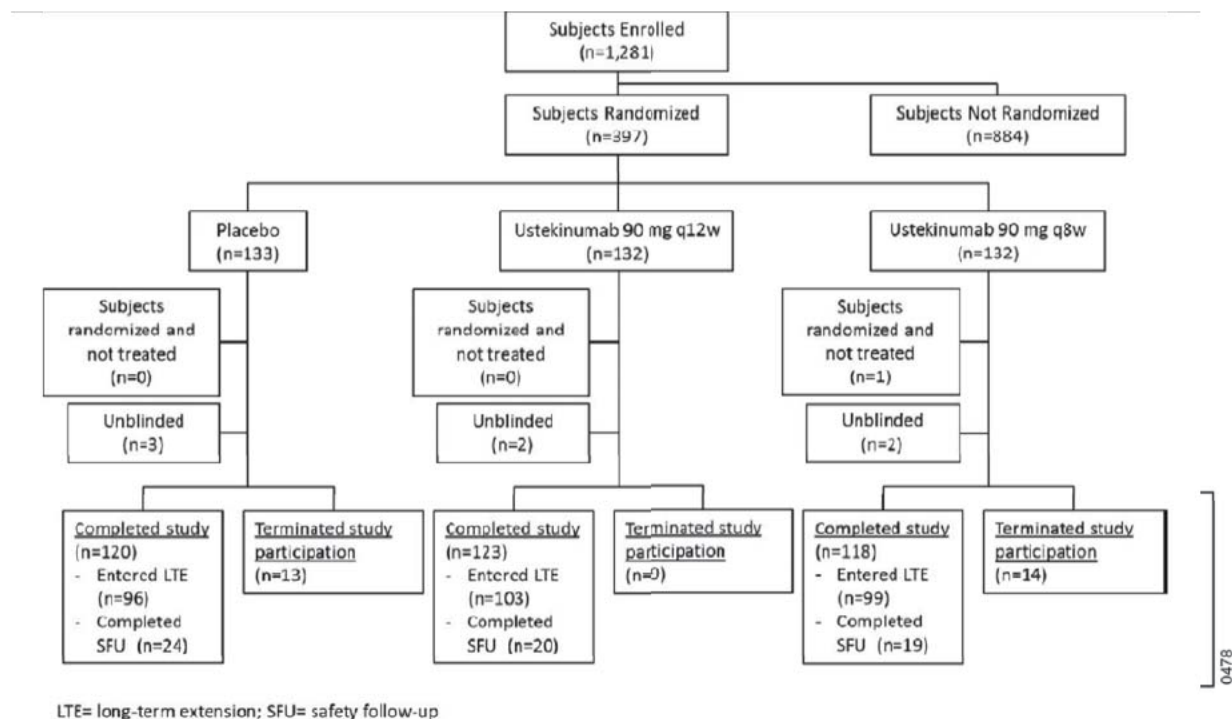
- 22.1% (29/131 patients) patients in the 90mg SC q8w regimen continued on the same dose regimen after dose adjustment (maintained blinding)

The majority (76.1%) of dose adjustments in the primary population occurred by Week 20. For patients who had a dose adjustment, the proportions of patients who discontinued study agent administration after dose adjustment were 15/51 (29.4%), 10/29 (34.5%), and 12/29 (41.4%) in the placebo, ustekinumab 90 mg q12w, and q8w groups, respectively. The most common reason for discontinuation of study agent among these patients was lack of efficacy (21.6% [11/51 patients], 24.1% [7/29 patients], and 20.7% [6/29 patients] in the placebo, ustekinumab 90 mg SC q12w and q8w groups, respectively). See Section 6.1.2 Study Results, Other Endpoints for maintenance Study 3003, for further discussion of the analysis of clinical efficacy by dose adjustment.

Study agent assignment was unblinded for 7/396 patients during the study, 3 in the placebo group and 2 each in the ustekinumab q12w and q8w groups. Each of these was due to suspected unexpected serious adverse reaction (SUSAR) and these were spread evenly across the treatment doses.

All patients received the treatment to which they were assigned. All of these patients except one received at least 1 study drug infusion and were included in the Full Analysis Set (FAS). One patient in the q8w dosing arm missed 2 or more consecutive administrations of the study agent. The FAS was used for all efficacy and safety analyses. The efficacy analyses were repeated using the mPP population and the results were very similar to the analyses conducted using the FAS. Therefore, the conclusions were unchanged and the analyses conducted using the FAS will be presented in this document. See statistical review by Dr. Min Min for further details. The overall disposition for patients screened, enrolled, and randomized is shown below.

Figure 11: Disposition of Patients in Study 3003



Source: Applicant’s submission, BLA 761044, clinical study report for study 3003, page 51/366)

Protocol Violations/Deviations

Induction Study 3001

Of the 741 randomized patients, 72 had a major protocol deviations, with fewer patients in the placebo group (n=19) than in the ustekinumab groups (n=28 and n=25 in the 130 mg and tiered 6 mg/kg ustekinumab groups, respectively). Of those 72 patients, 65 patients had deviations before randomization (i.e. did not meet all protocol entry criteria), with the remainder occurring after randomization. 32 patients did not meet entry criteria for baseline CDAI (10 had CDAI <220 [too low] to enroll and 22 had CDAI >450 [too high] to enroll. Removing these patients from the efficacy analyses did not change the overall conclusions of the study’s primary or key secondary endpoints. See Statistical Review by Dr. Min Min for further details. Of the 741 enrolled patients, 708/741 (95.5%) patients completed the induction studies and 670/741 continued into the maintenance study 3003.

In this reviewer’s opinion, the protocol deviations did not appear to have any clinically relevant impact on data integrity or patient safety. There were 32 patients that did not meet entry

criteria for baseline CDAI score (10 with baseline CDAI <220 and 22 with baseline CDAI >450); however, removing them from the efficacy analyses did not change the overall conclusions of the study's primary or key secondary endpoints. The major protocol deviations for the study were divided into the categories described below:

- Patients who entered the study but did not meet inclusion criteria:
 - Crohn's disease criteria: baseline CDAI out of range, surgical complications of Crohn's expected, and no endoscopic confirmation of disease 5/741 (0.07%)
 - Of note, the sponsor describes 2 patients who did not meet CDAI screening criteria, the statistical review notes 32 patients, a difference of 30 patients
 - Medical History Criteria: Patients were withdrawn after being randomized for negative CXRs that were not read prior to randomization as per protocol, histories of melanoma and multiple myeloma, abscess, and incomplete or indeterminate TB screening 10/741 (1.3%)
- Patients who entered the study but did not meet exclusion criteria:
 - The results of negative stool testing for enteric pathogens was not available at the time of randomization and accounted for 25/741 (3.4%) study entry criteria deviations. Testing was subsequently performed in 22 of the 25 patients before administration of any additional study agent before the start of the maintenance study. Test results were negative for 20 patients and positive (*C. difficile* toxin) for 2 patients; those 2 patients were excluded from entering the maintenance study. The other 3 patients had entered the maintenance study but had already withdrawn before stool testing was completed.
 - Laboratory criteria: Deviations in screening of AST/ALT occurred in 5 (0.07%) patients and the deviation resulted in missing screening values rather than abnormal levels; all values were normal at the baseline visit.
 - Inadequate documentation of informed consent 1/741 (0.1%) patient.
- Patients who received the wrong treatment or incorrect dose;
 - 3 patients received the incorrect dose $n=3$ (0.4%)
- Patients who received disallowed concomitant medication:
 - received ant-TNF or other biologic agents <8 weeks before baseline or randomization, did not meet criteria for primary non-response, secondary non-response, or intolerance to previous anti-TNF therapy, did not maintain a stable dose of oral corticosteroids or received IV corticosteroids within 3 weeks of baseline, received TPN within 3 weeks of baseline, altered permissible concomitant medications within 3 weeks of baseline, and received BCG vaccination within one year of baseline: $n=23/741$ (3.1%)
- and other: $n=5$ (0.7%)

Of note, no patients received disallowed concomitant medication(s). Overall, the majority of these protocol deviations were resolved during the course of the trial and those that were not

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and still included in the trial did not affect the outcome of the safety or efficacy analyses.

Induction Study 3002

Of the 628 randomized patients, 79 patients had a major protocol deviation, with slightly more patients in the placebo group (n=33) than in the individual ustekinumab groups (n=23 in both ustekinumab groups). The majority of major protocol deviations in 74/79 patients were due to patients who entered the study but did not meet entry criteria; as detailed below, most of these were related to incomplete information at the time of randomization and patients were ultimately found to meet the relevant criteria.

Of the 628 patients enrolled, 602 met all protocol entry criteria. There were 26 patients who did not meet entry criteria for baseline CDAI scores (16 patients with CDAI scores <220 and 10 patients with CDAI scores >450); however, removing them from the efficacy analyses did not change the overall conclusions of the study's primary or key secondary endpoints. See Statistical Review by Dr. Min Min for further details.

The major protocol deviations for the study were divided into the categories described below:

- Patients who entered the study but did not meet inclusion criteria:
 - Crohn's disease criteria: baseline CDAI out of range, bowel resection occurred 8 days less than the 6 months prior to baseline for enrollment, and no endoscopic confirmation of disease, fecal calprotectin or CRP criteria were not met 10/628 (1.6%)
 - Of note, the sponsor describes 4 patients who did not meet CDAI screening criteria, the statistical review notes 26 patients, a difference of 24 patients
 - Medical History Criteria 25/628 (4.0%): Patients were withdrawn for CXRs that were not read prior to randomization as per protocol (all were eventually read as negative) or not having negative QuantiFERON-TB Gold test results prior to randomization (most patients were negative, remaining positives were discontinued from the study), pregnancy test not read/performed prior to randomization (all subsequently negative), and previous history of active TB (Applicant discontinued patient from the study)
- Patients who entered the study but did not meet exclusion criteria 34/628 (5.4%):
 - Testing was subsequently performed in 25 of the 34 patients before administration of any additional study agent prior to the maintenance study and was negative in all 25 patients. For another patient, testing (negative) had occurred 5 months prior to baseline; this patient was permitted to continue into the maintenance study without further testing. The 8 remaining patients in this category discontinued study agent for other reasons before stool testing could be performed. There were no adverse events related to enteric bacterial

pathogens and this reviewer does concludes that inclusion of and of these patients impacted the safety or efficacy analyses.

- Laboratory criteria: Two out of 628 (0.3%) patients did not satisfy the requirement for screening ALT and AST results within 2 times the upper limit of normal at the time of randomization due to missing values, and not due to abnormal results. In both cases, the screening AST was not available and later determined to be normal, and the screening ALT was normal. One patient, the Week 0 AST and ALT values were both normal. In the other patient, Week 0 AST and ALT were not available but both were normal at Week 3. Both patients were permitted to continue into the maintenance study.
- Patients who received the wrong treatment or incorrect dose:
 - 3 patients received the incorrect dose 3/628 (0.5%). These patients are described in the section on Patient Disposition above.
- Patients who received disallowed concomitant medication 16/628 (2.5%):
 - Previously had developed primary non-response, secondary non-response, or intolerance to previous anti-TNF therapy, did not maintain a stable dose of oral corticosteroids or received IV corticosteroids within 3 weeks of baseline, altered or initiated permissible concomitant medications within 3 weeks of baseline, received antibiotics for an SAE discovered at screening (patient withdrew), and received BCG vaccination within one year of baseline. This reviewer believes the patients who previously developed primary non-response or intolerance to previous anti-TNF therapy should have been withdrawn from the randomized population. However, it is unlikely that this number (5) affected the overall efficacy results of the induction study.
- Other: For 2/628 (0.3%) patients, the site did not report an SAE to the Applicant within 24 hours of site knowledge; in both cases, the SAE was subsequently reported to the Applicant and appropriate reporting and follow-up subsequently took place. One of the 2 patients entered the maintenance study while the other did not enter the maintenance study for unrelated reasons.

Of note, no patients received disallowed concomitant medication(s). Overall, the majority of these protocol deviations were resolved during the course of the trial and those that were not and still included in the trial did not affect the outcome of the safety or efficacy analyses.

Maintenance Study 3003

Of the 397 randomized patients, 12/397 [3.0%] patients, 3 patients in the every 12 week dosing group and 4 patients in the every 8 week dosing group, were found to have major protocol violations. The categories for major protocol deviations with the proportion of patients who fall into each category are described below.

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- Patients who entered the study but did not meet inclusion criteria:
 - Medical History Criteria 8/397 (2.0%): pregnancy test not read/performed prior to randomization (all subsequently negative)
 - Misclassified as responder 1/397 (0.3%): This patient was allowed to continue, however this reviewer does not believe this patient had an adverse effect on the efficacy or safety results.
 - Signed the wrong informed consent form 1/397 (0.3%)
- Patients who received the wrong treatment or incorrect dose;
 - 1 patient received the incorrect dose 1/397 (0.3%). This patient is described in the section on Patient Disposition above.
- Patients who received disallowed concomitant medication 1/397(0.3%):
 - Patient received IV corticosteroids for worsening Crohn’s disease in induction study 3002. It is unlikely that this number (1) affected the overall efficacy results of the maintenance study.

Tables of Demographic Characteristics

Induction Study 3001

Of the 741 randomized patients randomized in study 3001, 57.2% were women and 84.1% were white. The difference between males and females was small and this reviewer is not aware of data to suggest differences in disease severity or response to treatment based on sex. Additionally, Crohn’s disease has a slight predominance for females>males, therefore the study demographics reflect the disease population at large. The racial distribution reflects the larger, general population demographic that has Crohn’s, which is predominantly a Caucasian population. The median age was 36.0 years and median weight was 67.0 kg. As shown in the table below, baseline demographic characteristics were generally similar across the treatment groups. The proportion of male patients in the placebo group (47.8%) was slightly higher compared with the ustekinumab 130 mg (40.0%) and 6 mg/kg (40.6%) groups, respectively.

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Figure 12: Demographics from Study 3001

	Placebo	Ustekinumab		Total
		130 mg	6 mg/kg ^a	
Analysis set: Randomized subjects in CNTO1275CRD3001 excluding those enrolled prior to study re-start	247	245	249	741
Sex				
N	247	245	249	741
Male	118 (47.8%)	98 (40.0%)	101 (40.6%)	317 (42.8%)
Female	129 (52.2%)	147 (60.0%)	148 (59.4%)	424 (57.2%)
Age (years)				
N	247	245	249	741
Mean (SD)	37.3 (11.83)	37.4 (11.77)	37.3 (12.54)	37.3 (12.04)
Median	36.0	37.0	36.0	36.0
Range	(18; 71)	(18; 70)	(18; 71)	(18; 71)
Age Group				
N	247	245	249	741
≥ 18 - < 65 years	242 (98.0%)	238 (97.1%)	244 (98.0%)	724 (97.7%)
≥ 65 years	5 (2.0%)	7 (2.9%)	5 (2.0%)	17 (2.3%)
≥ 65 - < 75 years	5 (2.0%)	7 (2.9%)	5 (2.0%)	17 (2.3%)
≥ 75 years	0	0	0	0
Race				
N	247	245	249	741
White	210 (85.0%)	202 (82.4%)	211 (84.7%)	623 (84.1%)
Black or African American	8 (3.2%)	7 (2.9%)	8 (3.2%)	23 (3.1%)
Asian	20 (8.1%)	20 (8.2%)	23 (9.2%)	63 (8.5%)
American Indian or Alaska Native	0	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0	0
Other ^b	9 (3.6%)	16 (6.5%)	7 (2.8%)	32 (4.3%)
Ethnicity				
N	247	245	249	741
Hispanic or Latino	8 (3.2%)	10 (4.1%)	12 (4.8%)	30 (4.0%)
Not Hispanic or Latino	235 (95.1%)	233 (95.1%)	232 (93.2%)	700 (94.5%)
Not reported or Unknown	4 (1.6%)	2 (0.8%)	5 (2.0%)	11 (1.5%)
Region				
N	247	245	249	741
United States	117 (47.4%)	99 (40.4%)	88 (35.3%)	304 (41.0%)
Canada	10 (4.0%)	21 (8.6%)	21 (8.4%)	52 (7.0%)
South America	2 (0.8%)	0	1 (0.4%)	3 (0.4%)
Europe	90 (36.4%)	95 (38.8%)	108 (43.4%)	293 (39.5%)
Asia	19 (7.7%)	19 (7.8%)	21 (8.4%)	59 (8.0%)
Africa	1 (0.4%)	1 (0.4%)	0	2 (0.3%)
Rest of World (Australia, Israel, New Zealand)	8 (3.2%)	10 (4.1%)	10 (4.0%)	28 (3.8%)

^a 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).

^b Unknown, Not reported, or Multiple; also includes other specified races: Biracial (African American and Caucasian), Brown, Caucasian, Hispanic, Indian, Italian, Moroccan, Mixed race.

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Source: Provided by Applicant in response to FDA Information Request dated May 10, 2016.

Induction Study 3002

Of the 628 randomized patients randomized in study 3002, 52.9% were women and 83.8% were white. The difference between males and females was small and this reviewer is not aware of data to suggest differences in disease severity or response to treatment based on sex. Additionally, Crohn's disease has a slight predominance for females>males, therefore the study demographics reflect the disease population at large. The racial distribution reflects the larger, general population demographic that has Crohn's, which is predominantly a Caucasian population. The median age was 37.0 years and median weight was 70.8 kg. As shown in the table below, baseline demographic characteristics were generally similar across the treatment groups. The proportion of patients ≥ 65 was slightly lower in the 6 mg/kg group (2.9%) than in the 130 group (4.8%) or placebo group (4.8%). Otherwise, the proportions of sex, age, and race were distributed evenly between dosing arms.

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Figure 13: Demographics of Study 3002

	Placebo	Ustekinumab		Total
		130 mg	6 mg/kg ^a	
Analysis set: Randomized subjects in CNTO1275CRD3002 excluding those enrolled prior to study re-start	210	209	209	628
Sex				
N	210	209	209	628
Male	99 (47.1%)	104 (49.8%)	90 (43.1%)	293 (46.7%)
Female	111 (52.9%)	105 (50.2%)	119 (56.9%)	335 (53.3%)
Age (years)				
N	210	209	209	628
Mean (SD)	40.2 (13.10)	39.1 (13.78)	38.4 (13.12)	39.2 (13.34)
Median	39.0	37.0	36.0	37.0
Range	(18; 77)	(18; 75)	(18; 74)	(18; 77)
Age Group				
N	210	209	209	628
≥ 18 - < 65 years	200 (95.2%)	199 (95.2%)	203 (97.1%)	602 (95.9%)
≥ 65 years	10 (4.8%)	10 (4.8%)	6 (2.9%)	26 (4.1%)
≥ 65 - < 75 years	9 (4.3%)	9 (4.3%)	6 (2.9%)	24 (3.8%)
≥ 75 years	1 (0.5%)	1 (0.5%)	0	2 (0.3%)
Race				
N	210	209	209	628
White	177 (84.3%)	175 (83.7%)	174 (83.3%)	526 (83.8%)
Black or African American	7 (3.3%)	6 (2.9%)	7 (3.3%)	20 (3.2%)
Asian	17 (8.1%)	17 (8.1%)	16 (7.7%)	50 (8.0%)
American Indian or Alaska Native	0	0	1 (0.5%)	1 (0.2%)
Native Hawaiian or other Pacific Islander	0	0	2 (1.0%)	2 (0.3%)
Other ^b	9 (4.3%)	11 (5.3%)	9 (4.3%)	29 (4.6%)
Ethnicity				
N	210	209	209	628
Hispanic or Latino	3 (1.4%)	7 (3.3%)	4 (1.9%)	14 (2.2%)
Not Hispanic or Latino	204 (97.1%)	198 (94.7%)	200 (95.7%)	602 (95.9%)
Not reported or Unknown	3 (1.4%)	4 (1.9%)	5 (2.4%)	12 (1.9%)
Region				
N	210	209	209	628
United States	68 (32.4%)	68 (32.5%)	72 (34.4%)	208 (33.1%)
Canada	14 (6.7%)	18 (8.6%)	10 (4.8%)	42 (6.7%)
South America	2 (1.0%)	5 (2.4%)	2 (1.0%)	9 (1.4%)
Europe	84 (40.0%)	80 (38.3%)	81 (38.8%)	245 (39.0%)
Asia	16 (7.6%)	15 (7.2%)	15 (7.2%)	46 (7.3%)
Africa	14 (6.7%)	5 (2.4%)	14 (6.7%)	33 (5.3%)
Rest of World (Australia, Israel, New Zealand)	12 (5.7%)	18 (8.6%)	15 (7.2%)	45 (7.2%)

^a Subjects who were in clinical response to ustekinumab IV induction dosing and were randomized to placebo SC on entry into the maintenance study.

^b Unknown, Not reported, or Multiple; also includes other specified races: Arabic, Brown, Caucasian, Coptic, East Indian, Filipino, Gipsy, Lebanese, Moroccan, Mulatto, Roma, South African Coloured, South African Mixed race, Mixed race.

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Maintenance Study 3003

Of the 349 randomized patients randomized in study 3003, 56.4% were women and 84.9% were white. The difference between males and females was small and this reviewer is not aware of data to suggest differences in disease severity or response to treatment based on sex. Additionally, Crohn's disease has a slight predominance for females>males, therefore the study demographics reflect the disease population at large. The racial distribution reflects the larger, general population demographic that has Crohn's, which is predominantly a Caucasian population. The median age was 36.0 years and median weight was 69.0 kg. As shown in the table below, baseline demographic characteristics were generally similar across the treatment groups. The proportion of Asian patients was lower in the placebo group (5.3%) than in the q12w group (9.1%) or q8w group (9.8%). Otherwise, the proportions of sex, age, and race were distributed evenly between dosing arms.

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Figure 14: Demographics of Study 3003

	placebo SC ^a	ustekinumab		Total
		90 mg SC q12w	90 mg SC q8w	
Analysis set: Randomized subjects in CNTO1275CRD3003	133	132	132	397
Sex				
N	133	132	132	397
Male	59 (44.4%)	58 (43.9%)	56 (42.4%)	173 (43.6%)
Female	74 (55.6%)	74 (56.1%)	76 (57.6%)	224 (56.4%)
Age (years)				
N	133	132	132	397
Mean (SD)	39.5 (12.69)	38.6 (13.65)	37.9 (13.20)	38.7 (13.17)
Median	38.0	36.5	35.0	36.0
Range	(18; 75)	(18; 74)	(18; 72)	(18; 75)
Age Group				
N	133	132	132	397
≥ 18 - < 65 years	129 (97.0%)	125 (94.7%)	126 (95.5%)	380 (95.7%)
≥ 65 years	4 (3.0%)	7 (5.3%)	6 (4.5%)	17 (4.3%)
≥ 65 - < 75 years	3 (2.3%)	7 (5.3%)	6 (4.5%)	16 (4.0%)
≥ 75 years	1 (0.8%)	0	0	1 (0.3%)
Race				
N	133	132	132	397
White	115 (86.5%)	111 (84.1%)	111 (84.1%)	337 (84.9%)
Black or African American	5 (3.8%)	5 (3.8%)	3 (2.3%)	13 (3.3%)
Asian	7 (5.3%)	12 (9.1%)	13 (9.8%)	32 (8.1%)
American Indian or Alaska Native	0	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0	0
Other ^b	6 (4.5%)	4 (3.0%)	5 (3.8%)	15 (3.8%)
Ethnicity				
N	133	132	132	397
Hispanic or Latino	9 (6.8%)	5 (3.8%)	4 (3.0%)	18 (4.5%)
Not Hispanic or Latino	124 (93.2%)	123 (93.2%)	128 (97.0%)	375 (94.5%)
Not reported or Unknown	0	4 (3.0%)	0	4 (1.0%)
Region				
N	133	132	132	397
United States	41 (30.8%)	42 (31.8%)	40 (30.3%)	123 (31.0%)
Canada	10 (7.5%)	4 (3.0%)	12 (9.1%)	26 (6.5%)
South America	1 (0.8%)	1 (0.8%)	3 (2.3%)	5 (1.3%)
Europe	59 (44.4%)	64 (48.5%)	56 (42.4%)	179 (45.1%)
Asia	7 (5.3%)	11 (8.3%)	11 (8.3%)	29 (7.3%)
Africa	5 (3.8%)	2 (1.5%)	5 (3.8%)	12 (3.0%)
Rest of World (Australia, Israel, New Zealand)	10 (7.5%)	8 (6.1%)	5 (3.8%)	23 (5.8%)

^a Subjects who were in clinical response to placebo IV induction dosing and received placebo SC on entry into the maintenance study.

^b Unknown, Not reported, or Multiple; also includes other specified races: Indian, Italian, Roma, South African Coloured, Mixed race.

Source: Provided by Applicant in response to FDA Information Request dated May 10, 2016.

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Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Induction Study 3001

Baseline disease characteristics of Crohn's disease, including the baseline CDAI score, were balanced across the 3 treatment groups. The median duration of disease at baseline was 10.14 years, the median CDAI score was 317, and the median CRP concentration was 9.88 mg/L. These scores would indicate the Applicant enrolled a moderate to severe Crohn's population that was not newly diagnosed with Crohn's disease and indicate active disease. As this population was made up of those that had previously failed biologic treatment, these numbers appear consistent with that the expected disease severity of that patient population. The median CRP concentration was slightly lower in the placebo group at baseline (8.53 mg/L) compared with the ustekinumab groups (10.40 mg/L and 9.93 mg/L in the 130 mg and 6 mg/kg groups, respectively). This reviewer does not believe this difference impacted the final efficacy or safety analyses.

Study inclusion criteria required radiologic or endoscopic documentation of Crohn's disease activity in either the ileum or colon. Isolated colonic disease was present in 124/740 (16.8%) patients, 103/740 (13.9%) patients had only ileal involvement, and 508/740 (68.6%) patients were reported to have involvement in both areas. A total of 321/740 (43.4%) patients had current or prior perianal disease and 156/740 (21.1%) patients reported proximal GI tract involvement (defined as proximal small intestine, stomach, or esophagus). Half of the patients (376/740 [50.8%]) had at least 1 extraintestinal manifestation of Crohn's disease, with the most prevalent being arthritis/arthralgia in 350/740 (47.3%) patients. Many patients had a penetrating phenotype, with a history of intra-abdominal abscess in 104/741 (14%) patients, current or prior sinus tracts or perforation in 59/741 (8%) patients, and current or prior fistulizing disease in 352/741 (47.5%) patients. Clinically apparent fistula was present at baseline in 143/741 (19.3%) patients. A stricturing phenotype was also common: 332/741(44.8%) patients had a current or prior stricture and 72/741 (9.7%) patients had some degree of stricture present at baseline. Overall, the extent of extra-intestinal involvement and the proportions and types of Crohn's disease complications were similar across treatment groups and reflect a moderate to severely active disease population.

Relevant baseline characteristics are summarized in the table below.

Figure 15: Baseline Disease Characteristics Study 3001

	Placebo	130 mg	Ustekinumab 6 mg/kg ^a	Combined	Total
Analysis set: Randomized subjects excluding those enrolled prior to study re-start					
Crohn's disease duration (yrs)	247	245	249	494	741
N	246	245	249	494	740
Mean (SD)	12.13 (8.414)	11.79 (8.324)	12.69 (9.246)	12.24 (8.803)	12.21 (8.670)
Median	9.69	9.90	10.97	10.28	10.14
IQ range	(6.00; 16.69)	(5.14; 15.90)	(5.80; 17.83)	(5.41; 16.46)	(5.62; 16.65)
Range	(0.5; 45.0)	(0.5; 40.1)	(0.1; 51.9)	(0.1; 51.9)	(0.1; 51.9)
Involved GI areas					
N	246	245	249	494	740
Ileum only	28 (11.4%)	38 (15.5%)	37 (14.9%)	75 (15.2%)	103 (13.9%)
Colon only	48 (19.5%)	36 (14.7%)	40 (16.1%)	76 (15.4%)	124 (16.8%)
Ileum and colon	166 (67.5%)	171 (69.8%)	171 (68.7%)	342 (69.2%)	508 (68.6%)
Proximal gastrointestinal tract	45 (18.3%)	57 (23.3%)	54 (21.7%)	111 (22.5%)	156 (21.1%)
Perianal	107 (43.5%)	107 (43.7%)	107 (43.0%)	214 (43.3%)	321 (43.4%)
Extra intestinal involvement					
N	246	245	249	494	740
Any extra intestinal manifestations	121 (49.2%)	127 (51.8%)	128 (51.4%)	255 (51.6%)	376 (50.8%)
Arthritis/arthralgia	112 (45.5%)	122 (49.8%)	116 (46.6%)	238 (48.2%)	350 (47.3%)
Iritis/uveitis	6 (2.4%)	7 (2.9%)	8 (3.2%)	15 (3.0%)	21 (2.8%)
E. nodosum	3 (1.2%)	3 (1.2%)	11 (4.4%)	14 (2.8%)	17 (2.3%)
Pyoderma gangrenosum	0	1 (0.4%)	0	1 (0.2%)	1 (0.1%)
Aphthous stomatitis	12 (4.9%)	10 (4.1%)	9 (3.6%)	19 (3.8%)	31 (4.2%)
PSC	2 (0.8%)	2 (0.8%)	3 (1.2%)	5 (1.0%)	7 (0.9%)
CDAI score					
N	247	245	249	494	741
Mean (SD)	319.0 (59.67)	321.0 (64.67)	327.6 (62.02)	324.4 (63.37)	322.6 (62.17)
Median	313.0	318.0	319.0	319.0	317.0
IQ range	(272.0; 356.0)	(270.0; 357.0)	(276.0; 372.0)	(274.0; 366.0)	(274.0; 360.0)
Range	(198; 515)	(198; 512)	(210; 498)	(198; 512)	(198; 515)
IBDQ score (32-224)					
N	244	243	248	491	735
Mean (SD)	120.0 (29.27)	119.5 (29.47)	118.2 (26.64)	118.8 (28.06)	119.2 (28.45)
Median	120.0	120.0	118.0	119.0	120.0
IQ range	(99.0; 140.0)	(98.0; 138.0)	(98.0; 138.0)	(98.0; 138.0)	(98.0; 138.0)
Range	(60; 202)	(51; 185)	(57; 198)	(51; 198)	(51; 202)
CRP (mg/L)					
N	247	245	249	494	741
Mean (SD)	16.56 (21.064)	19.96 (24.792)	19.50 (25.347)	19.73 (25.049)	18.67 (23.827)
Median	8.53	10.40	9.93	10.15	9.88
IQ range	(3.38; 21.90)	(3.48; 26.60)	(3.72; 26.60)	(3.55; 26.60)	(3.48; 24.40)
Range	(0.1; 180.0)	(0.1; 157.0)	(0.1; 145.0)	(0.1; 157.0)	(0.1; 180.0)
Crohn's Disease Complications					
N	247	245	249	494	741
Intra-abdominal abscess (Past)	34 (13.8%)	32 (13.1%)	38 (15.3%)	70 (14.2%)	104 (14.0%)
Sinus tracts / perforation^b	16 (6.5%)	21 (8.6%)	22 (8.8%)	43 (8.7%)	59 (8.0%)
Fistula^b	127 (51.4%)	113 (46.1%)	112 (45.0%)	225 (45.5%)	352 (47.5%)
Current	53 (21.5%)	43 (17.6%)	47 (18.9%)	90 (18.2%)	143 (19.3%)
Bowel Strictureing^b	108 (43.7%)	109 (44.5%)	115 (46.2%)	224 (45.3%)	332 (44.8%)
Current	20 (8.1%)	29 (11.8%)	23 (9.2%)	52 (10.5%)	72 (9.7%)

Source: Applicant's table entitled, *TSIDEM03: Summary of Crohn's Disease Characteristics at Baseline; Randomized Patients Excluding Those Enrolled Prior to Study Restart, Study 3001 CSR, BLA 761044, p 127/396.*

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Induction Study 3002

Baseline disease characteristics of Crohn's disease, including the baseline CDAI score, were generally balanced across the 3 treatment groups. The median duration of disease at baseline was 6.4 years (8.28 years in the placebo vs 5.61 years and 6.21 years in 130 mg and 6 mg/kg groups, respectively), the median CDAI score was 292.5 points, and the median CRP concentration was 8.05 mg/L. These scores would indicate the Applicant enrolled a moderate to severe Crohn's population with active disease that was not newly diagnosed with Crohn's disease, but had had a shorter disease duration than those in the induction study 3001. As this population was made up of patients that had previously failed conventional, but not biologic treatment, these numbers appear consistent with the population. This reviewer concludes the difference between placebo and the ustekinumab treatment groups in duration of time with disease does not impact the final efficacy or safety analyses.

Study inclusion criteria required radiologic or endoscopic documentation of Crohn's disease activity in either the ileum or colon. Isolated colonic disease was present in 124/627 (19.8%) patients, 146/627 (23.3%) patients had only ileal involvement, and 355/627 (56.6%) patients were reported to have involvement in both areas. A total of 178/627 (28.4%) patients had current or prior perianal disease and 95/627 (15.2%) patients reported proximal GI tract involvement (defined as proximal small intestine, stomach, or esophagus). Half of the patients (349/628 [55.6%]) had at least 1 extraintestinal manifestation of Crohn's disease, with the most prevalent being arthritis/arthralgia in 330/628 (52.5%) patients. Many patients had a penetrating phenotype, with a history of intra-abdominal abscess in 64/628 (10.2%) patients, current or prior sinus tracts or perforation in 35/628 (5.6%) patients, and current or prior fistulizing disease in 220/628 (35.0%) patients. Clinically apparent fistula was present at baseline in 98/628 (15.6%) patients. A stricturing phenotype was also common: 195/628(31.1%) patients had a current or prior stricture and 66/628(10.5%) patients had some degree of stricture present at baseline. Overall, the extent of extra-intestinal involvement and the proportions and types of Crohn's disease complications were similar across treatment groups and reflect a moderate to severely active disease population.

Relevant baseline characteristics are summarized in the table below.

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Figure 16: Baseline Disease Characteristics of Study 3002

	Ustekinumab				
	Placebo	130 mg	6 mg/kg ^a	Combined	Total
Analysis set: Randomized subjects excluding those enrolled prior to study re-start					
Crohn's disease duration (yrs)	210	209	209	418	628
N	210	209	209	418	628
Mean (SD)	10.37 (9.831)	8.69 (8.462)	8.68 (8.436)	8.68 (8.439)	9.25 (8.956)
Median	8.28	5.61	6.21	5.82	6.40
IQ range	(2.39; 13.98)	(2.42; 12.25)	(2.01; 12.50)	(2.13; 12.46)	(2.22; 13.07)
Range	(0.3; 52.4)	(0.3; 47.1)	(0.3; 43.2)	(0.3; 47.1)	(0.3; 52.4)
Involved GI areas					
N	210	208	209	417	627
Ileum only	44 (21.0%)	53 (25.5%)	49 (23.4%)	102 (24.5%)	146 (23.3%)
Colon only	37 (17.6%)	44 (21.2%)	43 (20.6%)	87 (20.9%)	124 (19.8%)
Ileum and colon	129 (61.4%)	109 (52.4%)	117 (56.0%)	226 (54.2%)	355 (56.6%)
Proximal gastrointestinal tract	32 (15.2%)	34 (16.3%)	29 (13.9%)	63 (15.1%)	95 (15.2%)
Perianal	57 (27.1%)	60 (28.8%)	61 (29.2%)	121 (29.0%)	178 (28.4%)
Extra intestinal involvement					
N	210	209	209	418	628
Any extra intestinal manifestations	120 (57.1%)	113 (54.1%)	116 (55.5%)	229 (54.8%)	349 (55.6%)
Arthritis/arthralgia	114 (54.3%)	108 (51.7%)	108 (51.7%)	216 (51.7%)	330 (52.5%)
Iritis/uveitis	11 (5.2%)	5 (2.4%)	2 (1.0%)	7 (1.7%)	18 (2.9%)
E. nodosum	6 (2.9%)	4 (1.9%)	10 (4.8%)	14 (3.3%)	20 (3.2%)
Pyoderma gangrenosum	0	1 (0.5%)	3 (1.4%)	4 (1.0%)	4 (0.6%)
Aphthous stomatitis	13 (6.2%)	7 (3.3%)	11 (5.3%)	18 (4.3%)	31 (4.9%)
PSC	0	2 (1.0%)	0	2 (0.5%)	2 (0.3%)
CDAI score					
N	210	209	209	418	628
Mean (SD)	302.2 (61.67)	304.1 (56.97)	302.2 (58.85)	303.1 (57.86)	302.8 (59.11)
Median	289.5	294.0	286.0	293.0	292.5
IQ range	(254.0; 339.0)	(257.0; 340.0)	(257.0; 342.0)	(257.0; 342.0)	(257.0; 341.0)
Range	(204; 608)	(208; 465)	(198; 459)	(198; 465)	(198; 608)
IBDQ score (32-224)					
N	208	208	207	415	623
Mean (SD)	122.4 (31.45)	118.2 (30.99)	122.8 (31.62)	120.5 (31.35)	121.1 (31.37)
Median	120.0	115.5	124.0	121.0	121.0
IQ range	(102.0; 144.0)	(95.0; 144.0)	(99.0; 148.0)	(96.0; 146.0)	(98.0; 146.0)
Range	(49; 193)	(46; 189)	(56; 195)	(46; 195)	(46; 195)
CRP (mg/L)					
N	210	209	209	418	628
Mean (SD)	15.03 (16.827)	15.25 (21.381)	17.52 (24.139)	16.39 (22.803)	15.93 (20.990)
Median	8.50	7.38	7.82	7.71	8.05
IQ range	(3.22; 21.70)	(3.07; 19.40)	(3.75; 21.10)	(3.39; 19.80)	(3.34; 20.25)
Range	(0.1; 93.3)	(0.1; 124.0)	(0.1; 137.0)	(0.1; 137.0)	(0.1; 137.0)
Crohn's Disease Complications					
N	210	209	209	418	628
Intra-abdominal abscess (Past)	25 (11.9%)	17 (8.1%)	22 (10.5%)	39 (9.3%)	64 (10.2%)
Sinus tracts / perforation ^b	12 (5.7%)	14 (6.7%)	9 (4.3%)	23 (5.5%)	35 (5.6%)
Fistula ^b	77 (36.7%)	69 (33.0%)	74 (35.4%)	143 (34.2%)	220 (35.0%)
Current	33 (15.7%)	34 (16.3%)	31 (14.8%)	65 (15.6%)	98 (15.6%)
Bowel Stricture ^b	74 (35.2%)	63 (30.1%)	58 (27.8%)	121 (28.9%)	195 (31.1%)
Current	25 (11.9%)	25 (12.0%)	16 (7.7%)	41 (9.8%)	66 (10.5%)

Source: Applicant's table entitled, *TSIDEM03: Summary of Crohn's Disease Characteristics at Baseline; Randomized Patients Excluding Those Enrolled Prior to Study Restart, Study 3002 CSR*, CDER Clinical Review Template 2015 Edition
 Version date: November 5, 2015 for initial rollout (NME/original BLA reviews)

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Maintenance Study 3003

Baseline disease characteristics of Crohn's disease, including the baseline CDAI score, were generally balanced across the 3 treatment groups. The median duration of disease at baseline was 7.57 years, the median CDAI score was 311.0, and the median CRP concentration was 9.27 mg/L. As the maintenance study was populated from the two induction studies, it is not surprising that these scores indicate the Applicant enrolled a moderate to severe Crohn's population that was not newly diagnosed with Crohn's disease and indicate active disease.

Study inclusion criteria required radiologic or endoscopic documentation of Crohn's disease activity in either the ileum or colon. Isolated colonic disease was present in 80/397(20.2%) patients, 64/397 (64.1%) patients had only ileal involvement, and 253/397 (63.7%) patients were reported to have involvement in both areas. A total of 128/397 (32.2%) patients had current or prior perianal disease and 65/397(16.4%) patients reported proximal GI tract involvement (defined as proximal small intestine, stomach, or esophagus). Half of the patients (206/397 [51.9%]) had at least 1 extraintestinal manifestation of Crohn's disease, with the most prevalent being arthritis/arthralgia in 195/397(49.1%) patients. Many patients had a penetrating phenotype, with a history of intra-abdominal abscess in 45/397 (11.3%) patients, current or prior sinus tracts or perforation in 23/397 (5.8%) patients, and current or prior fistulizing disease in 146/397 (36.8%) patients. Clinically apparent fistula was present at baseline in 59/397 (14.9%) patients. A stricturing phenotype was also common: 134/397(33.8%) patients had a current or prior stricture and 39/397(9.8%) patients had some degree of stricture present at baseline. Overall, the extent of extra-intestinal involvement and the proportions and types of Crohn's disease complications were similar across treatment groups and reflect a moderate to severely active disease population.

Relevant baseline characteristics are summarized in the table below.

Figure 17: Baseline Disease Characteristics for Maintenance Study 3003

	placebo SC*	ustekinumab			Total
		90 mg SC q12w	90 mg SC q8w	Combined	
Analysis set: Randomized subjects	133	132	132	264	397
Crohn's disease duration (yrs)					
N	133	132	132	264	397
Mean (SD)	10.61 (9.467)	9.47 (8.667)	10.30 (8.682)	9.89 (8.668)	10.13 (8.938)
Median	8.39	6.81	8.52	7.14	7.57
IQ range	(3.86; 13.21)	(3.94; 12.76)	(2.98; 15.71)	(3.53; 13.99)	(3.64; 13.81)
Range	(0.3; 53.7)	(0.3; 51.9)	(0.4; 36.3)	(0.3; 51.9)	(0.3; 53.7)
Involved GI areas					
N	133	132	132	264	397
Ileum only	19 (14.3%)	19 (14.4%)	26 (19.7%)	45 (17.0%)	64 (16.1%)
Colon only	28 (21.1%)	29 (22.0%)	23 (17.4%)	52 (19.7%)	80 (20.2%)
Ileum and colon	86 (64.7%)	84 (63.6%)	83 (62.9%)	167 (63.3%)	253 (63.7%)
Proximal gastrointestinal tract	28 (21.1%)	19 (14.4%)	18 (13.6%)	37 (14.0%)	65 (16.4%)
Perianal	43 (32.3%)	46 (34.8%)	39 (29.5%)	85 (32.2%)	128 (32.2%)
Extra intestinal involvement					
N	133	132	132	264	397
Any extra intestinal manifestations	70 (52.6%)	74 (56.1%)	62 (47.0%)	136 (51.5%)	206 (51.9%)
Arthritis/arthralgia	65 (48.9%)	70 (53.0%)	60 (45.5%)	130 (49.2%)	195 (49.1%)
Iritis/uveitis	2 (1.5%)	4 (3.0%)	4 (3.0%)	8 (3.0%)	10 (2.5%)
E. nodosum	6 (4.5%)	8 (6.1%)	2 (1.5%)	10 (3.8%)	16 (4.0%)
Pyoderma gangrenosum	1 (0.8%)	0	0	0	1 (0.3%)
Aphthous stomatitis	4 (3.0%)	6 (4.5%)	5 (3.8%)	11 (4.2%)	15 (3.8%)
Primary sclerosing cholangitis	1 (0.8%)	1 (0.8%)	1 (0.8%)	2 (0.8%)	3 (0.8%)
CDAI score					
N	133	132	132	264	397
Mean (SD)	319.1 (60.82)	320.4 (66.71)	313.1 (58.01)	316.7 (62.50)	317.5 (61.88)
Median	321.0	311.5	307.5	309.5	311.0
IQ range	(269.0; 362.0)	(269.0; 355.5)	(269.5; 345.0)	(269.0; 351.0)	(269.0; 355.0)
Range	(210; 468)	(214; 498)	(218; 465)	(214; 498)	(210; 498)
IBDQ score (32-224)					
N	132	131	130	261	393
Mean (SD)	117.4 (31.20)	122.8 (29.87)	120.5 (30.28)	121.6 (30.03)	120.2 (30.46)
Median	115.0	124.0	120.5	122.0	119.0
IQ range	(92.0; 137.0)	(104.0; 144.0)	(98.0; 145.0)	(100.0; 144.0)	(98.0; 143.0)
Range	(49; 198)	(56; 185)	(63; 186)	(56; 186)	(49; 198)
CRP (mg/L)					
N	133	132	132	264	397

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	placebo SC*	ustekinumab		Combined	Total
		90 mg SC q12w	90 mg SC q8w		
Mean (SD)	17.08 (20.902)	19.15 (26.274)	16.87 (21.816)	18.01 (24.129)	17.70 (23.076)
Median	9.58	9.13	8.79	9.11	9.27
IQ range	(3.85; 21.90)	(3.45; 23.20)	(2.40; 23.50)	(2.96; 23.20)	(3.13; 22.60)
Range	(0.1; 134.0)	(0.2; 133.0)	(0.1; 136.0)	(0.1; 136.0)	(0.1; 136.0)
Crohn's Disease Complications					
N	133	132	132	264	397
Intra-abdominal abscess (Past)	15 (11.3%)	17 (12.9%)	13 (9.8%)	30 (11.4%)	45 (11.3%)
Sinus tracts / perforation^b	8 (6.0%)	9 (6.8%)	6 (4.5%)	15 (5.7%)	23 (5.8%)
Fistula^b	53 (39.8%)	43 (32.6%)	50 (37.9%)	93 (35.2%)	146 (36.8%)
Current	24 (18.0%)	18 (13.6%)	17 (12.9%)	35 (13.3%)	59 (14.9%)
Bowel Stricture^b	45 (33.8%)	41 (31.1%)	48 (36.4%)	89 (33.7%)	134 (33.8%)
Current	13 (9.8%)	10 (7.6%)	16 (12.1%)	26 (9.8%)	39 (9.8%)

* Subjects who were in clinical response to ustekinumab IV induction dosing and were randomized to placebo SC on entry into the maintenance study.

^b Current or past

Source: Applicant's table entitled, *TSIDEM03: Summary of Crohn's Disease Characteristics at Baseline; Randomized Patients Excluding Those Enrolled Prior to Study Restart, Study 3003 CSR, BLA 761044, p 845/1619.*

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance: All Studies

For studies 3001 and 3002, doses of IV ustekinumab were administered by appropriately licensed and authorized health professionals according to the treatment groups assigned by the interactive voice response system (IVRS). For study 3003, ustekinumab was to be administered as an SC injection and/or an IV infusion by qualified staff and the details of each administration were to be recorded in the CRF, including date, time of injection, and, if applicable, start and stop times of the IV infusion and volume infused. Compliance with the treatment assignments was controlled by the study site personnel. Site personnel administered the study agent and recorded the amount of study agent given. A site monitor designated by the Applicant was to monitor all patient eCRFs. During these monitoring visits, all procedures were evaluated for compliance with the protocol. Missed study visits were recorded on the eCRF.

Blinded site monitors designated by the Applicant verified source documents, performed drug accountability, and ensured overall site compliance. Patient charts were reviewed and compared with data entries on the eCRFs to ensure consistency. Study agent was not to be used for any purpose other than that outlined in the protocol. Used vials of study agent were to be retained at the site until the study agent accountability forms had been checked by the site monitor.

By study:

- Study 3001 - 740/741 received 1 dose of ustekinumab or placebo at Week 0, 1 patient in the placebo arm did not receive an infusion

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- Study 3002 – 627/628 received 1 dose of ustekinumab or placebo at Week 0, 1 patient in the placebo arm did not receive an infusion
- Study 3003 – 396/397 received at least 1 dose of study agent during the maintenance study

Concomitant Medications

Patients were permitted to receive oral 5-ASA compounds, the immunomodulators AZA, 6-MP, and MTX, oral corticosteroids, and/or antibiotics for the treatment of Crohn's disease during the study, provided that the patient was on a stable dose for a specified period (See Study Design, 6.1.1, Inclusion Criteria). Patients who received these medications at baseline were to maintain a stable dose throughout both induction studies.

Concomitant Medications: Study 3001/Study 3002

In study 3001 (for patients who had previously failed at least 1 TNF antagonist), 537/741 (72.5%) patients were receiving 1 or more concomitant medications for Crohn's disease. A total of 340/741 (45.9%) patients were receiving oral corticosteroids, including budesonide. Of those, 285 patients were receiving oral corticosteroids, excluding budesonide, at baseline, and the median dose was 20 mg/day of prednisone or its equivalent in each of the 3 treatment groups. A total of 233/741 (31.4%) patients were receiving immunomodulators (AZA, 6-MP, or MTX). The proportions of patients receiving each class of Crohn's disease medication at baseline were balanced across the 3 treatment groups.

In Study 3002 (for patients who had previously conventional therapy), 489/628 (77.9%) patients were receiving 1 or more concomitant medications for Crohn's disease. A total of 247/628 (39.3%) patients were receiving oral corticosteroids, including budesonide. Of those, 187 patient were receiving oral corticosteroids, excluding budesonide, at baseline, and the median dose was 20 mg/day of prednisone or its equivalent in each of the 3 treatment groups. A total of 219/628 (34.9%) patients were receiving immunomodulators (AZA, 6-MP, or MTX). The proportions of patients receiving each class of Crohn's disease medication at baseline were balanced across the 3 treatment groups.

Concomitant Medications: Study 3003

In study 3003, 313/397 (78.8%) patients were receiving 1 or more concomitant medications for Crohn's disease. A total of 181/397 (45.6%) patients were receiving oral corticosteroids, including budesonide. Of those, 148 patients were receiving oral corticosteroids, excluding budesonide, at Week 0 of the maintenance study. A total of 139/397 (35.0%) patients were receiving immunomodulators (AZA, 6-MP, or MTX). The proportions of patients receiving each class of Crohn's disease medication at baseline were balanced across the 3 treatment groups

Rescue Medications

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Rescue Medications: Studies 3001 and 3002

The use of rescue medications was not allowed during the studies 3001 or 3002. As per the Applicant, no patient received disallowed or concomitant medications between Week 0 and Week 8 in either study 3001 or 3002. Patients who required additional therapies for the treatment of Crohn's disease considered in protocol violation and would be considered for withdrawal from the randomized study population, which was the population used for the efficacy and safety analyses. Therefore, the use of rescue medication would not affect the analysis of the primary endpoint as data obtained from these patients were excluded.

Rescue Medications: Study 3003

The use of rescue medications was not allowed during the studies 3001 or 3002. As per the Applicant, no patient received disallowed or concomitant medications between Week 0 and Week 8 in either study 3001 or 3002. Patients who required additional therapies for the treatment of Crohn's disease were considered in protocol violation and would be considered for withdrawal from the randomized study population, which was the population used for the efficacy and safety analyses. Therefore, the use of rescue medication would not affect the analysis of the primary endpoint as data obtained from these patients were excluded.

Efficacy Results – Primary Endpoint

Induction Study 3001

A total of 741 patients were randomized after the study was restarted for an instability issue with a batch of intravenous dosing (see Section 3.1): 247 in the placebo group, 245 in the ustekinumab 130 mg group, and 249 in the ustekinumab 6 mg/kg group. Baseline demographic and disease characteristics were generally similar across the treatment groups and are described in Section 6.1.1. Among the 33 patients (4.5%) who terminated their study participation, most (3.1%, n=23) did so before Week 8: 2.8%, 2.9%, and 3.6% in the placebo, 130 mg ustekinumab, and 6 mg/kg ustekinumab groups, respectively. The most common reason for termination before Week 8 was withdrawal of consent. (See 6.1.2, Study Results, study 3001 on Patient Disposition above).

For inclusion into the study, patients must have previously failed at least 1 TNF antagonist: 78.8% of patients failed infliximab, 59.8% failed adalimumab, and 22.1% failed certolizumab pegol. Concomitant medications were allowed in study 3001 long as patients met the criteria specified in the inclusion criteria Study Design, Section 6.1.1. Five hundred thirty seven out of 741 (72.5%) patients were receiving 1 or more concomitant medications for Crohn's disease at baseline, and the proportions of patients receiving each class of Crohn's disease medication at baseline were similar across the 3 treatment groups. Of the 741 patients, 340 (45.9%) patients were receiving oral corticosteroids (including budesonide), and 233 (31.4%) patients were

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receiving immunomodulators (AZA, 6-MP, or methotrexate).

Induction Study 3002

Six hundred twenty eight patients were randomized after the study was restarted for an instability issue with a batch of intravenous dosing (see Section 3.1): 210 in the placebo group, 209 in the ustekinumab 130 mg group, and 209 in the ustekinumab 6 mg/kg group. Data for 1 patient were retrospectively excluded from the efficacy analyses because the Applicant was unable to determine the accuracy and validity of the patient's data due to concerns over compliance with Good Clinical Practice identified at the study site. The Applicant believed all data for this patient was falsified. The efficacy analyses were therefore based on 627 patients after removal of this patient from the efficacy database. All 628 patients were initially included in safety and PK analyses, however 1 patient from the placebo group who was randomized but did not receive the study agent and the final number was 627 for these analyses as well.

Among the 628 patients, baseline demographic and disease characteristics were generally similar across the treatment groups and can be reviewed in Section 6, Patient Disposition. Among the 23 patients (3.7%) who terminated their study participation, most (2.2%, n=14) did so before Week 8: 4.3%, 1.4%, and 1.0% in the placebo, 130 mg ustekinumab, and 6 mg/kg ustekinumab groups, respectively. The most common reason for termination before Week 8 was withdrawal of consent. (See 6.1.2, Study Results, study 3002 on Patient Disposition above).

Baseline disease characteristics were representative of a population of patients with moderate to severe Crohn's disease (i.e., fistulizing disease, structuring disease, extraintestinal manifestations, and CDAI ≥ 220 and ≤ 450) who had previously failed or were intolerant to conventional systemic therapy, and were generally well balanced across the 3 treatment groups. The median duration of disease at baseline was 6.4 years, median CDAI score was 292.5, and median CRP concentration was 8.05 mg/L.²² For inclusion into the study, patients had to have previously failed conventional therapy, which included either corticosteroids or immunomodulators. Patients were allowed to have received prior TNF antagonist therapy but patients who previously failed (i.e., demonstrated inadequate response or intolerance) were not permitted to be enrolled. The patient population included 623/628 (99.4%) patients who failed conventional therapy, an additional 197/628 (31.4%) had previously received TNF antagonists and 194/197 (98.5%) patients had not demonstrated failure or intolerance.

Concomitant medications were allowed in study 3002 as long as they met criteria specified in the inclusion criteria, Section 6.1.1, Study Design. Four hundred eighty nine out of 628 (77.9%)

²² CRP > 3.0 mg/mL was considered abnormal per the central lab.

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patients were receiving 1 or more concomitant medications for Crohn's disease at baseline, and the proportions of patients receiving each class of Crohn's disease medication at baseline were similar across the 3 treatment groups. Of the 628 patients, a total of 247 (39%) patients were receiving oral corticosteroids (including budesonide); and 219 (35%) of patients were receiving immunomodulators (AZA, 6-MP, or methotrexate).

Maintenance Study 3003

Out of the 1313 patients who completed induction studies 3001 and 3002, 1281 patients were enrolled in this study. The patient population was divided into two analysis sets, randomized and non-randomized patients.

Randomized Population

- 397 patients (31.0%) were included in the primary analysis population (i.e., in clinical response to ustekinumab IV induction at Week 8 of an induction study. These patients were considered to be "randomized patients":
 - 133 patients randomized to placebo
 - 132 patients randomized to ustekinumab 90 mg q12w
 - 132 patients randomized to ustekinumab 90 mg q8w

Nonrandomized Population

- 884 patients (69.0%) were enrolled but not randomized (i.e., nonrandomized patients):
 - 123 placebo induction responders who continued to receive placebo
 - 285 placebo induction nonresponders who received an ustekinumab 130 mg IV infusion at Week 0. Patients who achieved clinical response by Week 8 of maintenance continued to receive ustekinumab 90 mg q12w (subsequent induction responders).
 - 476 ustekinumab induction nonresponders who received ustekinumab 90 mg at Week 0.
 - 221 patients who achieved clinical response by Week 8 of maintenance continued to receive ustekinumab 90 mg q8w (delayed responders).

This efficacy section will focus on the randomized study population as that is the primary patient population used by the Applicant in the efficacy and safety analyses, and the population that will be used to support approval and labeling.

The Applicant initially enrolled 1275 patients, however, dosing of patients was suspended temporarily in November 2011 for a stability issue identified with the batch of the IV drug used in the induction studies (130 mg ustekinumab in 26 mL [5 mg/mL; (b) (4)]). In order to maintain the originally planned sample size in each of the induction studies, an additional 40 patients were to be enrolled in the induction studies. The Applicant felt knowledge of the stability issue could potentially bias the assessments and any data from patients enrolled in

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maintenance study 3003 before the study was suspension. Therefore, 9 randomized patients and 17 nonrandomized patients were excluded from the planned efficacy analyses.

Among the 397 randomized patients, baseline demographic and disease characteristics were generally similar across the treatment groups and is described in Figure 14: Demographics of Study 3003 and Figure 17: Baseline Disease Characteristics for Maintenance Study 3003 above. Discontinuation prior to Week 44 was similar across treatment groups: 31/133(23.3%), 29/132(22.0%), and 30/132(22.7%) in the placebo SC, ustekinumab 90 mg SC q12w, and q8w groups, respectively) and the most common reasons were lack of efficacy or an adverse event. Lack of efficacy was similar across treatment groups; however, adverse events (AE) were reported more frequently in the every 12 week treatment group (placebo 9/133 [6.8%], q12w dosing 12/132 [9.1%], and q8w dosing 6/132 [4.5%]). As the majority of AEs was due to Crohn's disease (See Section 7.4.5 Treatment Emergent Adverse Events and Adverse Reactions), this appears to illustrate that q12w dosing has an inferior treatment effect to q8w dosing.

The enrollment criteria for the two induction studies, studies 3001 and 3002, differed with respect to the requirements for failure or intolerance to prior therapy. Therefore, the maintenance study (study 3003) included a combination of patients who had previously failed or were intolerant to TNF antagonists, conventional therapy, or received prior TNF antagonists but were not considered as failures. Of the randomized patients in this study, 178/397 (44.8%) patients were TNF antagonist failures, 62/397 (15.6%) patients had received TNF antagonists and had not demonstrated failure or intolerance, and 157/397 (39.5%) patients had not received any TNF antagonist therapy prior to study participation. Concomitant medications were allowed in study 3002 so long as they met criteria specified in the inclusion criteria (See Section 6.1.1 for Study Design). Three hundred fifteen out of 397 (79.3%) patients were receiving 1 or more concomitant medications for Crohn's disease at baseline, and the proportions of patients receiving each class of Crohn's disease medication at baseline were similar across the 3 treatment groups. A total of 181/397 (45.6%) patients were receiving corticosteroids (including budesonide); 143/397 (36.0%) patients were receiving immunomodulators (azathioprine [AZA], 6-mercaptopurine [6-MP], or methotrexate [MTX]).

Primary Endpoints:

Induction Studies 3001 and 3002

The primary endpoint was the same for induction studies 3001 and 3002: clinical response at Week 6, defined as a reduction from baseline in the CDAI score of ≥ 100 points. Patients with a baseline CDAI score of ≥ 220 to ≤ 248 were considered to be in clinical response if a CDAI score of < 150 (also defined as clinical remission) was attained. Previous approvals for products indicated for the treatment of Crohn's disease have defined clinical response as a reduction

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from baseline CDAI score of ≥ 100 points (e.g., certolizumab, vedolizumab) or ≥ 70 points (e.g., infliximab, adalimumab). This reviewer concludes that the Applicant's definition of response is consistent with recent drug approvals for Crohn's disease.

While past approvals have relied upon the CDAI to define the efficacy endpoints, this reviewer notes that the Division has moved away from the CDAI as a primary endpoint and moved towards a responder definition comprised of key signs and symptoms as well as endoscopic evidence of remission. The CDAI lacks standardization in its measurements, appropriate interviewer script, and response rating criteria for the physician interviewer. In addition, multiple concepts (i.e., pain severity, pain interference, and pain duration) are included in the CDAI as a single abdominal pain item. In addition, the CDAI correlates poorly with endoscopy²³, in which clinical improvement often lags behind symptoms.²⁴ However, at the time that this study was designed and initiated, the CDAI was still acceptable as a primary endpoint to evaluate Crohn's disease. The Applicant also collected exploratory efficacy data using the new endpoints to inform future studies.

Summary tables for the primary endpoint for studies 3001 and 3002 is below:

Table 3: Primary Endpoint for Study 3001

	Placebo N=247 n (%)	Ustekinumab 130 mg (N=245) n (%)	Ustekinumab 6 mg/kg (N=249) n (%)
Clinical Response at Week 6	53 (21.5)	84 (34.3) p=0.002	84 (33.7) p=0.003

Reviewer's table adapted from Applicant's BLA 761044 CSR Study 3001 p. 66/396.

²³ Cellier et al. 1994. Correlations between clinical activity, endoscopic severity, and biological parameters in colonic or ileocolonic Crohn's disease. A prospective multicenter study of 121 cases. The Group d'Etudes Therapeutiques des Affections Inflammatoires Digestives. *Gut* 35: 213-235. Ferrante et al. 2013 Validation of Endoscopic Activity Scores in Patients With Crohn's Disease Based on a Post Hoc Analysis of Data From SONIC. *Gastroenterology* 145(5): 978-986.

²⁴ Ferrante et al. 2013 Validation of Endoscopic Activity Scores in Patients With Crohn's Disease Based on a Post Hoc Analysis of Data From SONIC. *Gastroenterology* 145(5): 978-986.

Table 4: Primary Endpoint for Study 3002

	Placebo (N=209) n (%)	Ustekinumab 130 mg N=209 n (%)	Ustekinumab 6 mg/kg (N=209) n (%)
Clinical Response at Week 6	60(28.7)	108 (51.7) p<0.001	116 (55.5) p<0.001

Reviewer’s table adapted from Applicant’s BLA 761044 CSR Study 3002 p. 66/396.

Induction Study 3001

The proportion of patients in clinical response at Week 6 (the primary endpoint) was statistically significant for both ustekinumab 6 mg/kg (84/249 [33.7%]) and 130 mg (84/245 [34.3%]) groups as compared to the placebo group (53/247 [21.5%]) with p-values of p=0.003 and p=0.002, respectively.

The Applicant pre-specified the primary endpoint to be examined with respect to subgroups related to demographics and baseline characteristics, such as concomitant medications, Crohn’s treatment history and disease characteristics. In general, efficacy results for subgroups examining the primary endpoint of clinical response at Week 6 were consistent with those of the overall study population, with 2 exceptions where the Odds Ratio(OR) was <1 for both ustekinumab doses compared with placebo:

- Patients with Crohn’s disease limited to the ileum only, which represented a small proportion of the overall study population (approximately 15% of the patients per group).
- Non-responders to initial TNF antagonist therapy (defined as primary failures to TNF antagonist therapy as opposed to loss of response to therapy over time). These patients represented approximately 25% of the total patients per each dosing group, and this definition was where the initial TNF antagonist therapy was defined as the first anti-TNF agent to which they were exposed.

The number of patients examined in both cases points towards a trend effect, but does not rise to the level of statistical significance.

Induction Study 3002

The proportion of patients in clinical response at Week 6 (the primary endpoint) was statistically significant for both the ustekinumab 6 mg/kg (116/209 [55.5%]) and 130 mg (108/209 [51.7%]) groups as compared to the placebo group (60/209 [28.7%]) with a p-value of

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$p < 0.001$ for each. The Applicant pre-specified the primary endpoint to be examined with respect to subgroups related to demographics and baseline characteristics, such as concomitant medications, Crohn's treatment history, including TNF exposure, and disease characteristics. Efficacy results for subgroups examining the primary endpoint of clinical response at Week 6 were consistent with those of the overall study population, with no subgroups having an OR < 1 for either of the ustekinumab doses versus placebo. Notably, subgroup analyses demonstrated similar efficacy for ustekinumab in patients previously treated with TNF antagonists (but who had otherwise not failed nor developed intolerance to anti-TNF therapy) and those who were anti-TNF naive.

The Applicant pre-specified the primary endpoint to be examined with respect to subgroups related to demographics and baseline characteristics, such as concomitant medications, Crohn's treatment history and disease characteristics. In general, efficacy results for subgroups examining the primary endpoint of clinical response at Week 6 were consistent with those of the overall study population with no subgroups having an OR < 1 for either of the ustekinumab doses versus placebo. Of note, subgroup analyses demonstrated no difference in efficacy for ustekinumab in patients previously treated with TNF antagonists (but who had otherwise not failed nor developed intolerance to anti-TNF therapy) and those who were anti-TNF naive.

Maintenance Study 3003

The primary endpoint for maintenance study 3003 was the proportion of patients in clinical remission at Week 44, defined as CDAI < 150 . This definition of remission is consistent with previous approved applications for Crohn's disease. Patients who had specified changes in concomitant Crohn's disease medications, a Crohn's disease-related surgery, loss of clinical response (defined as a CDAI score ≥ 220 points and a ≥ 100 point increase from the Week 0 CDAI score between Week 8 and Week 32), or discontinuation of study agent due to lack of efficacy or due to an AE of worsening Crohn's disease, prior to Week 44 were not considered to be in clinical remission for the primary endpoint analysis (i.e., considered to be treatment failures), regardless of the actual CDAI score. Patients who had insufficient data to calculate the CDAI score (i.e., less than 4 of the 8 CDAI components available) were also not considered to be in clinical remission at Week 44.

Table 5: Primary Endpoint Remission at Week 44 (CDAI <150)

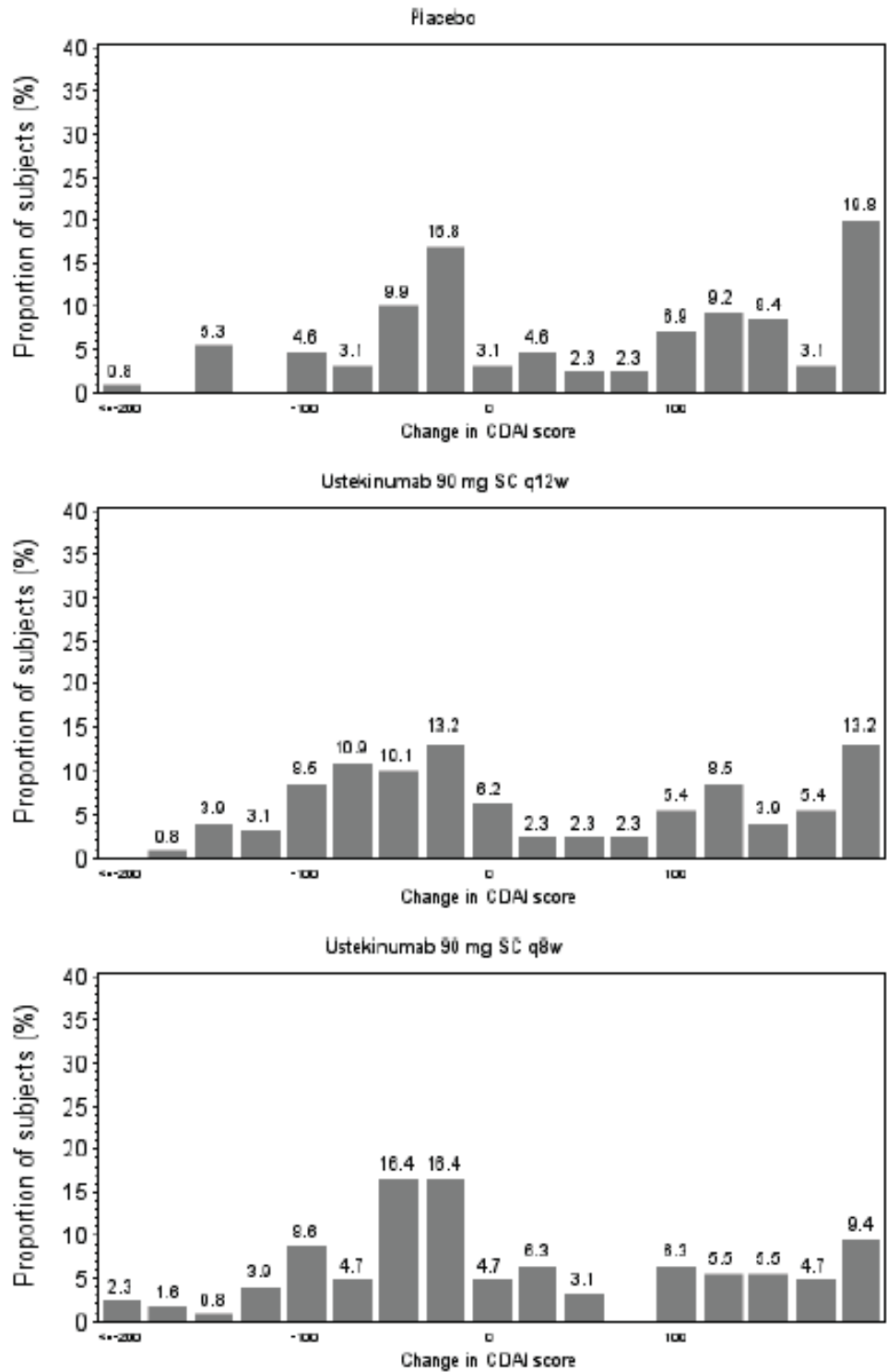
	Placebo N=131 n (%)	Ustekinumab 90mg q 12 N=129 n (%)	Ustekinumab 90mg q 8 N=128 n (%)
Clinical Remission at Week 44	47 (35.9)	63 (48.8) p=0.040	68 (53.1) p=0.005

Reviewer's table adapted from Applicant's BLA 761044 CSR Study 3003 p. 85/1619.

The proportion of patients in clinical remission at Week 44 (the primary endpoint) was statistically significant for both the 90mg q 12 and 90mg q 8 SC doses of ustekinumab (63/129 [48.8%]) and (68/128 [53.1%]) ustekinumab groups than as compared to the placebo group (47/131 [35.9%]) with p-values of p=0.04 and p=0.005, respectively.

An overall summary of change in CDAI by dosing regimen is shown in the figure below. The figure illustrates that overall, patients in the placebo group experienced increases (worsening) in the CDAI score, where the patients who received ustekinumab experienced decreases (improvement) in CDAI. See Figure 18 below.

Figure 18: Histogram of the change from baseline in the CDAI Score at Week 44 for randomized patients



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Source: Applicant submission BLA 761044, CSR 3003 report attachment GEFCDAI05 p 980/1619

For those patients who met criteria for treatment failure, the most common reason was 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 3001 or 3002), which was assessed between Week 8 and Week 32 in IVRS. Patients who exhibited loss of response were greatest in the placebo dosing arm 51/131 (38.9%), followed by the ustekinumab 90 q 12 dosing arm 29/129 (36.4%), and then the ustekinumab 90mg q8 dosing arm 28/128 (28.9%). In the figure below, the proportion of patients who had specified changes in concomitant Crohn's disease medications is larger in the q12 week dosing arm than either the q8 week dosing arm or placebo. These changes in concomitant medications all indicate increasing or initiating steroid, immunomodulator, or antibiotic dosing to treat Crohn's disease above baseline (at enrollment of induction study) levels. This may also indicate inferior treatment effect of q12 week dosing to q8 week dosing. See Figure 19 below:

Figure 19: Number of randomized patients who met treatment failure criteria prior to Week 44

	placebo SC ^a	ustekinumab	
		90 mg SC q12w	90 mg SC q8w
Analysis set: Randomized subjects excluding those enrolled prior to study re-start	131	129	128
Subjects who met the treatment-failure criteria	59 (45.0%)	47 (36.4%)	37 (28.9%)
Subjects who had specified changes in concomitant Crohn's disease medication	10 (7.6%)	16 (12.4%)	7 (5.5%)
Subjects who discontinued study agent due to lack of efficacy or due to an adverse event indicated to be worsening Crohn's disease	20 (15.3%)	22 (17.1%)	17 (13.3%)
Subjects who had a loss of clinical response	51 (38.9%)	29 (22.5%)	28 (21.9%)
Subjects who had a Crohn's disease-related surgery as a result of lack of efficacy of study agent	5 (3.8%)	4 (3.1%)	2 (1.6%)

^a Subjects who were in clinical response to ustekinumab IV induction dosing and were randomized SC on entry into this maintenance study.

Source: Applicant submission BLA 761044, CSR 3003 report attachment TEFTF01 p. 417/1619.

Subgroup analyses were performed for predefined demographic and Crohn's disease characteristics at baselines of both the induction and maintenance studies. When compared to placebo in the ustekinumab 90mg q8w dosing group, a single subgroup in both induction and

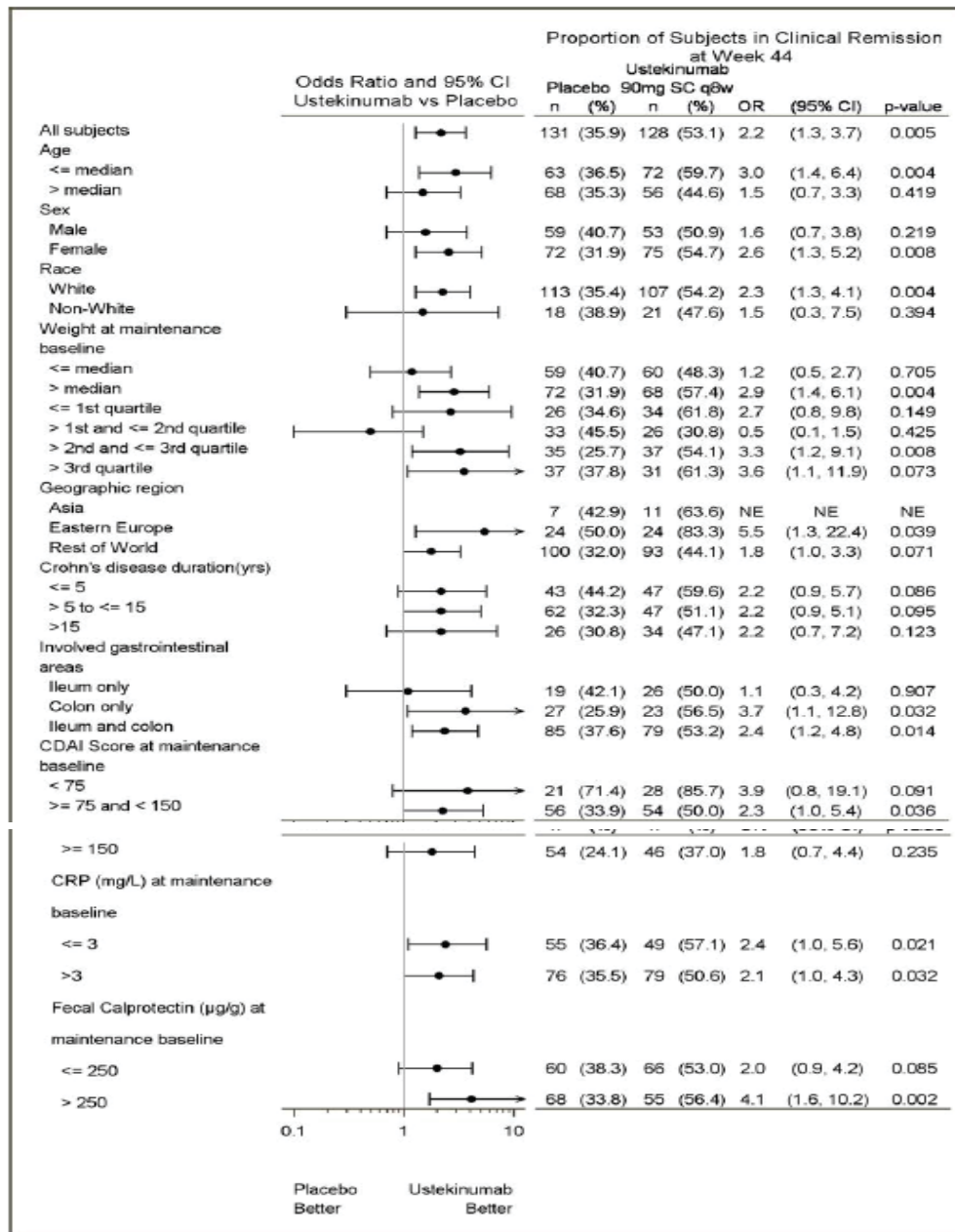
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maintenance baselines, had odds ratios (OR) < 1. Weight at maintenance baseline >1st and ≤2nd quartile (OR=0.5, 95% CI: 0.1, 1.5) and weight at induction baseline >1st and ≤2nd quartile (OR=0.6, 95% CI: 0.2, 1.9) when compared to weight at induction baseline. At the time of this review, the review team was concerned that there appears to be a correlation with lower exposures and decreased efficacy in the lower body weight patients (< 55 kg) who received the 6 mg/kg intravenous initial dose. It is possible this effect carries over into the maintenance study. A discipline review letter and information request was sent to the Applicant on July 21, 2016 to communicate these concerns and obtain additional information to potentially address this issue. Refer to the pharmacometrics review by Dr. Jee Eun Lee for details.

The figures below show the subgroup analyses for the baseline characteristics of the 90mg q8w dosing group in study 3003. Figure 20 below contains all measured demographics for both induction and maintenance baseline so the reader is familiar with the demographics measured. The Figure 21 shows the only demographic with an OR<1.

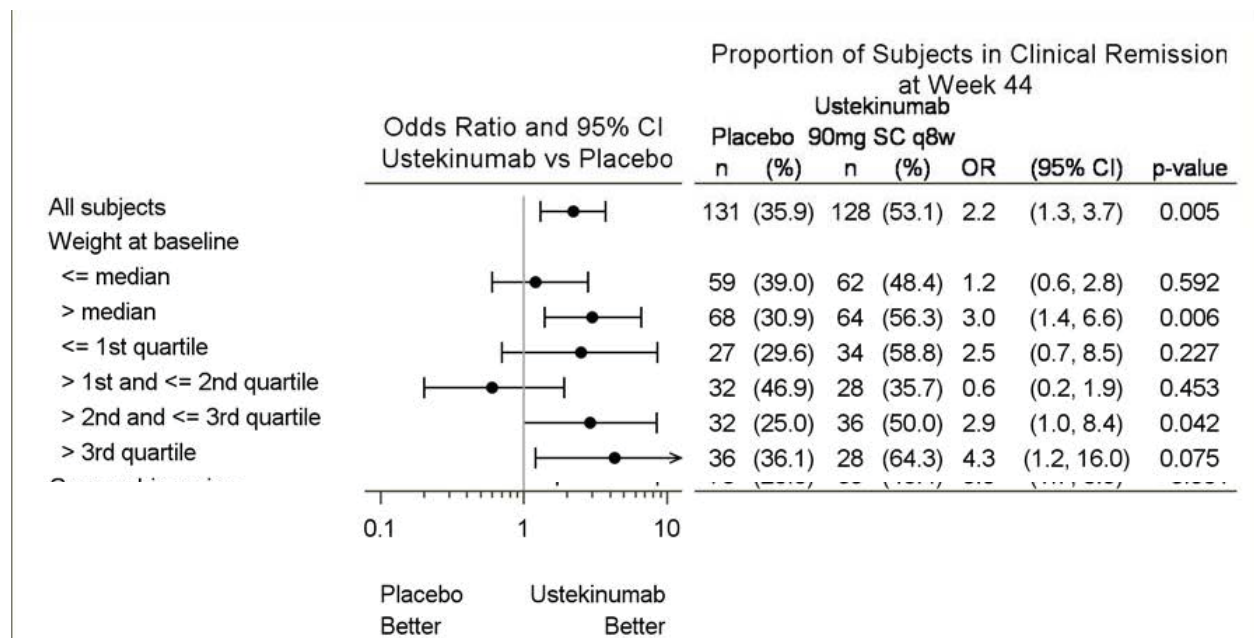
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Figure 20: Plots of Odds Ratio(OR) and 95% Confidence Intervals(CI) comparing the proportion of patients in clinical remission at Week 44 in the ustekinumab 90 mg SC q8w group versus the placebo group by demographics and clinical disease characteristics at maintenance baseline.



Source: Applicant submission BLA 761044, CSR 3003 report attachment GEFCREM06A App 971-972/1619.

Figure 21: Plots of Odds Ratio(OR) and 95% Confidence Intervals(CI) comparing the proportion of patients in clinical remission at Week 44 in the ustekinumab 90 mg SC q8w group versus the placebo group by weight at induction baseline



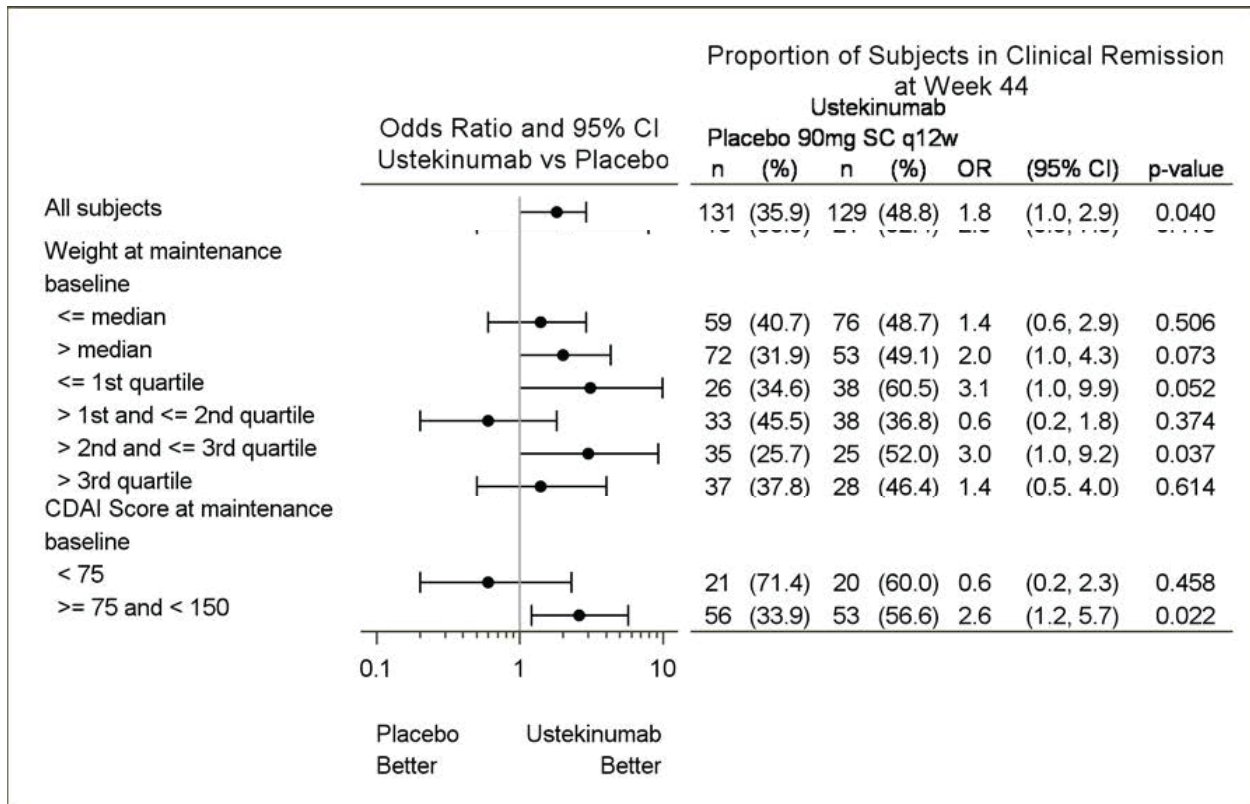
Source: Applicant submission BLA 761044, CSR 3003 report, attachment GEFCREM06 p 973/1619.

Three subgroups in the ustekinumab 90mg q12w dosing group had OR<1 when compared with placebo at Week 44:

- Maintenance baseline:
 - >1st quartile and ≤2nd quartile weight at maintenance baseline (OR=0.6, 95% CI: 0.2, 1.8),
 - CDAI <75 (OR=0.6, 95% CI: 0.2)
- Induction baseline: CRP concentrations ≤3 mg/L at induction baseline (OR=0.9, 95% CI: 0.3, 2.8)

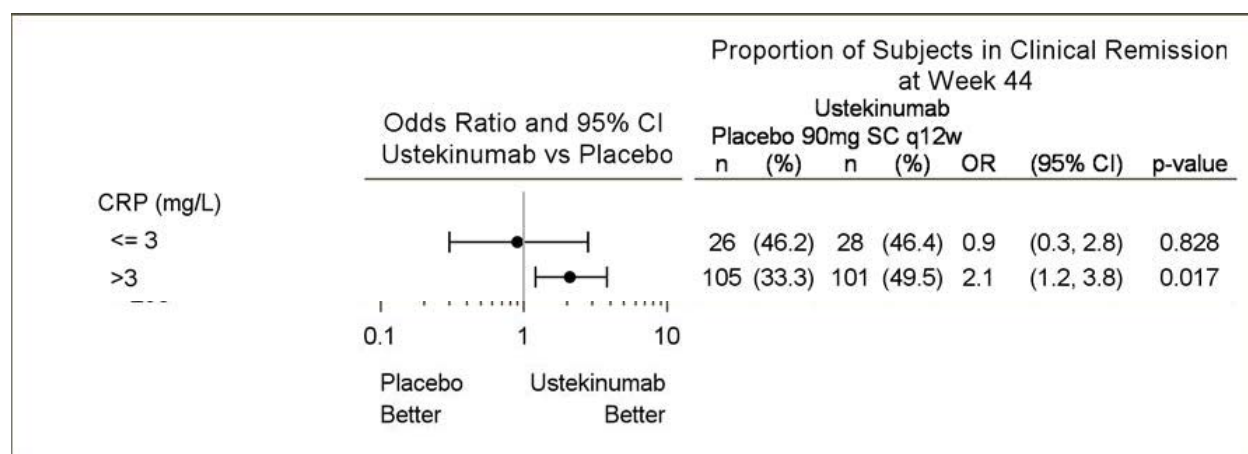
Below are Figure 22 and Figure 23 for maintenance baselines for the 90mg q12w dosing group in Study 3003. Both figures show only the demographic with an OR<1. For a complete list of demographics and disease characteristics, please see Figure 20 above.

Figure 22: Plots of Odds Ratio(OR)<1 and 95% Confidence Intervals for comparing the proportion of patients in clinical remission at Week 44 in the ustekinumab 90 mg SC q12w group versus the placebo group by demographics and clinical disease characteristics at maintenance baseline



Source: Applicant submission BLA 761044, CSR 3003 report Attachment GEFCREM05A p 975/1619

Figure 23: Plots of Odds Ratio(OR)<1 and 95% Confidence Intervals for comparing the proportion of patients in clinical remission at Week 44 in the ustekinumab 90 mg SC q12w group versus the placebo group by demographics and clinical disease characteristics at induction baseline



Source: Applicant submission BLA 761044, CSR 3003 report attachment GEFCREM05 p 978/1619.

The subgroups that demonstrated differences between the ustekinumab q8w and q12w dosing regimens included patient body weight (above and below the baseline median) and inflammatory markers (CRP and fecal calprotectin). These subgroup analyses suggest that patients above the median weight as well as those with elevated inflammatory markers (at either induction or maintenance baseline) attained greater benefit with the ustekinumab q8w regimen compared with placebo, versus patients receiving an ustekinumab q12w regimen compared with placebo. In contrast, patients with low CRP or fecal calprotectin levels at induction baseline, as well as after completing induction, appear to be clinically similar with q12w or q8w dosing regimen for maintenance throughout study 3003 primary endpoint at Week 44.

Concomitant and prior Crohn’s disease medications were also assessed and did not differ from the analysis of the primary population with the exception of those receiving *both* oral corticosteroids and immunomodulators such as 6-MP, azathioprine, or methotrexate. The OR was < 1 for both treatment groups compared with placebo (OR=0.5, 95% CI: 0.1, 2.9 for q12w dosing regimen and OR=0.9, 95% CI: 0.2, 4.1 for q8w dosing regimen). These patients likely had more recalcitrant disease as they were being treated with additional medication as compared to their counterparts.

Key Secondary Endpoints

Induction Studies 3001 and 3002

All key secondary endpoints for studies 3001 and 3002, which are proposed by the Applicant to be included in the label, met statistical significance for both ustekinumab doses investigated. Secondary endpoints in this section are listed in the hierarchical order in which they were tested. Summary tables for induction studies 3001 and 3002 are below:

Table 6: Key Secondary Endpoints for Induction Study 3001

	Placebo N=247 n (%)	Ustekinumab 130 mg N=245 n (%)	Ustekinumab 6 mg/kg N=249 n (%)
Clinical Remission at Week 8 (CDAI<150)	18 (7.3)	39 (15.9) p=0.003	52 (20.9) p<0.001
Clinical Response at Week 8	50 (20.2)	82 (33.5) p=0.001	94 (37.8) p<0.001
70 point CDAI Reduction at Week 6 Response	75 (30.4)	113 (46.1) p<0.001	109 (43.8) p=0.002
70 point CDAI Reduction at Week 3 Response	67 (27.1)	94 (38.4) p=0.009	101 (40.6) p=0.001

Source: Reviewer table comprised from data in BLA 761044 CSR 3001, Section 6.3.

Table 7: Key Secondary Endpoints for Induction Study 3002

	Placebo N=209) n (%)	Ustekinumab 130 mg N=209 n (%)	Ustekinumab 6 mg/kg N=209 n (%)
Clinical Remission at Week 8 (CDAI<150)	41 (19.6)	64 (30.6) p=0.009	84 (40.2) p<0.001
Clinical Response at Week 8	67 (32.1)	99 (47.4) p<0.001	121 (57.9) p=<0.001
70 point CDAI Reduction at Week 6 Response	81 (38.8)	123 (58.9) p<0.001	135 (64.6) p<0.001
70 point CDAI Reduction at Week 3 Response	66 (31.6)	103 (49.3) p<0.001	106 (49.3) p<0.001

Source: Reviewer table comprised from data in BLA 761044 CSR 3002, Section 6.3.

Clinical Remission at Week 8

Clinical remission at Week 8 was defined as a CDAI score of <150 points. Clinical remission at Week 8 was also pre-specified to examine results by demographics, baseline disease characteristics, concomitant medications at baseline, Crohn’s disease-related medication history, and TNF antagonist therapy history. Among all of the same subgroups examined for the primary endpoint of clinical response at Week 6, analyses performed for the endpoint of clinical remission at Week 8 were consistent with those for remission in the overall study population, with no subgroups having an OR <1 for both ustekinumab doses.

Study 3001

The proportion of patients in clinical remission at Week 8 was statistically significant for both the 6 mg/kg and 130 mg doses of ustekinumab (52/249 [20.9%] and 39/245 [15.9%], respectively) compared with the placebo group (18/247 [7.3%]; with p-values of p<0.001 and p=0.003, respectively (See **Table 6** above). The proportion of patients in remission at Week 8 was numerically greater in the 6 mg/kg dose group than in the 130 mg group.

Study 3002

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The proportion of patients in clinical remission at Week 8 was statistically significant for both the 6 mg/kg (84/209 [40.2%]) and 130 mg (64/209 [30.6%]) doses of ustekinumab as compared to the placebo group (41/209 [19.6%]) with p-values of $p < 0.001$ and $p = 0.009$, respectively. (See **Table 7** above).

Clinical Response at Week 8

Clinical response at Week 8 was defined as a reduction from baseline in the CDAI score of ≥ 100 points at Week 8. Patients with a baseline CDAI score of ≥ 220 to ≤ 248 were considered in clinical response if a CDAI score of < 150 was attained.

Study 3001

The proportion of patients in clinical response at Week 8 was statistically significant for both the 6 mg/kg and 130 mg doses of ustekinumab (94/249 [37.8%] and 82/245 [33.5%], respectively) compared with the placebo group (50/247 [20.2%]) with p values of $p < 0.001$ and $p = 0.001$, respectively (See **Table 6** above).

Study 3002

The proportion of patients in clinical response at Week 8 was statistically significant for both the 6 mg/kg and 130 mg doses of ustekinumab (121/209 [57.9%] and 99/209 [47.4%]) as compared with placebo group (67/209 [32.1%]) with p-values of $p < 0.001$ for both doses (See **Table 7** above).

70-point Response at Week 6

The endpoint of 70-point response at Week 6 was defined as a reduction from baseline in the CDAI score of ≥ 70 points at Week 6. Clinical response has been defined as a reduction from baseline of ≥ 70 points in previous drugs approved for Crohn's disease (e.g. infliximab, adalimumab), however, more recent approvals have defined clinical response as a reduction from baseline of ≥ 100 points. The Applicant included both definitions in their key secondary endpoints, however, in this reviewer's opinion, a reduction of 100 points is clinically more meaningful than a reduction of 70 points.

Study 3001

The proportion of patients with a 70-point response at Week 6 was statistically significant for both 6 mg/kg and 130 mg (109/249 [43.8%] and 113/245 [46.1%]) doses of ustekinumab as compared to the placebo group (75/247 [30.4%]) with p-values of $p = 0.001$ and $p = 0.009$, respectively (See **Table 6** above).

Study 3002

The proportion of patients with a 70-point response at Week 6 was statistically significant for both the 6 mg/kg and 130 mg doses of ustekinumab (135/209 [64.6%] and 123/209 [58.9%]) as

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compared to the placebo group (81/209 [38.8%]) with p-values of p<0.001 for both doses (See **Table 7** above).

70-point Response at Week 3

The endpoint of 70-point response at Week 3 was defined as a reduction from baseline in the CDAI score of ≥70 points at Week 3.

Study 3001

The proportion of patients with a 70-point response at Week 3 was statistically significant for both the 6 mg/kg and 130 mg doses of ustekinumab (101/249 [40.6%] and 94/245 [38.4%]) as compared to the placebo group (67/247 [27.1%]) with p-values of p=0.001 and p=0.009, respectively (See **Table 6** above).

Study 3002

The proportion of patients with a 70-point response at Week 3 was statistically significant for both the 6 mg/kg and 130 mg doses of ustekinumab (106/209 [50.7%] and 103/209 [49.3%]) groups as compared to the placebo group (66/209 [31.6%]) with p-values of p<0.001 for both (See **Table 7** above).

Secondary Endpoints: Maintenance Study 3003

Key secondary endpoints were evaluated using the primary (randomized) population.

Table 8: Summary of Key Secondary Endpoints for Maintenance Study 3003

	Placebo N=131 (n) %	Ustekinumab 90mg q 12 N=129 (n) %	Ustekinumab 90mg q 8 N=128 (n) %	Combined N=257 (n) %
Clinical Response at Week 44	58 (44.3)	75 (58.1) p=0.033	76 (59.4) p=0.018	131 (58.8) p=0.009
Clinical remission at Week 44 among patients in clinical remission to ustekinumab at Week 0 of Maintenance*	36/79 (45.6)	44/78 (56.4) p=0.189	52/78 (66.7) p=0.007	96/156 (61.5) p=0.019
Corticosteroid-free remission at Week 44	39 (29.8)	55(42.6) p=0.035	60 (46.9) p=0.004	115 (44.7) p=0.004

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Clinical remission at Week 44 (in TNF refractory/intolerant patients)*	16/61 (26.2)	22/57 (38.6) p=0.140	23/56 (39.8) p=0.070	45/113 (39.8) p=0.070

*N for these endpoints differs from the overall N in the dosing arm

Source: Reviewer table comprised from data in BLA 761044 CSR 3003, Section 5.3

Clinical Response at Week 44

Clinical response in maintenance study 3003 was defined as defined as a reduction from Week 0 of induction study 3001 or 3002 of the CDAI score of ≥ 100 points.

The proportion of patients with clinical response at week 44 was statistically significant for both the ustekinumab 90 mg q12w (75/129 [58.1%]) and the 90 mg q8w (76/128 [59.4%]) dosing regimens as compared to the placebo group (58/131 [44.3%]) with p-values of p=0.033 and p=0.018, respectively (see above **Table 8**). The q8w dosing regimen appeared to show slightly numerically greater improvement as compared to the q12w dosing regimen.

Clinical remission at Week 44 among patients in clinical remission to ustekinumab at Week 0 of Maintenance

Of the patients in the primary analysis population, 235/397 (59.1%) patients in the were in clinical remission at Week 0 of the maintenance study. Among those patients, the proportions of patients who maintained clinical remission (i.e., were in clinical remission at both Week 0 and Week 44) was numerically greater, but not statistically significant in the ustekinumab 90 mg q12w dosing regimen (44/78 [56.4%]; p=0.189). However, the proportion of patients who remained in remission in the ustekinumab q8w dosing regimen (52/78 [66.7%]; p=0.007) was significantly greater in compared with the placebo group. As per the statistical analysis plan, all subsequent secondary endpoints were treated as exploratory as one of the doses failed to meet statistical significance for this hierarchical endpoint. This reviewer notes that in this clinically important endpoint, q12w dosing regimen appears to have an inferior treatment effect as compared to q8w dosing regimen.

Corticosteroid-free remission at Week 44

The proportions of patients in clinical remission and not receiving concomitant corticosteroids at Week 44 met statistical significance for both the ustekinumab 90mg q12w (55/129 [42.6%]) and 90mg q8 week (60/128 [46.9]) dosing regimens with p values of p=0.035 and p=0.004, respectively, versus placebo (39/131[29.8]). However, the Applicant notes that while the nominal p-values for the comparisons of each of the ustekinumab groups with placebo were <0.05 for this endpoint, only the ustekinumab q8w regimen can be considered to be significantly different from placebo within the global multiple testing procedure. Under the US-specific multiple testing procedure, neither of the two ustekinumab groups could be considered

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as statistically significant.

Clinical remission at Week 44 in the subset of patients who were refractory or intolerant to TNF antagonist therapy (i.e., patients from induction study 3001)

This endpoint evaluated 174 of the 397 patients who continued into the maintenance study after completion of induction study 3001. This subset of patients included patients were required, at entry into induction study 3001, to have had documented failure to at least 1 TNF antagonist (i.e., infliximab, adalimumab, or certolizumab pegol), either by having an inadequate initial response (primary nonresponders), by having a response followed by loss of response (secondary nonresponders), or by being intolerant. The proportion of patients who experienced clinical remission at week 44 among this subset of patients was numerically greater for ustekinumab over placebo, but not statistically significant for either the 90mg q12w (22/57 [38.6%]) or 90mg q8w(23/56 [39.8%]) dosing regimens with p values of p=0.14 and p=0.07, respectively against placebo (16/61 [26.2%]). The Applicant states that this endpoint was not powered to show statistically significant difference.

Data Quality and Integrity – Reviewers’ Assessment

The results of the OSI inspections and site analysis excluding sites that received significant financial compensation are reported in Section 4.1 Office of Scientific Investigations (OSI) regarding the studies conducted for BLA 761044. This reviewer does not believe that the results were influenced by the disclosed financial interests/arrangements as for this double blinded population with objective primary efficacy endpoints (CDAI) confirmed by exploratory analysis using patient reported components of the CDAI (abdominal pain and stool frequency).

During site selection for OSI inspections, efficacy analyses were performed excluding sites with large effect sizes for each Study (3001, 3002 and 3003) As well as sites that had investigators that had received large financial investments (>\$25,000) that were *also* high enrollers. None of these sites had any effect on the significance of the primary endpoint achieved in the induction studies of 3001 or 3002, or the q8w dosing regimen of the maintenance study. Three high enroller sites (5104, 4803, and 3415) did affect the primary endpoint for the q12w dosing regimen of the maintenance study (e.g. rendering it not significant in achieving the primary endpoint of clinical remission). Two of these three sites were inspected (5104 in Serbia and 4803 in Poland) and the study was found to have been conducted adequately according to the OSI inspections.

Efficacy Results – Secondary and other relevant endpoints

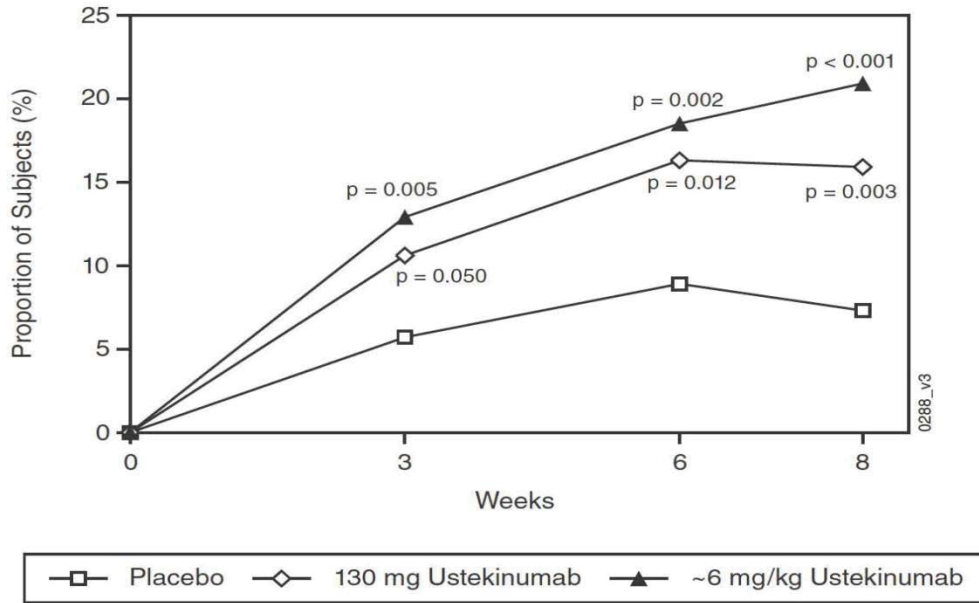
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The Applicant investigated a number of additional secondary endpoints. These endpoints were not included in the ranked, hierarchy of statistical testing.

Clinical Remission Over Time: Study 3001

The Applicant explored the proportion of patients in clinical remission at time points of weeks 3, 6 (time at which the primary efficacy endpoint assessment occurred), and week 8 (first-ranked key secondary endpoint) to determine the onset of action of ustekinumab and evaluate if patients achieve clinical remission at time points other than week 6. At the first post baseline visit (Week 3) greater proportions of patients were in clinical remission in both ustekinumab dose groups (32/249 [12.9%] and 26/245 [10.6%] in the 6 mg/kg and 130 mg dose groups, respectively) compared with the placebo group (14/247[5.7%]; $p=0.005$ and $p=0.05$, respectively). From Week 3 through Week 8, the proportion of patients in clinical remission continued to increase in the 6 mg/kg group, and in the 130 mg group, the proportion of patients in clinical remission increased from Week 3 to Week 6 and was maintained at Week 8, which suggests that while some patients will achieve clinical remission earlier than week 6, many patients will require additional time after the first induction dose to achieve remission. At Weeks 6 and 8, the proportions of patients in clinical remission were significantly greater in both dose groups compared with placebo (Week 6: $p=0.002$ and $p=0.012$, respectively; Week 8: $p<0.001$ and $p=0.003$, respectively). At each visit, the proportion of patients in remission was numerically greater in the 6 mg/kg group than in the 130 mg group at Weeks 3, 6, and 8, with the greatest difference occurring at Week 8 (32/249 [12.9%], 46/249 [18.5%], and 52/249 [20.9%] compared with 26/245 [10.6%], 40/245[16.3%], and 39/245 [15.9%], respectively). The proportion of patients in clinical remission over is shown in Figure 24 below.

Figure 24: The proportion of patients in clinical remission over time for Study 3001



^a Subjects who had a prohibited Crohn's disease-related surgery or had prohibited concomitant medication changes are considered not to be in clinical remission, regardless of their CDAI score.

^b Subjects who had insufficient data to calculate the CDAI score are considered not to be in clinical remission.

Data source: [TEFCREM02.rtf] [CNT01275\CRD3001\DBR_W8_W20\RE_W8_W20\tefcrem02.sas] 16AUG2013, 16:00

Source: Applicant's Figure 4 entitled Number of Subjects in Clinical Remission through Week 8; Randomized Subjects Excluding Those Enrolled Prior to Study Re-start, BLA 761044 CSR 3001, p. 70/396.

The figure above illustrates that while a small proportion of patients in the placebo group will achieve clinical remission, consistent with what is known about the relapsing and remitting behavior of Crohn's disease, a larger proportion of patients treated with ustekinumab will require at least 6 to 8 weeks to achieve clinical remission after the single induction dose. The data also suggest that the 6 mg/kg ustekinumab dose induces remission in a larger proportion of patients more quickly. This supports this reviewer's conclusion that the 6 mg/kg dose is preferred for the initial single IV dose, as compared to the 130 mg dose.

Clinical Remission over Time: Study 3002

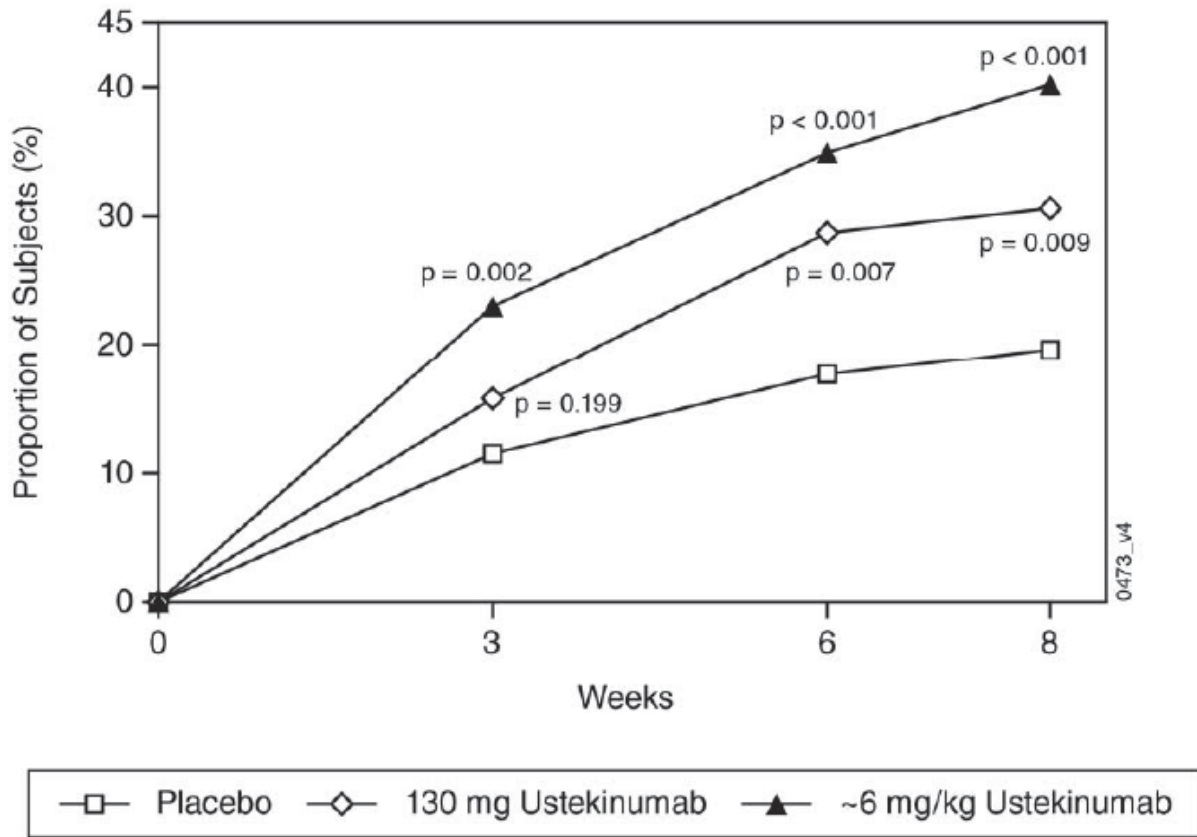
The Applicant explored the proportion of patients in clinical remission at time points of Weeks 3, 6 (time at which the primary efficacy endpoint assessment occurred), and Week 8 (first-ranked key secondary endpoint) to determine the onset of action of ustekinumab and evaluate if patients achieve clinical remission at time points other than Week 6. At the first post baseline visit (Week 3) a significant proportion of patients were in clinical remission in the ustekinumab

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6 mg/kg dosing group ($p=0.002$; 48/209 [23%]) while the 130 mg dosing group was not significantly different when compared with the placebo group ($p=0.20$; 33/209 [15.8%] vs 24/209 [11.5%]). From Week 3 through Week 8, the proportion of patients in clinical remission continued to increase in both the 6 mg/kg and in the 130 mg dose groups. The proportion of patients in remission in the placebo group increased as well, but markedly more slowly. This suggests that some patients in the 6 mg/kg dose group achieved remission earlier than the week 8 time point, while a smaller proportion of patients in the 130 mg dose group were also able to obtain remission before the Week 8 time point (first ranked key secondary endpoint). Additionally, for both dose arms, while some patients may achieve clinical remission earlier than Week 6, many patients will require additional time after the first induction dose to achieve remission. At Weeks 6 and 8, the proportions of patients in clinical remission were significantly greater in both the 6 mg/kg and 130 mg dose groups compared with placebo (Week 6: $p<0.001$ and $p=0.007$, respectively; Week 8: $p<0.001$ and $p=0.009$, respectively). At each visit, the proportion of patients in remission was numerically greater in the 6 mg/kg dose group as compared to both the 130 mg dose group and placebo, with the greatest difference occurring at Week 8: 84/209 (40.2%), 64/209 (30.6%), and 41/209 (19.6%). The proportion of patients in clinical remission over is shown in Figure 25 below.

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Figure 25: The proportion of patients in clinical remission over time for Study 3002



^a Subjects who had a prohibited Crohn's disease-related surgery or had prohibited concomitant medication changes are considered not to be in clinical remission, regardless of their CDAI score.
^b Subjects who had insufficient data to calculate the CDAI score are considered not to be in clinical remission.

Source: Applicant's Figure 4 entitled Number of Subjects in Clinical Remission through Week 8; Randomized Subjects Excluding Those Enrolled Prior to Study Re-start and Excluding Site 1127, BLA 761044 CSR 3002, p. 75/366.

The figure above illustrates that while a small proportion of patients in the placebo group will achieve clinical remission, consistent with what is known about the relapsing and remitting behavior of Crohn's disease, a larger proportion of patients treated with ustekinumab will require at least 6 to 8 weeks to achieve clinical remission after the single induction dose. The data shown in the figure above also suggests that the initial IV dose of 6 mg/kg ustekinumab has the ability to induce remission in a larger proportion of patients more quickly, as compared to the 130 mg dose and placebo. This supports the reviewer's conclusions that the 6 mg/kg

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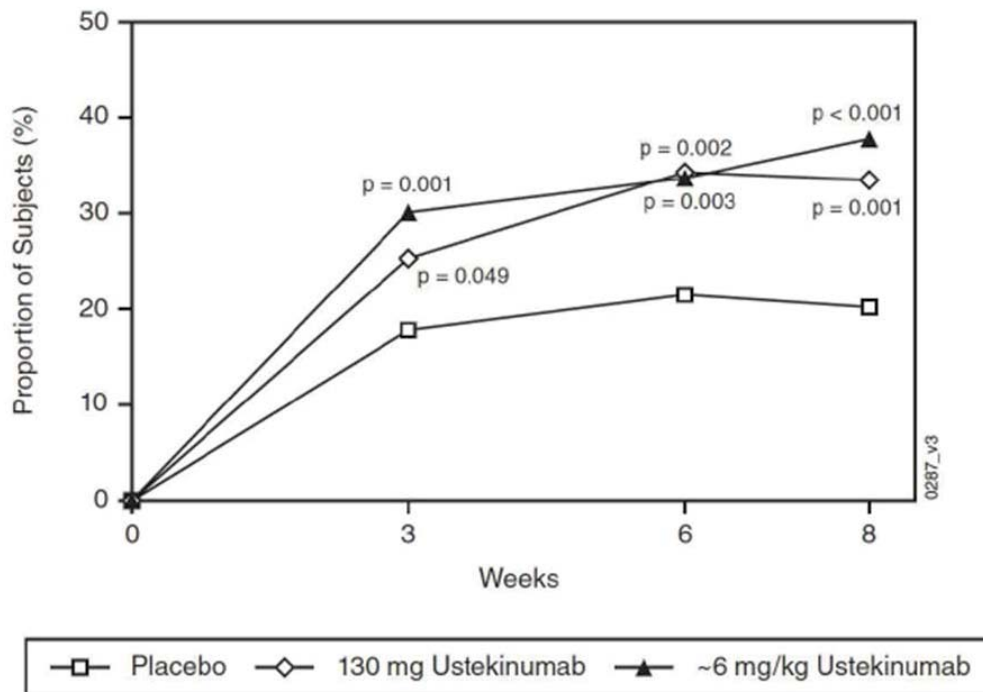
weight tiered dosing is preferred as the single initial IV dose.

Clinical Response Over Time: Study 3001

From the first post baseline visit at Week 3, a greater proportion of patients were in clinical response in both ustekinumab dose groups (75/249 (30.1%) and 62/245 (25.3%) in the 6 mg/kg and 130 mg groups, respectively) as compared with the placebo group (44/247 (17.8%); $p=0.001$ and $p=0.049$, respectively). At Weeks 6 and 8, the proportions of patients in clinical response remained significantly greater in both the 6 mg/kg and 130 mg dose groups compared with placebo (Week 6: 84/249 [33.7%] and 84/245 [34.3%] vs 53/247[21.5%], with p values of $p=0.003$ and $p=0.002$, respectively; Week 8: 94/249 [37.8%] and 82/245 [33.5%] vs 50/247 [20.2%] with p values of $p<0.001$ and $p=0.001$, respectively). The trend over time for clinical response in the ustekinumab groups shows an initial steep rise for the 6 mg/kg dose group over the 130 mg dose group, but by week 6 clinical response is comparable for the two doses, and by week 8 the 130 mg dose group has eclipsed the 6 mg/kg dose. However, both dose groups performed significantly better than placebo and this reviewer finds clinical remission to be a more meaningful clinical endpoint than response. See Figure 26 below.

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Figure 26: The percent of patients in clinical response over time in Study 3001



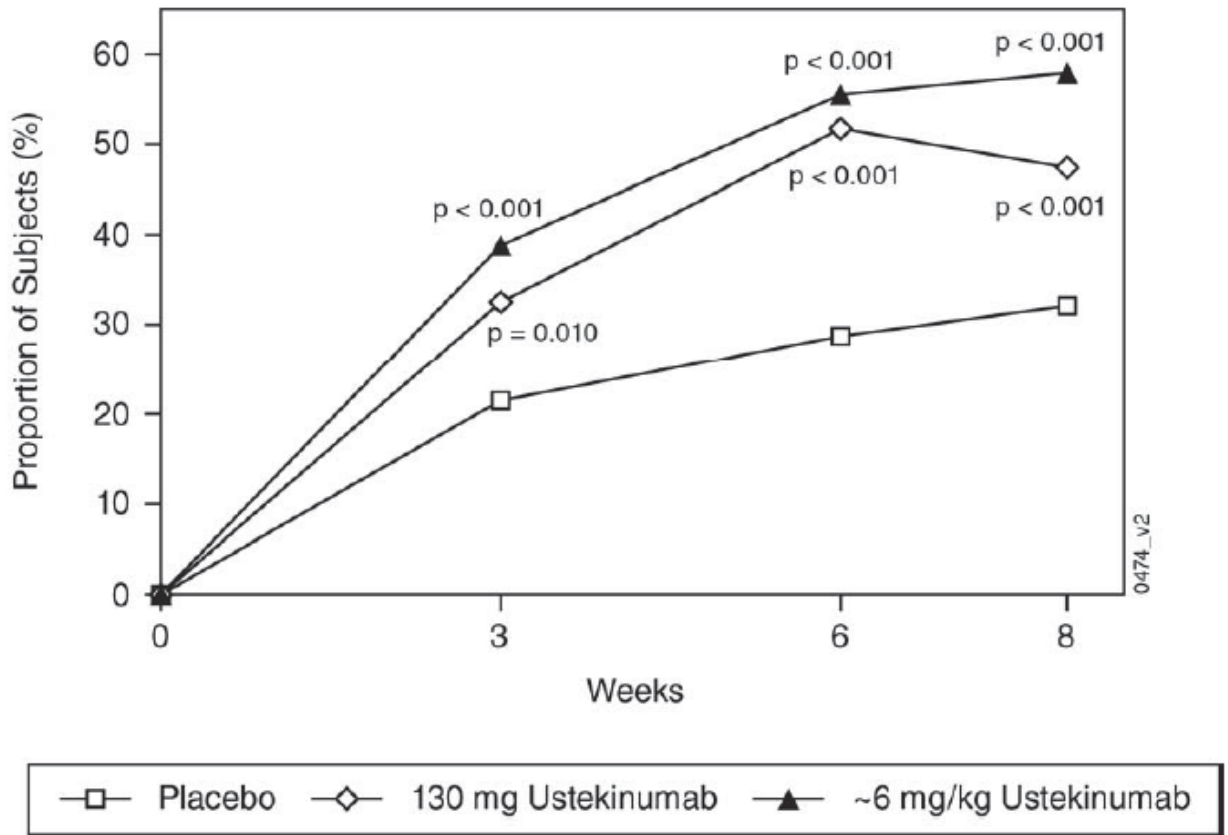
^a Subjects who had a prohibited Crohn's disease-related surgery or had prohibited concomitant medication changes are considered not to be in clinical response, regardless of their CDAI score.
^b Subjects who had insufficient data to calculate the CDAI score are considered not to be in clinical response.

Source: Applicant's Figure 5 entitled Number of Subjects in Clinical Response through Week 8; Randomized Subjects Excluding Those Enrolled Prior to Study Re-start, BLA 761044 CSR 3001, p. 71/396.

Clinical Response Over Time: Study 3002

A significantly greater proportion of patients were in clinical response as early as week 3 in both the 6 mg/kg (81/209 [38.8%], $p < 0.001$) and 130 mg (68/209 [32.5%], $p = 0.01$) ustekinumab dose groups as compared with the placebo group (45/209 [21.5%]). At Weeks 6 and 8, the proportions of patients in clinical response remained significantly greater in both the ustekinumab 6 mg/kg at Week 6 (116/209 [55.5%], $p < 0.001$) and Week 8 (99/209 [57.9%]), and 130 mg at Week 6 (108/209 [51.7%], $p < 0.001$) and Week 8 (99/209 [47.4%]) dose groups vs placebo for Week 6 (60/209 [28.7%]) and Week 8 (67/209 [32.1%]). The trend over time for clinical response in the ustekinumab groups was similar to that observed for clinical remission in the ustekinumab groups except that the 130 mg dose group where the proportion of responders declines slightly between Weeks 6 and 8; however, there is no change in statistical significance vs placebo. See Figure 27 below.

Figure 27: The percent of patients in clinical response over time in Study 3002



^a Subjects who had a prohibited Crohn's disease-related surgery or had prohibited concomitant medication changes are considered not to be in clinical response, regardless of their CDAI score.
^b Subjects who had insufficient data to calculate the CDAI score are considered not to be in clinical response.

Source: Applicant's Figure 5 entitled Number of Subjects in Clinical Response through Week 8; Randomized Subjects Excluding Those Enrolled Prior to Study Re-start and Excluding Site 1127, BLA 761044 CSR 3002, p. 76/366.

Again the figure above illustrates that while a small proportion of patients in the placebo group achieved clinical remission, consistent with what is known about the relapsing and remitting behavior of Crohn's disease, the majority of patients treated with ustekinumab required at least 6 to 8 weeks to achieve clinical remission after the single induction dose. The figure also illustrates that a larger proportion of patients in the 6 mg/kg dosing group achieved clinical remission as early as Week 3 as compared to patients in the 130 mg and placebo dose groups.

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Also of note, there appears to be a slight decline between Week 6 and 8 in the 130 mg dose group, supporting the 6 mg/kg dose as the preferred induction dose. This again supports that the 6 mg/kg weight tiered dosing is preferred as the initial dose.

70-Point Response Over Time: Study 3001

A significantly greater proportion of patients in the 6 mg/kg ustekinumab and 130 mg ustekinumab dose groups achieved clinical response, defined by a 70-point reduction from baseline CDAI, at Week 3 (101/249 [40.6%] and 94/245 [38.4%], respectively) as compared with the placebo group (667/247 [27.1%]; $p=0.001$ and $p=0.009$, respectively). At Weeks 6 and 8, the proportions of patients in 70-point response remained greater in both dose groups as compared with placebo (Week 6: $p=0.002$ and $p<0.001$, respectively; Week 8: $p<0.001$ and $p=0.001$, respectively). The trend over time for 70-point response in the ustekinumab groups showed both ustekinumab doses rising quickly by Week 3, plateauing by Week 6, and then a small elevation in the 6 mg/kg dose and decline in the response of the 130 mg dose by Week 8.

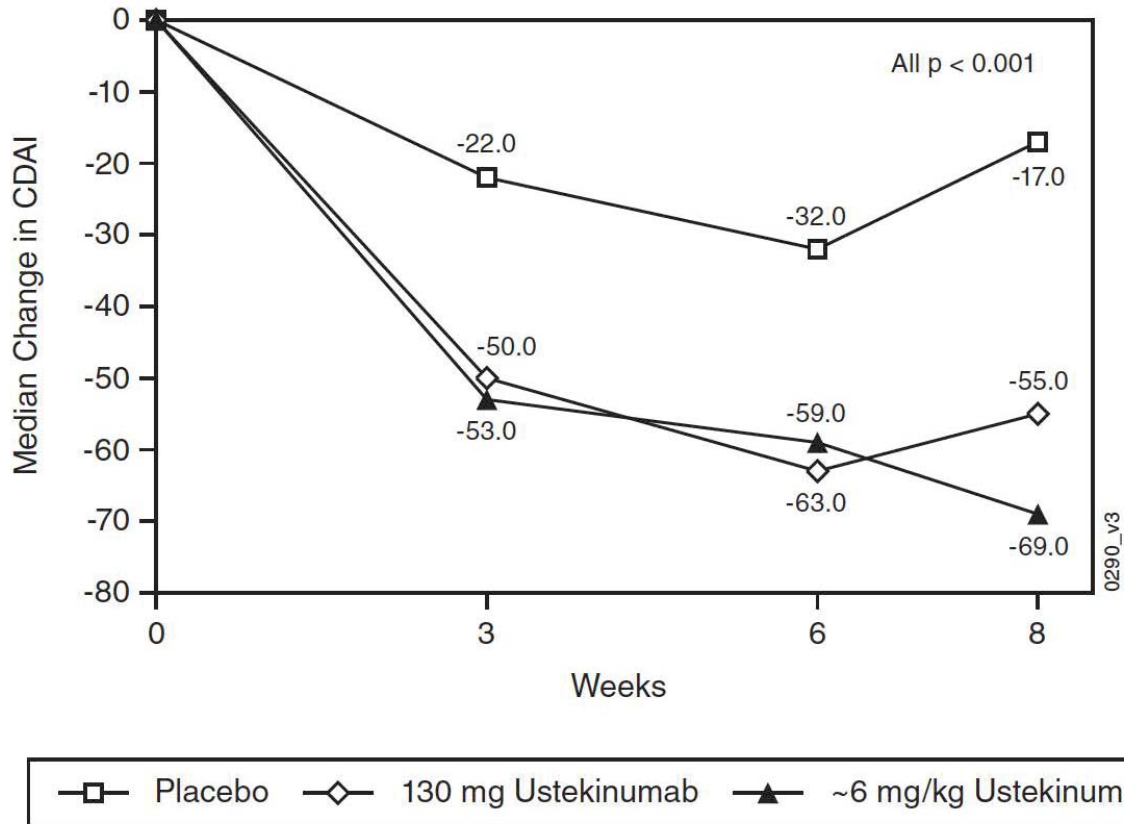
70-Point Response Over Time: Study 3002

A significantly greater proportion of patients in both the 6 mg/kg ustekinumab and 130 mg ustekinumab groups achieved clinical response, defined by a 70-point reduction from baseline CDAI, for Week 3. At Week 3, proportions of patients were 106/209 (50.7%) for the 6 mg/kg dose group, 103/209 (49.3%) for the 130 mg dose group vs 66/209 (31.6%) for placebo with p values of $p<0.001$ for both dosing groups. In Week 6 the proportion of patients in 70-point response had increased across all 3 groups 135/209 (64.6%) for the 6 mg/kg dose group, 123/209 (58.9%) for the 130 mg dose group vs 81/209 (38.8%) for placebo with p values of $p<0.001$ for both dose groups. In Week 8 there were slower increases for the proportion of patients gaining 70 point responses in the 6 mg/kg (139/209 [66.5%]) and placebo (92/209 [44.0%]) dose groups and a small decrease in the 130 mg patient dose group (121/209 [57.9%]) with p values of $p<0.001$ and $p=0.003$, in the 6 mg/kg and 130 mg dose groups, respectively as compared to placebo. This is another example where patients treated with the 130 mg dose appear to lose response between Weeks 6 and 8, thus, supporting the selection of the 6 mg/kg dose as the initial dose.

Change From Baseline in the CDAI Score Over Time: Study 3001

The Applicant measured a change from baseline across dosing groups in CDAI scores over time. Median CDAI scores were 313, 319, and 218 in the placebo, 6 mg/kg, and 130 mg dose groups. Figure 28 below summarizes the change in baseline CDAI through Week 8.

Figure 28: Median Change from Baseline in CDAI at Weeks 3, 6, and 8 in Study 3001



Source: The Applicant's Figure 7, entitled Median Change from Baseline in CDAI at Weeks 3, 6, and 8; Randomized Patients Excluding Those Enrolled Prior to Study Re-start provided in BLA 761044, CSR 3001, p 73/396.

At Week 3, there was a greater reduction in the CDAI score in both ustekinumab treatment groups (median CDAI score changes from baseline of -53.0 and -50.0 in the 6 mg/kg and 130 mg ustekinumab dose groups, respectively) compared with the placebo group (-22.0; $p < 0.001$ for both). At Week 6, reductions in the CDAI score continued for both the 6 mg/kg and 130 mg doses (median CDAI score changes from baseline of -59.0 and -63.0, respectively) compared with the placebo group (-32.0 with p values of $p < 0.001$ for both ustekinumab doses). At Week 8, the median CDAI continued to decline for the 6 mg/kg dose while the median CDAI rose for both the 130 mg dose and placebo (median CDAI score changes from baseline: -69.0 and -55.0, respectively vs placebo -17.0 with p values of $p < 0.001$ for both dose groups). The continued improvement from baseline in CDAI score through Week 8, shown in Figure 28 above, further supports the selection of 6 mg/kg IV as the single induction dose.

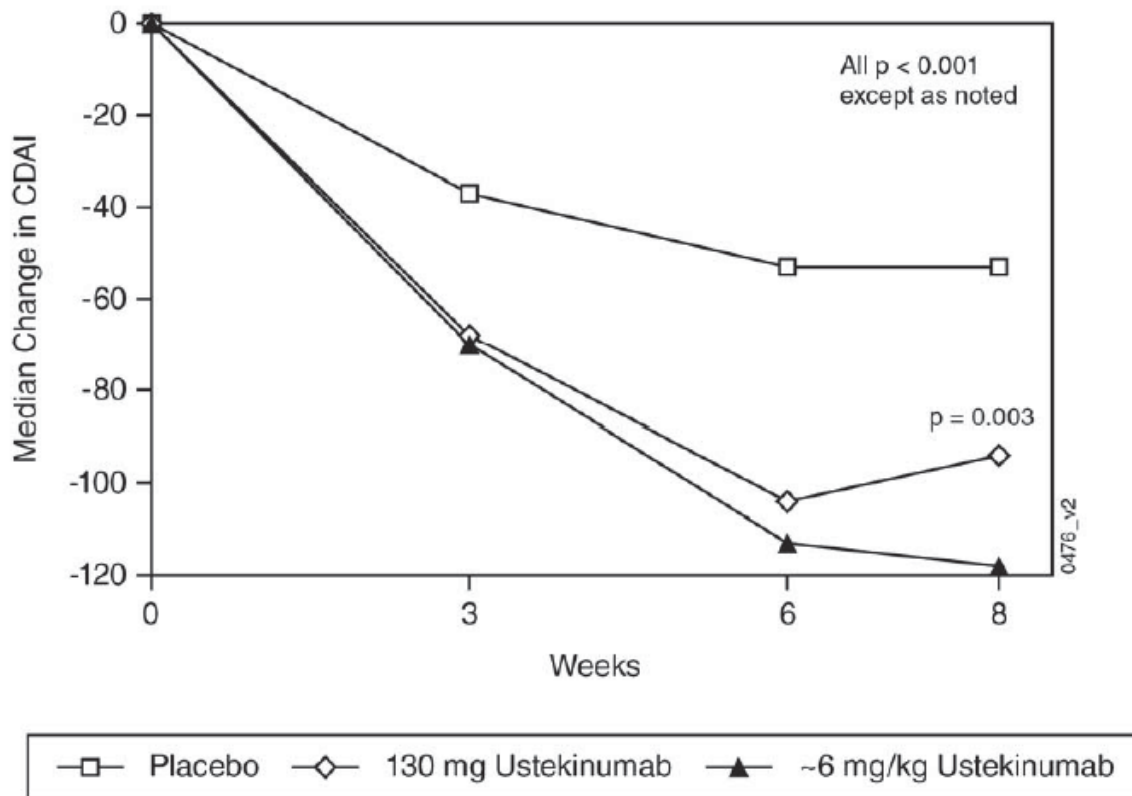
Change From Baseline in the CDAI Score Over Time: Study 3002

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The Applicant measured a change from baseline across dosing groups in CDAI scores over time. Median CDAI scores were generally similar across the treatment groups at baseline measured at 290.0, 286.0, and 294.0 in the placebo, ustekinumab 6 mg/kg, and ustekinumab 130 mg dose groups, respectively. Overall, there was a significantly greater reduction in the CDAI scores in both the 6 mg/kg and 130 mg ustekinumab dose groups when compared with placebo at all timepoint ($p < 0.001$ for all timepoints except 130 mg at week 8; $p = 0.003$). At Week 3, the reduction in the CDAI score in both ustekinumab treatment groups was similar (median CDAI score changes from baseline of -70.0 points and -68.0 points in the 6 mg/kg and 130 mg ustekinumab groups, respectively) and was greater than the change from baseline in the placebo group (-37.0 ; $p < 0.001$ for both dose groups). At Week 6, median reductions in the CDAI score continued to decrease with a more rapid rate in both the 6 mg/kg and 130 mg ustekinumab dose groups compared with placebo (-113.0 points and -104.0 points, respectively vs -53.0 points in the placebo arm; $p < 0.001$ for both dose groups). At Week 8, the median change from baseline continued decrease for patients in the 6 mg/kg group with a change of -118.0 from baseline. However, the median CDAI score for the rose for the 130 mg dose to -94.0 from baseline and plateaued for placebo at -53.0 ; $p < 0.001$ and $p = 0.003$ for the 6 mg/kg dose group and 130 mg dose groups, respectively). As a result, the treatment effect was largest by Week 8 for the 6 mg/kg group than for the 130 mg group.

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Figure 29: Median Change from Baseline in CDAI at Weeks, 3, 6, and 8 in Study 3002



- ^a Subjects who, prior to the designated analysis timepoint, had a prohibited Crohn's disease-related surgery or had prohibited concomitant medication changes had their baseline value carried forward.
- ^b Subjects who had insufficient data at the designated analysis timepoint had their last value carried forward.

Source: The Applicant's Figure 7, entitled Median Change from Baseline in CDAI at Weeks 3, 6, and 8; Randomized Subjects Excluding Those Enrolled Prior to Study Re-start and Excluding Site 1127 provided in BLA 761044, CSR 3002, p 78/366.

The continued improvement from baseline in CDAI score through week 8 for the 6 mg/kg dose shown in Figure 29 above, further supports the selection of 6 mg/kg IV as the single induction dose.

Introduction to CRP as a Measure of Inflammation in IBD

C-reactive protein (CRP) is a serum marker of inflammation often followed in clinical practice to monitor disease activity inflammatory bowel disease. Elevations in serum CRP can be reflective of, but are not specific to IBD and the CRP level that reflects active inflammation is not standardized. In addition, data are lacking at this time to support that CRP levels can reliably

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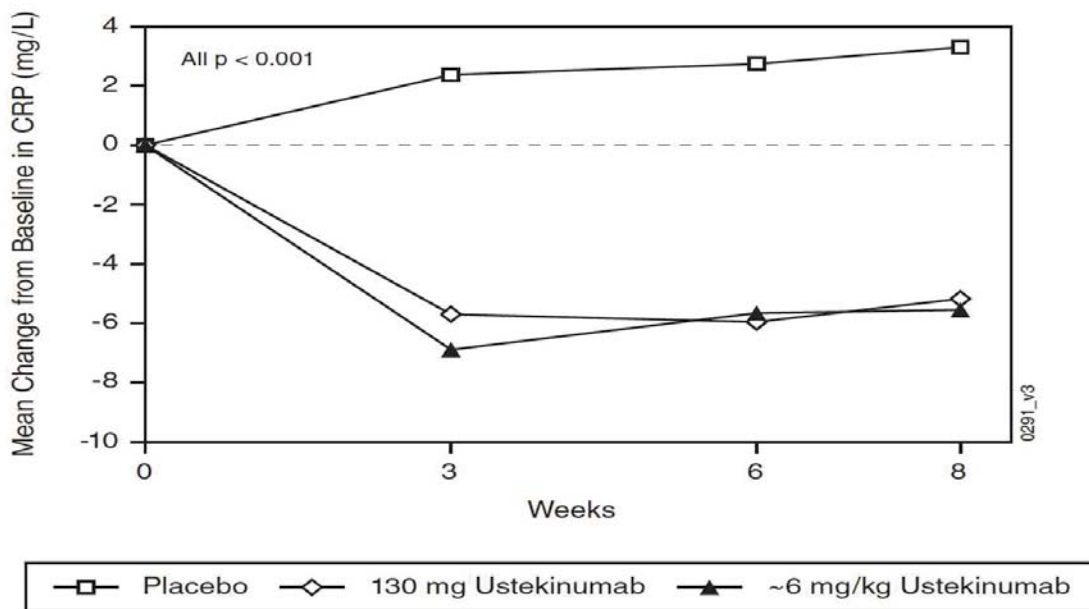
predict intestinal inflammation. Therefore, the results of CRP analyses are considered as exploratory, but could inform future use of CRP in clinical studies. The Applicant measured both change from baseline and normalization of CRP over time as exploratory endpoints. All lab values were measured through a central lab.

Change From Baseline in CRP Concentration Over Time: Study 3001

At baseline, mean CRP concentrations at in the ustekinumab groups were slightly higher in the 6 mg/kg and 130 mg ustekinumab dose groups (19.50 and 19.96 mg/L, respectively) compared with the placebo group (16.56 mg/L). At Week 3, the mean reductions in CRP concentrations were greater in each of the ustekinumab groups (-6.89 and -5.70 mg/L, respectively) compared with the placebo group (2.37 mg/L; $p < 0.001$ for both dose groups). At Weeks 6 and 8, the mean reductions in CRP concentrations remained significantly greater in both ustekinumab dose groups compared with placebo ($p < 0.001$ for both groups at both time points); however, no further reductions in CRP were observed in the ustekinumab dose groups after Week 3.

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Figure 30: Mean Change from Baseline in CRP Concentration (mg/L) through Week 8 in Study 3001



^a Subjects who, prior to the designated analysis timepoint, had a prohibited Crohn's disease-related surgery or had prohibited concomitant medication changes, had their baseline value carried forward.
^b Subjects who had insufficient data at the designated analysis timepoint had their last value carried forward.

Data source: [TEFCRP02.rtf] [CNT01275\CRD3001\DBR_W8_W20\RE_W8_W20\tefcrp02.sas] 16AUG2013, 16:01

Source: The Applicant's Figure 8, entitled Mean Change from Baseline in CRP Concentration (mg/L) through Week 8: Randomized Subjects Excluding Those Enrolled Prior to Study Re-start provided in BLA 761044, CSR 3001, p 74/396.

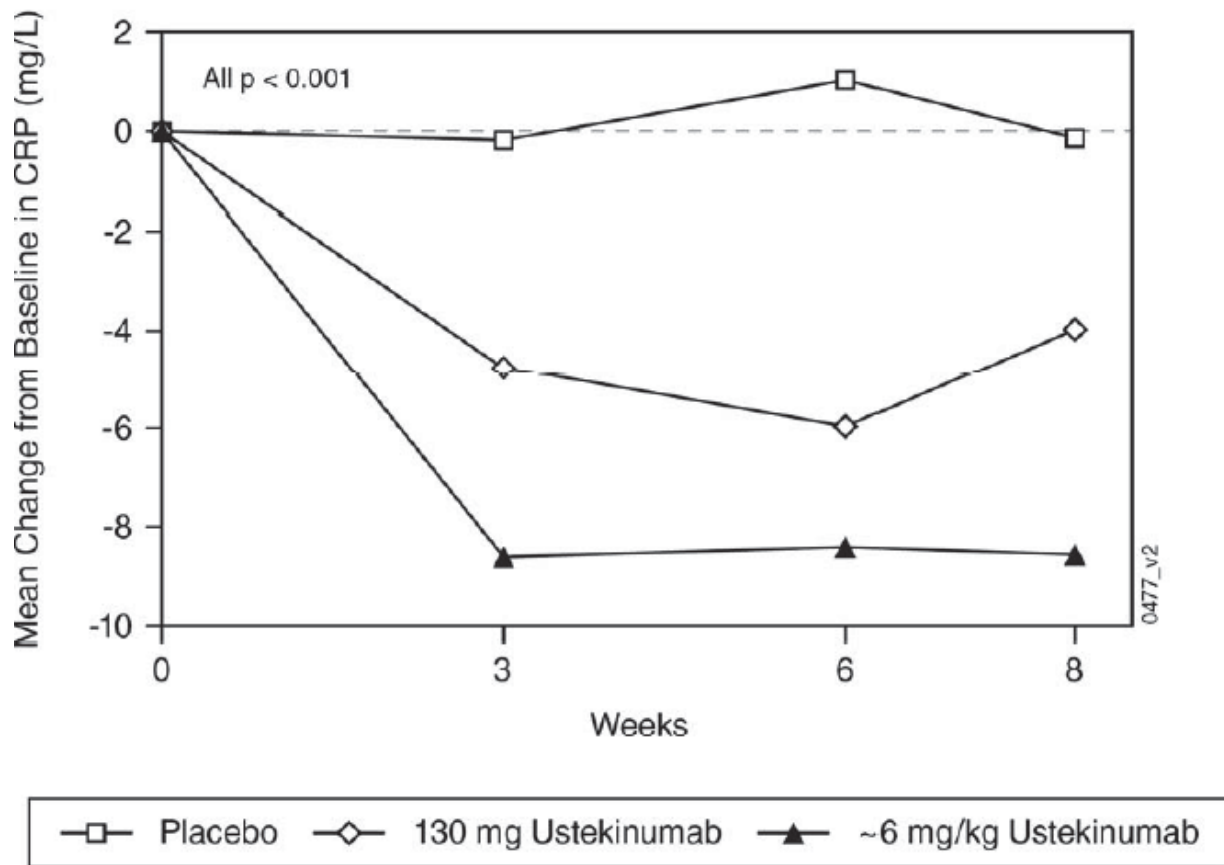
Change From Baseline in CRP Concentration Over Time: Study 3002

The Applicant evaluated both the change from baseline CRP and the normalization of CRP. The change from baseline will be reviewed first, followed by the normalization of CRP.

Normalization of CRP is more clinically meaningful as it indicates inflammation in the body is quiescent. Mean reductions in CRP concentrations were greater in both the 6 mg/kg and 130 mg ustekinumab groups compared with placebo at each timepoint ($p < 0.001$ for both groups). At all timepoints, however, the magnitude of reduction was largest for the 6 mg/kg dose. The maximum mean reduction in CRP was achieved by Week 3 for the 6 mg/kg dose group (-8.61 mg/L [± 20.14]) and remained stable at Week 6 (-8.41 mg/L [± 20.97]) and Week 8 mg/L (-8.56 mg/L [± 19.60]). In the 130 mg dose group, the maximum reduction in CRP was achieved by Week 6 (-5.97 mg/L [± 15.15]) but the mean reduction from baseline was lower at Week 8 (-3.97

mg/L [± 22.00]).

Figure 31: Mean Change from Baseline in CRP Concentration (mg/L) through Week 8 in Study 3002



- ^a Subjects who, prior to the designated analysis timepoint, had a prohibited Crohn's disease-related surgery or had prohibited concomitant medication changes, had their baseline value carried forward.
- ^b Subjects who had insufficient data at the designated analysis timepoint had their last value carried forward.

Source: The Applicant's Figure 8, entitled Mean Change from Baseline in CRP Concentration (mg/L) through Week 8: Randomized Subjects Excluding Those Enrolled Prior to Study Re-start and Excluding Site 1127 provided in BLA 761044, CSR 3002, p 79/366.

The sustained improvement from baseline in CRP score through Week 8 for the 6 mg/kg dose shown in Figure 31 above vs the loss of improvement by week 8 in the 130 mg dose further supports the selection of 6 mg/kg IV as the single initial dose.

Normalization of CRP Concentration Over Time in Patients With Abnormal CRP at Baseline:

CDER Clinical Review Template 2015 Edition

Version date: November 5, 2015 for initial rollout (NME/original BLA reviews)

Study 3001

In addition to tracking CRP through Week 8 of the single dose induction Study 3001, the Applicant analyzed patients with elevated CRP at baseline to track normalization of CRP over time. At baseline, 192/247, 197/245, and 191/249 patients in the placebo, 6 mg/kg and 130 mg ustekinumab dose groups, respectively, had abnormal CRP, which was defined in the protocol and the SAP as a CRP value >3 mg/L and measured at a central lab. The Applicant's cutoff appears reasonable to this reviewer. Some labs utilize <2.0 mg/L as normal; however, the majority of lab references cite <3.0mg/L as a normal level. Among these patients, a greater proportion of patients in the 6 mg/kg and 130 mg ustekinumab dose groups had normalized CRP at Week 3 compared with the placebo group (p<0.001 and p=0.018, respectively). At Weeks 6 and 8, the proportions of patients with normalized CRP remained significantly greater in both ustekinumab dose groups 6 mg/kg and 130 mg compared with placebo (See **Table 9** below.)

Table 9: Normalization of CRP: Study 3001

	Week 3	Week 6	Week 8
Placebo	12/192 (6.3%)	9/192 (4.7%)	16/192 (8.3%)
130 mg Dose	26/191 (13.6%)	25/191 (13.1%)	32/191(16.8%)
6 mg/kg Dose	34/197 (17.3%)	42/197 (21.3%)	42/197 (21.3%)

Source: Reviewer created table using Applicant data from BLA 761044, CSR 3001, attachment TEF CRP01 p 185/396.

The table above illustrates that a larger proportion of patients treated with ustekinumab, in both dose groups, normalized CRP as compared to placebo at all three time points. However, for the study population in 3001, by Week 8 a smaller proportion of patients had normal CRP in the 130 mg dose group than in the 6 mg/kg dose group. As CRP normalization is more clinically meaningful than the reduction of CRP (absence of inflammation as opposed to just the reduction of inflammation) these data continue to favor the 6 mg/kg dosing over the 130 mg induction dose

Normalization of CRP Concentration Over Time in Patients With Abnormal CRP at Baseline: Study 3002

In addition to tracking CRP through Week 8 of the single dose induction Study 3002, the Applicant analyzed patients with elevated CRP at baseline to track normalization of CRP over time. At baseline, the proportion of patients with abnormal CRP was 160/209, 165/209, and 157/209 patients in the placebo, 6 mg/kg, and 130 mg ustekinumab dose groups, respectively. Abnormal CRP was defined in the protocol and the SAP as a CRP value >3 mg/L and measured at a central lab. The Applicant's cutoff appears reasonable. Some labs utilize <2.0 mg/L as normal;

however, the majority of lab references cite <3.0mg/L as a normal level. Among these patients, a greater proportion of patients in the 6 mg/kg and 130 mg ustekinumab dose groups ($p<0.001$ and $p=0.02$, respectively). At Weeks 6 and 8, the proportions of patients with normalized CRP remained significantly greater in both ustekinumab dose groups 6 mg/kg and 130 mg (Week 6: $p<0.001$ for both doses; Week 8: $p<0.001$ and $p=0.004$, respectively). (See **Table 10** below for proportions).

Table 10: Normalization of CRP: Study 3002

	Week 3	Week 6	Week 8
Placebo	12/160 (6.3%)	9/160 (5.6%)	15/160 (9.4%)
130 mg Dose	28/157 (17.8%)	35/157 (22.3%)	33 (21.0%)
6 mg/kg Dose	42/165 (25.5%)	51/165 (30.9%)	43/165 (26.1%)

Source: Reviewer created table using Applicant data from BLA 761044, CSR 3002, attachment TEF CRP01 p 196/366.

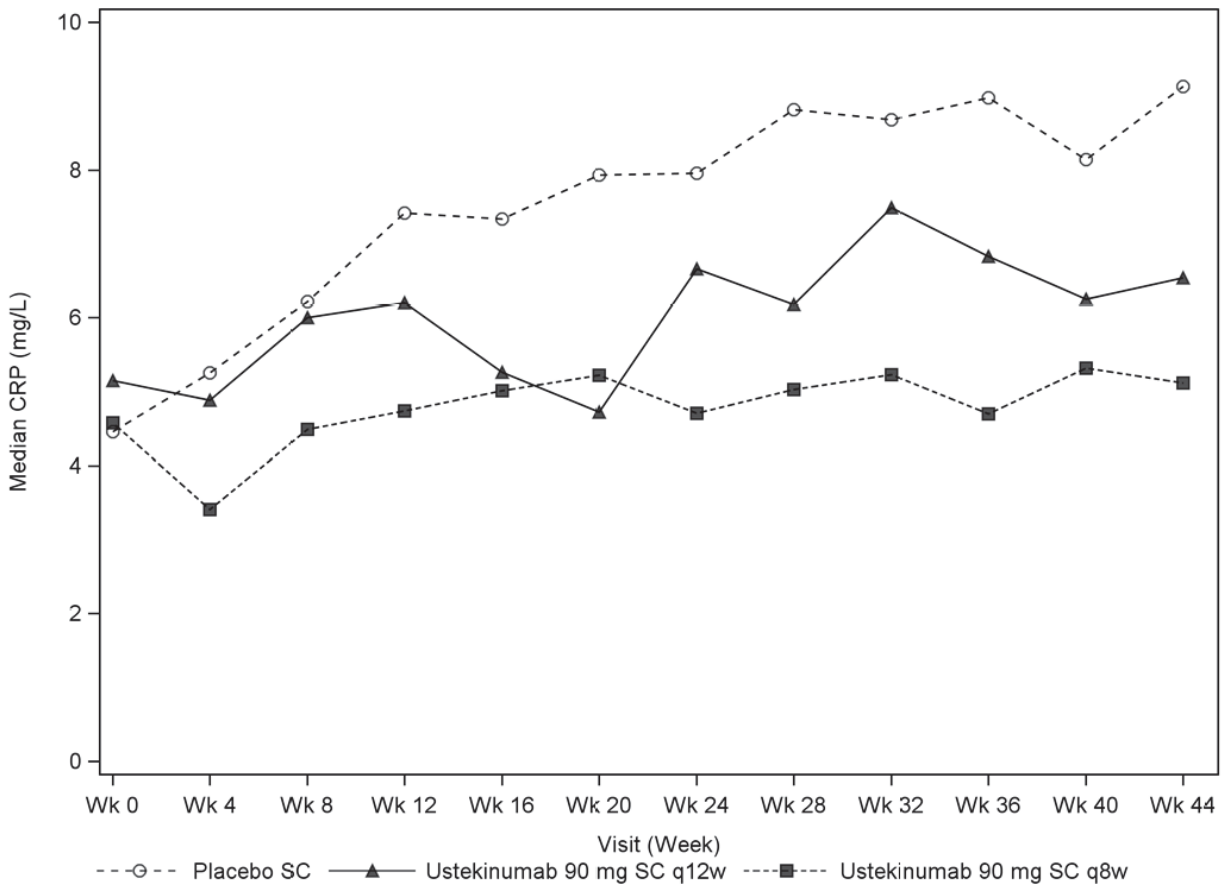
The table above illustrates that a larger proportion of patients treated with ustekinumab, in both dose arms, normalized CRP as compared to placebo at all three time points. However, for the study population in 3002, a smaller proportion of patients in the 130 mg dose group than the 6 mg/kg dose group had normal CRP values by Week 8. As CRP normalization is more clinically meaningful than the reduction of CRP (absence of inflammation as opposed to just the reduction of inflammation) these data continue to favor the 6 mg/kg dose over the 130 mg induction dose, these data continue to favor the 6 mg/kg dose over the 130 mg induction dose.

C-Reactive Protein (CRP) in Study 3003

CRP increased by a small but not clinically meaningful amount in both ustekinumab dosing regimens by the end of the maintenance phase (0.42 mg/L and 0.51 mg/L in the ustekinumab 90 mg q12w and q8w dosing regimens, respectively) as compared with the placebo group (4.07 mg/L), which increased by a larger amount, which could be clinically relevant depending on the baseline CRP of the patient; $p=0.002$ and $p<0.001$ for the q12w and q8w dosing regimens, respectively). At all timepoints except for week 20 the reduction of the CRP rate of increase was greater for the q8w dose than the q12w dosing regimens. The separation in median CRP between the q12w and placebo groups was less over time than between the q8w and placebo dosing regimens, particularly from Week 24 through Week 44.

At Week 44, the proportions of patients with normalized CRP (defined as ≤ 3 mg/L) concentrations were significantly greater in the ustekinumab q12w dosing regimen (23/101 [22.8%]) and numerically greater in the ustekinumab q8w dosing regimen (18/92 [19.6%]) compared with the placebo dosing regimen (11/105 [10.5%]; $p=0.02$ and $p=0.08$ for the ustekinumab q12w and q8w dosing regimens, respectively). See Figure 32 below.

Figure 32: Median Change from Baseline in CRP Concentration (mg/L) through Week 44: Study 3003



Source: Applicant's BLA 761044, Appendix GEFCRP03 figure entitled: Line plot of median CRP (mg/L) through Week 44; randomized patients, excluding those enrolled prior to study re-start, CSR 3003, p 961/1619.

While the median CRP value increased over time during the 44 week maintenance phase in all dosing regimens, the patients in the q8w regimen appeared to have less fluctuations and more stable CRP values as compared to the q12w regimen and placebo dosing regimens. This trend in change from baseline favors the q8w dose regimen; however, normalization of CRP appears to be supported by the q12w dose regimen for this exploratory endpoint.

*Introduction to Fecal Lactoferrin as a Measure of Inflammation in IBD*²⁵

²⁵ A normal fecal lactoferrin level was considered $\leq 7.24\mu\text{g/g}$.

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Fecal lactoferrin is a fecal marker of inflammation sometimes followed in clinical practice to monitor disease activity inflammatory bowel disease. Decreasing concentration of lactoferrin can be interpreted as a marker of therapeutic response in clinical practice, however, correlations to signs and symptoms or endoscopy have not been established. Currently, the results of fecal lactoferrin analyses are considered as exploratory, but could inform future use of fecal lactoferrin in clinical studies. It has been noted in the literature that in patients with Crohn's disease who have undergone ileocolonic resection, those with higher lactoferrin fecal levels may be more prone to postsurgical recurrence.²⁶

Change From Baseline in Fecal Lactoferrin Concentration at Week 6: Study 3001

Baseline median values for fecal lactoferrin concentration were higher in the placebo group (130.88 µg/g) than in the 6 mg/kg and 130 mg ustekinumab dose groups (107.52 and 92.00 µg/g, respectively); however, as change from baseline was measured rather than normalization, it is unlikely that this difference in baseline values affected the outcome of this endpoint. At Week 6, there was a significantly greater reduction in fecal lactoferrin median concentration in the 6 mg/kg and 130 mg ustekinumab dose groups (-6.43 and -3.70 µg/g, respectively) compared with the placebo dose group (0.00, p<0.001 and p=0.004). Among patients with a baseline fecal lactoferrin value >7.24 µg/g, which is considered elevated, the proportions of patients with a normalized (≤7.24 µg/g) fecal lactoferrin value at Week 6 were significantly higher in the 6 mg/kg and 130 mg ustekinumab dose groups (31/249 [14.0%] and 24/245 [11.3%], respectively) compared with the placebo dose group (5/247 [2.4%], p<0.001 for both groups).

Change From Baseline in Fecal Lactoferrin Concentration at Week 6: Study 3002

Baseline median values for fecal lactoferrin concentration were slightly higher in the 6 mg/kg and 130 mg ustekinumab dose groups (98.40 and 78.44 µg/g, respectively) compared with the placebo dose group (67.76 µg/g). At Week 6, there was a greater median reduction in fecal lactoferrin concentration in the ustekinumab 6 mg/kg and 130 mg dose groups (-25.93 µg/g and -10.35 µg/g, respectively) compared with no reduction in the placebo dose group (p<0.001 for both groups). Among patients with a baseline fecal lactoferrin value >7.24 µg/g, the proportions of patients with a normal (e.g., ≤7.24 µg/g) fecal lactoferrin values at Week 6 were significantly higher in the ustekinumab 6 mg/kg and 130 mg dose groups (26/209 [14.9%] and 24/174 [13.8%], respectively) compared with the placebo dose group (13/176 [7.4%] with p values of p=0.027 and p=0.045, respectively).

These results appear to indicate that fecal lactoferrin levels decrease in patients treated with ustekinumab, either dose, as compared to placebo.

²⁶ Gisbert JP, McNicholl AG, and F Gomollon. 2009. Questions and answers on the role of fecal lactoferrin as a biological marker in inflammatory bowel disease. *Inflamm Bowel Dis*. Nov;15(11):1746-54.

Change From Baseline in Fecal Lactoferrin Concentration at Week 44: Study 3003

At baseline, median fecal lactoferrin concentrations were highest in the q12w and placebo dosing regimens at 70.41 µg/g, 32.02 µg/g, and 58.15 µg/g for the ustekinumab 90 mg q12w, q8w and placebo dosing regimens, respectively. This may have affected results as groups with smaller averages were closer to normalization. At Weeks 24 and 44, the fecal lactoferrin showed little to no change from baseline in median values for both ustekinumab dosing regimens compared with the placebo dosing regimen. At Week 44, the median changes from baseline were -2.99 (p=0.007) in the ustekinumab 90 mg q12w dosing regimen and 0.00 (p=0.001) for the ustekinumab 90 mg q8w dosing regimen. The median change from baseline in the placebo dosing regimen was 26.75, suggesting a worsening in fecal lactoferrin (i.e., increase in inflammatory markers).

The proportions of patients who normalized fecal lactoferrin concentrations (normal ≤7.24 µg/g) remained stable or increased slightly over time in both ustekinumab dosing regimens and were numerically greater at Week 24. At week 24, 19/115 (16.5%, p=0.18) patients in the q12w dosing regimen normalized fecal lactoferrin as compared to 19/109 (17.4%, p=0.12) patients in the q8w dosing regimen, and 12/114 (10.5%) patients in placebo dosing regimen. At Week 44, the proportion of patients with normal fecal lactoferrin in the q12w dosing regimen was 20/115 (17.4%, p =0.02) patients, 16/109 (14.7%, p=0.07) patients in the q8w dosing regimen, and 8/114 (7.0%) patients in the placebo dosing regimen. The proportion of patients with normal fecal lactoferrin at week 44 was significantly greater than placebo in the ustekinumab 90 mg q12w dosing regimen at Week 44. The proportion of patients with normal fecal lactoferrin values in the placebo dosing regimen decreased over time.

While fecal lactoferrin values are considered to be exploratory at this time, the results of these exploratory analyses appear to indicate that patients treated with ustekinumab maintained lower fecal lactoferrin levels (i.e., suggesting lower levels of inflammation) as compared to patients in the placebo group. Additionally, the proportion of patients with normal fecal lactoferrin concentrations in the q12 dose regimen was statistically significant as compared to placebo. This reviewer notes that this is an exploratory endpoint and is not an established as a surrogate that is reasonably likely to predict clinical benefit in this population at this time.

Introduction to Fecal Calprotectin as a Measure of Inflammation in IBD²⁷

Calprotectin is a calcium and zinc binding protein found in the cytosol of human neutrophils and macrophages. It is released extracellularly in times of cell stress or damage and can be detected

²⁷ Generally levels of fecal calprotectin <50mg/kg are considered normal.
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2694246/>

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within feces. Published studies have examined it as marker of intestinal inflammation and clinically is used as a correlation with mucosal disease activity and is purported to help to predict response to treatment or relapse.²⁸ The use of fecal calprotectin in IBD to measure mucosal disease activity is exploratory at this time and the FDA has neither approved it as a diagnostic tool nor a measure of therapeutic intervention. Until additional data are available to support their use as markers of disease activity or inflammation in the context of a clinical study it will be considered an exploratory endpoint.

Change From Baseline in Fecal Calprotectin Concentration at Week 6: Study 3001

At baseline, median values for fecal calprotectin concentration were lower in the 130 mg ustekinumab dose group (399.90 mg/kg) than in the 6 mg/kg ustekinumab dose group and placebo groups (530.15 and 515.78 mg/kg, respectively). At Week 6, there was a significantly greater reduction in fecal calprotectin concentration in the 6 mg/kg and 130 mg ustekinumab groups (median reduction: -41.25 and -38.57) compared with the placebo group (0.00, $p < 0.001$ for both groups).

At baseline, the proportion of patients with elevated fecal calprotectin was 162/247, 150/245, and 158/249 patients in the placebo, 130 mg, and 6 mg/kg dosing, respectively. Among patients with an elevated baseline fecal calprotectin value (e.g. > 250 mg/kg), the proportions of patients with a fecal calprotectin value ≤ 250 mg/kg at Week 6 were significantly higher in the 6 mg/kg and 130 mg ustekinumab groups (44/158 [27.8%] and 35/150 [23.3%], respectively) compared with the placebo group (17/162 [10.5%] with p values of $p < 0.001$ and $p = 0.001$, respectively). Among patients with a baseline fecal calprotectin value > 250 mg/kg, the proportions of patients with fecal calprotectin values ≤ 100 mg/kg at Week 6 were also significantly higher in the ustekinumab groups (17/158 [10.8%] and 16/150 [10.7%], respectively) compared with the placebo group (6/162 [3.7%] with p value of $p = 0.015$ for both dose groups).

Change From Baseline in Fecal Calprotectin Concentration at Week 6: Study 3002

At baseline, median values for fecal calprotectin concentration were higher in the 6 mg/kg and 130 mg ustekinumab dose groups (523.23 and 519.63 mg/kg, respectively) as compared to the placebo dose group (415.54 mg/kg). This difference should not have affected a measurement of mean change. At Week 6, there was a greater median reduction from baseline in fecal calprotectin concentration in the 6 mg/kg (-106.32 mg/kg) and 130 mg ustekinumab dose groups (-55.03 mg/kg) compared with no reduction in the placebo dose group ($p < 0.001$ for both groups).

²⁸ Smith L and D Gaya. 2012. Utility of faecal calprotectin analysis in adult inflammatory bowel disease. *World J Gastroenterol*. Dec 14; 18(46): 6782-6789.

At baseline, the proportion of patients with elevated fecal calprotectin was 127/209, 133/209, and 135/209 patients in the placebo, 130 mg, and 6 mg/kg dose group, respectively. Among patients with an elevated baseline fecal calprotectin value (e.g. >250 mg/kg), the proportions of patients with a normal fecal calprotectin value (e.g. ≤250 mg/kg) at Week 6 were significantly greater in the 6 mg/kg (41/135 [30.4%]) and 130 mg ustekinumab dose groups (35/133 [26.3%]) compared with the placebo group (20/127 [15.7%], with p values of p=0.006 and p=0.029, respectively). Among patients with a baseline fecal calprotectin value >250 mg/kg, the proportions of patients with fecal calprotectin values that decreased ≤100 mg/kg at Week 6 were also greater in the 6 mg/kg and 130 mg ustekinumab dose groups (24/209 [17.8%] and 18/209 [13.5%], respectively) compared with the placebo dose group (5/127 [3.9%], with p values of p<0.001 and p=0.006, respectively). These data appear to suggest fecal calprotectin levels improve (are reduced) to a greater extent and by a greater amount for patients treated with ustekinumab compared to placebo.

Change From Baseline in Fecal Calprotectin Concentration at Week 44: Study 3003

At baseline, median fecal calprotectin concentrations were 493.48 mg/g, 191.06 mg/g, and 262.06 mg/g for the ustekinumab 90 mg q12w, q8w and placebo dosing regimens, respectively. At Week 44, there was no change from baseline for each ustekinumab-treated dosing regimen, compared with a median increase of 153.85 mg/g in the placebo dosing regimen (p=0.002 and p<0.001 for the q12w and q8w dosing regimens, respectively).

Among patients with an elevated baseline fecal calprotectin value (i.e., >250 mg/g), the proportion of patients with a normal fecal calprotectin value, ≤ 250 mg/g, at Week 44 were greater in the ustekinumab 90 mg q12w (25/91 [27.5%], p=0.005) and q8w dosing regimens (25/83 [30.1%], p=0.001) compared with the placebo dosing regimen(10/93 [10.8%]). Among patients with a baseline fecal calprotectin value >250 mg/g, the proportion of patients with fecal calprotectin values ≤100 mg/g at Week 44 were greater in both the ustekinumab 90 mg q12w (14/91 [15.4%], p=0.028) and q8w dosing regimen (16/83 [19.3%], p=0.008) compared with placebo (5/93 [5.4%]). These data suggest that patients treated with ustekinumab have a greater reduction in fecal calprotectin levels as compared to placebo.

Fistula Response Over Time: Study 3001

A fistula response was defined as a ≥50% reduction in the number of open/draining fistulas. Among the 12.6% (93 of 741) of patients who had a fistula at baseline, a greater proportion of patients were in fistula response at Week 8 in the combined ustekinumab dose groups compared with the placebo dose group (18.5% [n=10] vs 11.8% [n=4], respectively). However, this number was not significant and reviewing Table 11 below one notes that neither individual dose of ustekinumab produced significant improvement over placebo either. This reviewer concludes that neither dose of ustekinumab significantly outperformed placebo regarding fistula response.

Table 11: Fistula Response to Ustekinumab vs Placebo in Weeks 3, 6, and 8 in Study 3001

	Placebo	Ustekinumab		Combined
		130 mg	6 mg/kg ^a	
Analysis set: Randomized subjects excluding those enrolled prior to study re-start	247	245	249	494
Subjects with 1 or more fistulas at baseline	37	25	31	56
Week 3				
N	37	25	31	56
Subjects in fistula response	5 (13.5%)	4 (16.0%)	1 (3.2%)	5 (8.9%)
p-value		0.493	0.161	0.521
Week 6				
N	34	25	30	55
Subjects in fistula response	6 (17.6%)	6 (24.0%)	4 (13.3%)	10 (18.2%)
p-value		0.591	0.416	0.723
Week 8				
N	34	25	29	54
Subjects in fistula response	4 (11.8%)	6 (24.0%)	4 (13.8%)	10 (18.5%)
p-value		0.209	0.715	0.346

^a 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).

Source: Applicant's submission BLA 761044 Appendix TEFFIST01 entitled Number of Subjects in Fistula Response through Week 8; Randomized Subjects Excluding Those Enrolled Prior to Study Re-start, CSR 3001 p 191/396.

Of note, data on fistula response was examined in two Remicade (infliximab) studies with a similar definition of ≥50% reduction in number of enterocutaneous fistulas draining upon gentle compression on at least 2 consecutive visits without an increase in medication or surgery for Crohn's disease. The first Remicade trial demonstrated improvement in the induction trial after three doses at Weeks 0, 2, and 6 of 21/31 (68%) of patients in the 5mg/kg dose group (p=0.002) and 18/32 (56%) of patients in a 10 mg/kg dose group (p=0.02). The second trial demonstrated improvement in the maintenance trial, please see the section on Fistula Response Over Time: Study 3003 Remicade is indicated for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing Crohn's disease. While the sample size is small and there are limitations to cross-study comparisons, these data provide a reference to another product where fistula response was evaluated.²⁹

Fistula Response Over Time: Study 3002

A fistula response was defined as a ≥50% reduction in the number of open and draining fistulas. There were 68/627(10.8%) patients who had a fistula at baseline, and a greater proportion of patients were met the criteria for fistula response at Week 8 in the ustekinumab 6 mg/kg (6/19 [31.6%]; p=0.379) and 130 mg ustekinumab dose groups (8/2 [36.4%]; p=0.434) compared with

²⁹ Remicade label last approved 10/02/2015 accessed 8/25/2016 at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Search_Drug_Name

the placebo group (4/23 [17.4%]). However, this number was not statistically significant. In reviewing Table 12 below, this reviewer concludes that neither dose of ustekinumab significantly outperformed placebo regarding fistula response. Additionally, please see discussion on Remicade (above paragraph on fistula response for Study 3001) which was approved for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing Crohn’s disease.

Table 12: Fistula Response to Ustekinumab vs Placebo in Weeks 3, 6, and 8 in Study 3002

	Placebo	Ustekinumab		
		130 mg	6 mg/kg ^a	Combined
Analysis set: Randomized subjects excluding those enrolled prior to study re-start and excluding site 1127	209	209	209	418
Subjects with 1 or more fistulas at baseline	24	24	20	44
Week 3				
N	24	24	20	44
Subjects in fistula response	3 (12.5%)	4 (16.7%)	0	4 (9.1%)
p-value		0.885	0.129	0.516
Week 6				
N	24	24	19	43
Subjects in fistula response	3 (12.5%)	7 (29.2%)	5 (26.3%)	12 (27.9%)
p-value		0.450	0.291	0.340
Week 8				
N	23	22	19	41
Subjects in fistula response	4 (17.4%)	8 (36.4%)	6 (31.6%)	14 (34.1%)
p-value		0.434	0.379	0.268

^a Weight-range based ustekinumab doses approximating 6 mg/kg: 260 mg (weight ≤ 55 kg), 390 mg (weight > 55 kg and ≤ 85 kg), 520 mg (weight > 85 kg).

Source: Applicant’s submission BLA 761044, Appendix TEFFIST01: Number of Subjects in Fistula Response through Week 8; Randomized Subjects Excluding Those Enrolled Prior to Study Re-start and Excluding Site 1127 CSR 3002 p 202/366.

Fistula Response Over Time: Study 3003

A fistula response was defined as a ≥ 50% reduction in the number of open and draining fistulas. There were 34/388 (8.8%) patients who had a fistula at baseline of the maintenance study. Of the 34 patients who had a fistula at the start of the maintenance study, 5/7 (71.4%) patients in the ustekinumab q12 week group and 7/8 (87.5%) patients in the q8 week dose regimen met the criteria for fistula response at Week 44, as compared with the placebo dose regimen (5/11 [45.5%]). These results were not statistically significant. Furthermore, based on the small sample size, it is difficult to make generalizable conclusions to the broader patient population on the ability of ustekinumab to heal/reduce open and draining fistulas at this time. Of note, the data from the studies that supported approval of Remicade demonstrated fistula response in a maintenance trial with larger numbers of patients who received Remicade at

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5mg/kg at Weeks 0, 2, and 6, and then were randomized to placebo or 5mg/kg in maintenance dosing at Week 14 to begin the maintenance study, where 65% (177/273) of patients with previous fistulas were in fistula response and where then followed with either placebo or maintenance dosing every 8 weeks through Week 46. Fistula response was measured at Week 14 (beginning of maintenance) and Week 54 (end of trial). At Week 54, 38% (33/87) of Remicade-treated patients had no draining fistulas compared with 22% (20/90) of placebo-treated patients (P=0.02).³⁰

Introduction to Pyoderma Gangrenosum in IBD

Pyoderma gangrenosum (PG) is a debilitating skin disease most often associated with inflammatory bowel disease and is a rare cause of peristomal ulceration. In patients with Crohn's disease and PG, up to 82% of patients also have additional perineal complications.³¹ It can be difficult to find effective therapy.

Pyoderma Gangrenosum: Study 3001

Two patients (1007-10137 and 2712-10896), both in the 130 mg ustekinumab dose group, had pyoderma gangrenosum. Both patients experienced resolution of the primary lesion and reduction in the number of lesions during the course of treatment with ustekinumab. Patient 1007-10137 had 2 lesions at baseline, which were reported as resolved by Week 3, however, this patient was reported as again having 2 lesions at Week 8 that were smaller in size than the primary lesions. Patient 2712-10896 went from 1 lesion at baseline to 0 lesions at Week 6. This patient does not have a report of a measurement at Week 8. Given the small sample size of two patients, this reviewer cannot make conclusions on the ability of ustekinumab to treat pyoderma gangrenosum.

Pyoderma Gangrenosum: Study 3002

Four patients (1 in the ustekinumab 130 mg dose group and 3 in the ustekinumab 6 mg/kg dose group) had pyoderma gangrenosum. Resolution of the primary lesion occurred in 1 patient in the ustekinumab 6 mg/kg dose group. Given the small sample size of two patients, this reviewer cannot make conclusions on the ability of ustekinumab to treat pyoderma gangrenosum.

Pyoderma Gangrenosum: Study 3003

Two patients in the primary analysis population of this study had pyoderma gangrenosum, one in the placebo dosing regimen and one in the q12w dosing regimen. Both patients experienced resolution of the primary lesion and reduction in the number of lesions during the course of

³⁰ Remicade label last approved 10/02/2015 accessed 8/25/2016 at

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Search_Drug_Name

³¹ Cairns et al. 1994. Peristomal pyoderma gangrenosum and inflammatory bowel disease. *Arch Surg* 129 (7): 769-72.

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treatment. Given the small sample size of two patients, this reviewer cannot make conclusions on the ability of ustekinumab to treat pyoderma gangrenosum.

Patient Reported Outcome Measures in IBD

In general, while patient reported outcome measures are key components of a clinically meaningful endpoint in inflammatory bowel disease, the quality of life measures reported here (IBDQ and SF-36) have not undergone qualification [REDACTED] (b) (4) and therefore are exploratory [REDACTED] (b) (4).

The inflammatory bowel disease questionnaire (IBDQ) is a health-related quality of life (HRQoL) measure of illness perception on the part of the patient across four domains: bowel, emotional, social, and systemic. Total IBDQ score increases of 16-32 (e.g. ≥ 16) points are believed to be associated with significant QoL improvement. (See Appendix, [Figures] for sample IBDQ).

The SF-36 is a measure of patient reported health status used in health economics across diseases to measure quality of life. It is comprised of two summary measures of physical and mental health, the physical component summary (PCS) and the mental component summary (MCS). The general US population has mean norms of 50 in both the PCS and the MCS scoring component, lower scores indicate impaired health-related quality of life. While this reviewer acknowledges that quality of life scoring in relation to health economics is an important component relevant to the patient and disease process, these measures of quality of life have not been qualified by the FDA [REDACTED] (b) (4) for patients with Crohn's disease and the clinical meaningfulness of this score and its effect on the disease has not been established at this time. (See Appendix, [Figures] for sample of PCS and MCS).

Change from Baseline in the IBDQ Score at Week 8: Study 3001

Mean ($\pm$ SD) IBDQ scores at baseline were similar in the 3 treatment groups: 118.2 ($\pm$ 26.64) and 119.5 ($\pm$ 29.47) in the 6 mg/kg and 130 mg ustekinumab dose groups and 120.0 ($\pm$ 29.27) in the placebo group. At Week 8, the mean ($\pm$ SD) change from baseline in the IBDQ score was greater in the 6 mg/kg and 130 mg ustekinumab dose groups compared with the placebo group (22.1 [28.59] and 18.1 [28.02], respectively, vs 11.9 [26.51]; $p < 0.001$). The mean change in the IBDQ dimension scores at Week 8 was higher in the 6 mg/kg ustekinumab dose group compared with placebo ($p < 0.001$ for all 4 dimensions); in the 130 mg ustekinumab dose group, the mean change was significantly higher for the social ($p = 0.003$) and systemic ($p = 0.010$) dimensions compared with placebo.

A significantly greater proportion of patients in the 6 mg/kg and 130 mg ustekinumab dose groups (54.8% and 46.9%, respectively) had a ≥ 16 -point improvement from baseline in the IBDQ score at Week 8 compared with the placebo dose group (36.5%, $p < 0.001$ and $p = 0.019$,

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respectively).

Change from Baseline in the IBDQ Score at Week 8: Study 3002

Mean ($\pm$ SD) IBDQ scores at baseline were similar in the 3 treatment groups: 122.8 ($\pm$ 31.62) and 118.2 ($\pm$ 30.99) in the 6 mg/kg and 130 mg ustekinumab dose groups and 122.7 ($\pm$ 31.32) in the placebo group. At Week 8, the mean ($\pm$ SD) change from baseline in the IBDQ score was significantly greater in the 6 mg/kg and 130 mg ustekinumab dose groups compared with the placebo dose group (35.3 [$\pm$ 36.05] and 29.1 [$\pm$ 33.82], respectively, vs 11.9 [26.51]; $p < 0.001$). The mean change in the IBDQ dimension scores at Week 8 was significantly higher in the 6 mg/kg and 130 mg ustekinumab dose group compared with placebo ($p < 0.001$) for all 4 dimensions.

A significantly greater proportion of patients in the 6 mg/kg and 130 mg ustekinumab dose groups (141/207 [68.1%] and 122/208 [58.7%], respectively) had a ≥ 16 -point improvement from baseline in the IBDQ score at Week 8 compared with the placebo dose group (85/207 [41.1%], $p < 0.001$) for both ustekinumab dose groups with the 6 mg/kg dose group overall improvement being greater than the 130 mg dose group. This further supports the 6 mg/kg dose over the 130 mg dose. While this reviewer acknowledges that quality of life scoring is an important component to the total care of a patient, the clinical meaningfulness of this score and its effect on the disease is unknown.

Change from Baseline in the IBDQ Score at Week 44: Study 3003

Mean ($\pm$ SD) IBDQ scores at baseline were similar in the 3 treatment regimens: 165.8 ($\pm$ 32.82) and 170.5 ($\pm$ 29.33) in the q12w and q8w dosing regimens and 163.6 ($\pm$ 31.75) in the placebo dosing regimen. At Week 44, the mean change in IBDQ scores from Week 0 of this study was significantly smaller in the ustekinumab q12w and q8w dosing regimens when compared with placebo (-8.9 [$\pm$ 43.08] and -9.9 [$\pm$ 34.83], with p values of $p < 0.001$ and $p = 0.003$, respectively), compared with vs the placebo dosing regimen (-21.5 [$\pm$ 39.26 respectively). All patients entering this maintenance study were in clinical response from receiving ustekinumab in the induction study. The wider downswing in IBDQ scores by those on placebo could represent a loss of improvement obtained while in clinical response from the induction studies over those who remained on ustekinumab of either dose.

At Week 44, a numerically larger proportion of patients in the ustekinumab 90 mg q12w dosing regimen and a significantly larger proportion of patients in the ustekinumab 90 mg q8w dosing regimen had at least a 16-point improvement in IBDQ score (73/119 [61.3%] and 76/128 [67.9%]; p values of $p = 0.140$ and $p = 0.014$ for the ustekinumab 90 mg SC q12w and q8w dosing regimens, respectively) compared with patients in the placebo dosing regimen (60/119 [50.4%]) indicates patients on the q8w dosing regimen experienced a more significant

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improvement to their QoL scores using that IBDQ than those receiving q12w dosing regimen.

Change from Baseline in the PCS and MCS Scores of the SF-36 at Week 8: Study 3001

The mean ($\pm$ SD) PCS scores of the SF-36 at baseline were similar in the 2 treatment dose groups and placebo dose group: 37.15 ($\pm$ 7.094) and 37.77 ($\pm$ 7.117) in the 6 mg/kg and 130 mg ustekinumab dose groups, respectively, and 37.75 ($\pm$ 7.116) in the placebo dose group. (Baseline mean ($\pm$ SD) MCS scores were also similar across the 2 treatment dose groups and placebo dose group: 36.44 ($\pm$ 9.886) and 37.27 ($\pm$ 9.981) in the 6 mg/kg and 130 mg ustekinumab dose groups, respectively, and 37.81 ($\pm$ 10.639) in the placebo dose group. Both PCS and MCS at baseline were below the general US population mean norms of 50, indicating impaired health-related quality of life.

At Week 8, the mean ($\pm$ SD) change from baseline in the PCS score was numerically greater in the 6 mg/kg and 130 mg ustekinumab dose groups (3.57 [$\pm$ 6.750] and 3.21 [$\pm$ 6.434], respectively) compared with the placebo dose group (2.62 [$\pm$ 6.502]). This difference was not statistically significant. Additionally, a 3–5 point shift was derived from a study using the short-lived SF-20 HRQL instrument³², and based the minimal difference magnitude on a statistically significant cross-sectional difference between two very large-sized groups. This difference may not be clinically meaningful in the IBD population.³³

The mean ($\pm$ SD) change from baseline in the MCS score at the same time point was greater in the 6 mg/kg ustekinumab dose group (4.86 [$\pm$ 9.278]; $p=0.006$), but not for the 130 mg ustekinumab dose group (3.34 [$\pm$ 9.410]) compared with the placebo dose group (2.19 [$\pm$ 8.466]). The mean changes from baseline in norm-based scores of the SF-36 scales at Week 8 were numerically greater in both ustekinumab groups compared with placebo, particularly in the 6 mg/kg ustekinumab dose group for the bodily pain, vitality, social functioning, and mental health scales, which were statistically significantly greater than the placebo dose group. Numerically greater proportions of patients in both ustekinumab dose groups had at least a 5-point improvement from baseline in the PCS and MCS scores of the SF-36 at Week 8 compared with the placebo dose group, particularly the MCS score for the 6 mg/kg dose group, which was significantly greater than the placebo dose group (42.2% vs 30.0%, $p=0.007$). These results are considered exploratory for IBD.

³² Stewart A, Greenfield S, Hays R. 1989. "Functional Status and Well-Being of Patients with Chronic Medical Conditions: Results from the Medical Outcomes Study." *Journal of American Medical Association*;262:907–13

³³ Wyrwich, K. W. et al. 2005. A Comparison of Clinically Important Differences in Health-Related Quality of Life for Patients with Chronic Lung Disease, Asthma, or Heart Disease. *Health Services Research*, 40(2), 577–592. <http://doi.org/10.1111/j.1475-6773.2005.00373.x>

Change from Baseline in the PCS and MCS Scores of the SF-36 at Week 8: Study 3002

The mean ($\pm$ SD) PCS scores of the SF-36 at baseline were similar between the 2 treatment groups and the placebo dose group: 38.85 ($\pm$ 7.05) and 38.93 ($\pm$ 7.62) in the 6 mg/kg and 130 mg ustekinumab dose groups, respectively, and 39.70 ($\pm$ 7.19) in the placebo dose group. Baseline mean ($\pm$ SD) MCS scores were also similar in across the 2 treatment dose groups and placebo dose group: 37.94 ($\pm$ 11.15) and 37.20 ($\pm$ 10.81) in the 6 mg/kg and 130 mg ustekinumab dose groups, respectively, and 37.14 ($\pm$ 10.639) in the placebo dose group. Both PCS and MCS at baseline were below the general US population mean norms of 50, indicating impaired health-related quality of life.

At Week 8, the mean change from baseline in the PCS score was significantly greater in both the 6 mg/kg (6.01 [$\pm$ 7.00], $p < 0.001$) and 130 mg ustekinumab dose groups (5.05 [$\pm$ 7.23], $p = 0.002$) compared with the placebo dose group (2.59 [$\pm$ 5.88]). The mean change from baseline in the MCS score at the same timepoint was also significantly greater in both the 6 mg/kg (6.80 [$\pm$ 11.34], $p < 0.001$) and 130 mg ustekinumab dose groups (5.91 [$\pm$ 10.55], $p = 0.006$) compared with the placebo dose group (3.25 [$\pm$ 9.47]).

The mean changes from baseline in norm-based scores of the SF-36 scales at Week 8 were significantly greater in both ustekinumab dose groups compared with placebo.

Change from Baseline in the PCS and MCS Scores of the SF-36 at Week 44: Study 3003

The mean ($\pm$ SD) PCS scores of the SF-36 at baseline were similar between the 2 treatment dosing regimens and the placebo dosing regimen: 47.10 ($\pm$ 8.10) and 47.43 ($\pm$ 7.52) in the q12w and q8w ustekinumab dosing regimens, respectively, and 46.29 ($\pm$ 8.21) in the placebo dosing regimen. Baseline mean ($\pm$ SD) MCS scores were also similar in across the 2 treatment dosing regimens and placebo dosing regimen: 46.38 ($\pm$ 10.66), and 47.25 ($\pm$ 9.91) in the ustekinumab 90 mg q12w and q8w dosing regimens, respectively, and 45.66 ($\pm$ 10.89) in the placebo dosing regimen. Both PCS and MCS at baseline were below the general US population mean norms of 50, indicating impaired health-related quality of life.

At Week 44, the mean change from baseline in the PCS score was significantly smaller for only the q8w dosing regimen (-0.93 [$\pm$ 7.140]; $p = 0.003$) as compared to placebo -3.56 [$\pm$ 9.326]. The mean change from baseline in the MCS score at the same timepoint was also significantly smaller for both the q8w and q12w dosing regimens (-1.89 [$\pm$ 12.679] and -1.67 [$\pm$ 9.759] with p values of $p = 0.014$ and $p = 0.009$, respectively) at Week 44 compared with the placebo dosing regimen (-4.38 [$\pm$ 11.058]).

Again as only clinical responders were randomized into the maintenance study 3003, this could indicate patients in the ustekinumab dosing groups maintained physical and mental health

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improvements gained in their response to induction dosing better than those randomized to placebo. The q8w dosing regimen was the only regimen to meet significance in both the PCS and MCS components and this could indicate this regimens ability to better maintain QoL improvements over the q12w dosing regimen.

Other Secondary Endpoints: Maintenance Study 3003

Clinical Remission: Sustained Clinical Remission

The proportions of patients in sustained clinical remission by CDAI (i.e., clinical remission at Weeks 36, 40, and 44) were significantly greater in the ustekinumab 90 mg q12w (52/129 [40.3%], $p=0.023$) and q8w dosing regimens (59/128 [46.1%], $p<0.001$) compared with the placebo dosing regimen (34/131 [26.0%]). This reviewer notes that while the proportion of patients who met this endpoint in both dosing regimens were greater than placebo, a larger proportion of patients in the q8w dosing regimen sustained clinical remission in the last weeks of the study. This reviewer is concerned that “sustaining” remission only during the last few weeks of the study could include patients who experienced a flare or multiple flares at an earlier time point. This reviewer notes that this does not appear to be a pre-specified efficacy endpoint in the ranked testing order of endpoints and will be considered exploratory.

Clinical Response: Sustained Clinical Response

The proportions of patients in sustained clinical response based on CDAI score (i.e., patients who were in clinical response at Weeks 36, 40, and 44) were significantly greater in the ustekinumab 90 mg q12w and q8w dosing regimens (69/129 [53.5%] and 68/128 [53.1%], respectively) compared with the placebo dosing regimen (50/131 [38.2%]; $p=0.019$ for both the q12w and q8w comparisons). This reviewer notes that this does not appear to be a pre-specified efficacy endpoint in the ranked testing order of endpoints and will be considered exploratory.

CDAI: Change from Baseline

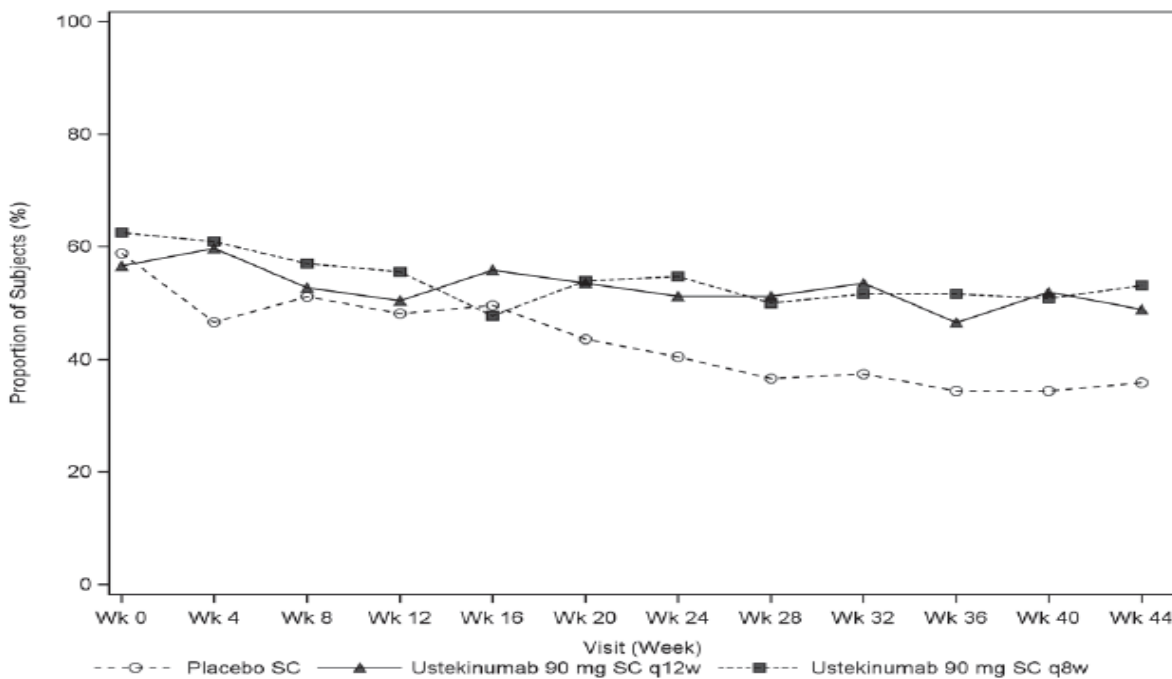
At week 44, the final assessment time point for the maintenance study, the Applicant reports that patients in the ustekinumab dosing regimens had maintained the improvement in CDAI score attained during induction, while patients in the placebo dosing regimen worsened. The median change from baseline in CDAI scores at Week 44 was -10.0 points ($p=0.030$) in the ustekinumab 90 mg q12w dosing regimen, and -6.0 points ($p<0.001$) in the ustekinumab q8w dosing regimen. While the ustekinumab treated patients showed improvement (i.e., decrease in CDAI score) from baseline, the placebo dosing regimen showed an increase in CDAI score of 74.0 points at the week 44 assessment.

Clinical Efficacy Over Time: Remission, Response, and CDAI Scores

Approximately 60% (257/397) of the patients in the primary analysis population were in clinical remission at Week 0 of this maintenance study. The proportions of patients in clinical remission over time were generally similar as compared to placebo in both dose groups (ustekinumab 90 mg q12w and q8w dosing regimens) from week 24 on, though remission rates were lower for the ustekinumab q12w dosing regimen at Weeks 12, 24, and 36, where trough serum levels were measured. The proportion of patients in the placebo group who were in clinical remission decreased over time, with separation from the ustekinumab groups observed by Week 20.

The figure below shows that the ustekinumab q8 week dosing regimen appears to have more patients in remission earlier, whereas the q12w dosing regimen is more similar to placebo for early weeks 8 and 12. The q8w dosing regimen appears to have fewer fluctuations in proportion of patients in remission over time and at trough serum concentration weeks as compared with q12w dosing regimen. This trend could be clinically relevant and may translate to fewer signs and symptom flares for Crohn’s disease patients in the q8w dosing regimen than the q12w dosing regimen.

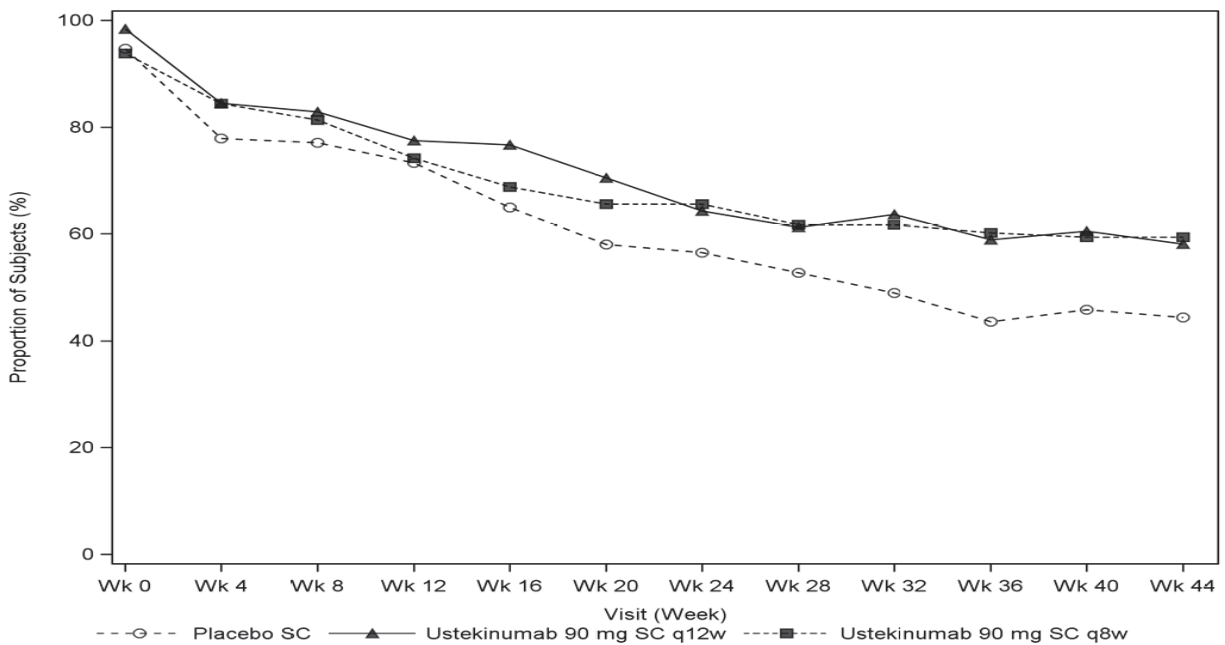
Figure 33: Proportion of Patients in Clinical Remission over Time in Study 3003



Source: The Applicant’s Figure 7: Proportion of patients in clinical remission at each visit through Week 44; randomized patients excluding those enrolled prior to study re-start provided in BLA 761044, CSR 3003, p 93/1619.

The proportions of patients in clinical response at each visit through Week 44 are shown in the figure below. The proportions of patients in clinical response in the ustekinumab groups were comparable for both dosing regimens q12w and q8w from week 32 through week 44, as compared to placebo. The figure below illustrates that over time, the proportion of patients in clinical response decreases over time from Week 0 of this study through Week 28. The proportion of patients in clinical response reaches a plateau at approximately 60% patients in clinical response through Week 44. The proportions of patients in the placebo dosing regimen in clinical response decreased more rapidly than ustekinumab dosing regimens.

Figure 34: Proportion of Patients in Clinical Response over Time in Study 3003



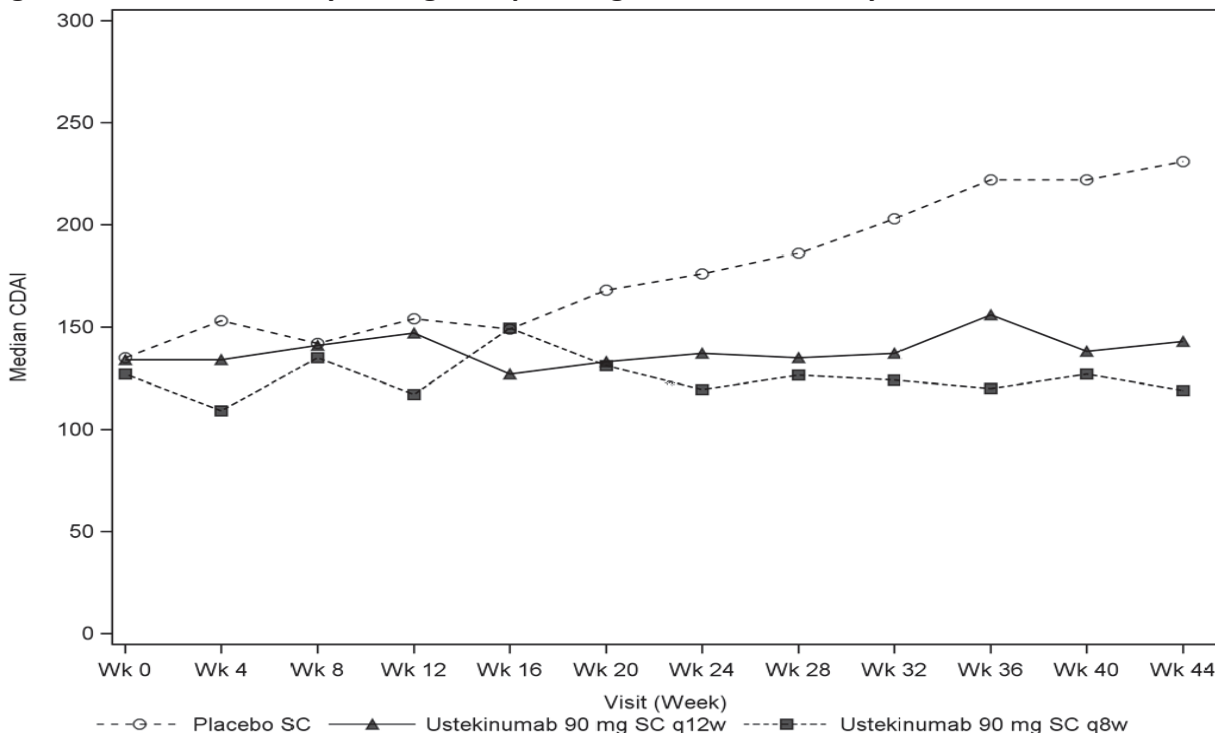
Source: Applicant's BLA 761044 from Appendix GEFRES16: Proportion of patients in clinical response at each visit through Week 44; randomized patients excluding those enrolled prior to study re-start, CSR 3003, p. 964/1619.

At week 0 of the maintenance study, the median CDAI scores were generally consistent across the placebo, ustekinumab 90 mg q12w, and q8w dosing regimens (135.0, 134.0, and 127.0, respectively). Figure 35 below illustrates that from Week 0 to Week 44, median CDAI scores were maintained over time for patients in the ustekinumab dosing regimens while scores increased (i.e., worsened) over time for patients in the placebo dosing regimen. The increase in CDAI score from baseline was notable after Week 16, with clear separation from the ustekinumab dosing regimens by Week 20. The median CDAI level in the q8w dosing regimen was consistently lower (i.e., improvement in CDAI score) than in the q12 w dosing regimen from CDER Clinical Review Template 2015 Edition

Version date: November 5, 2015 for initial rollout (NME/original BLA reviews)

week 24 on, suggesting that the q8w maintenance dosing regimen may be favorable for maintaining remission as compared to the q12w dosing regimen.

Figure 35: Median CDAI by Dosing Group through Week 44 in Study 3003



Source: Applicant's BLA 761044 from Appendix GEFCDAI06: Line plot of median CDAI through Week 44; randomized patients excluding those enrolled prior to study re-start, CSR 3003, p. 979/1619.

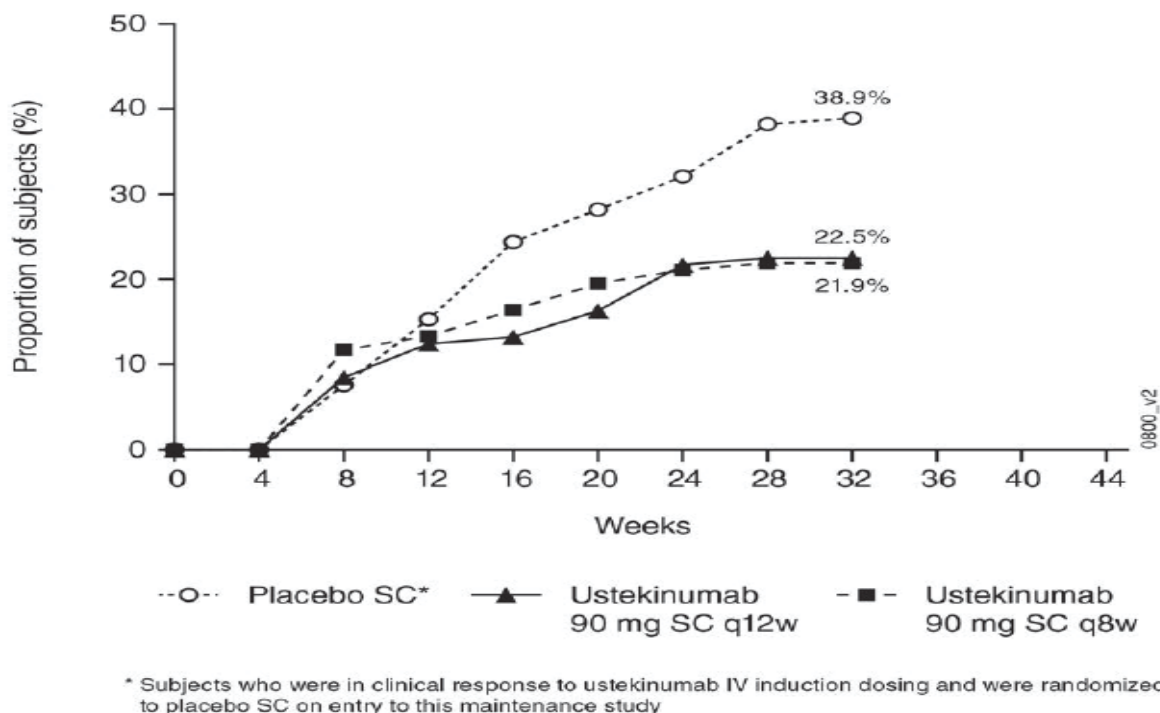
Clinical Efficacy and Dose Adjustment

Patients who achieved clinical response with ustekinumab at Week 8 in CRD3001 or CRD3002 (i.e., the primary population) and who subsequently had a loss of clinical response (LOR)³⁴ at any scheduled visit between Week 8 and Week 32 of this maintenance study were eligible for dose adjustment. Eligible patients randomized to the ustekinumab q12w dosing regimen had a dose adjustment to a q8w dosing regimen, while patients randomized to the ustekinumab q8w dosing regimen meeting LOR criteria remained on the q8w dosing regimen to maintain the blind. Patients in the placebo group meeting LOR criteria had a dose adjustment to the ustekinumab 90 mg q8w dosing regimen. Patients who had a dose adjustment were assessed

³⁴ defined as a CDAI score ≥ 220 points AND a ≥ 100 point increase from the Week 0 CDAI score (ie, Week 8 in the induction study 3001 or 3002), which was assessed between Week 8 and Week 32 in IVRS

16 weeks after the visit where LOR criteria were met to determine whether any benefit was achieved from the dose adjustment. The figure below shows the number of patients meeting the loss of response criteria for dose adjustment over time.

Figure 36: Proportion of Patients Meeting LOR Criteria for Dose Adjustment by Arm Over Time



Source: Applicant BLA 761044 entitled Figure 8: Cumulative proportion of patients in the primary population meeting loss of response criteria for dose adjustment over time; randomized population in study CNTO1275CRD3003, CSR 3003, p 95/1619.

Figure 36 above shows the similar numbers of patients in each ustekinumab arm who met LOR criteria and an increased number of patients in the placebo arm.

Clinical Efficacy in Patients Who Underwent Dose Adjustment

The table below describes the results for patients who met LOR criteria. This includes patients in the placebo and q12w dosing regimen s who dose adjusted to the q8w dosing regimen, and patients treated with q8w dosing who remained in q8w dosing. Patients were assessed for clinical remission or response 16 weeks after dose adjustment.

Table 13: Clinical Remission Rate and Change in CDAI Score for Patients Who Met Loss of Response (LOR) Criteria With and Without Dose Adjustment in Study 3003

	Clinical Remission n (%)	Regained Clinical Response n (%)	Median Change in CDAI
Placebo→ ustekinumab 90 mg q8w (N=51)	20 (39.2%)	36 (70.6%)	-121
ustekinumab 90 mg q12w→ustekinumab 90 mg q8w (N=29)	12 (41.4%)	29 (55.2%)	-141.0
ustekinumab 90 mg q8w→ustekinumab 90 mg q8w (N=28)	9 (32.1%)	13 (46.4%)	-78.5

Source: Reviewer created table from data in BLA 761044 from Appendix TEFCREMO4, TEFCRES04, and TEFCDAI04 pp172, 241, 291/161.

The above table shows the proportion of patients who adjusted from the q12w to q8w dosing regimen and attained clinical remission and the proportion of patients who regained clinical response 16 weeks after dose adjustment. Patients who met LOR criteria without dose adjustment (i.e., q8w→q8w) also achieved remission and response, although at slightly lower rates 16 weeks later. In addition, the median change in the CDAI score was almost twice as great in the LOR with dose adjustment groups as compared with the LOR without dose adjustment group. Based on limited sample size, the placebo group data seem to indicate that in the subset of patients who responded to the ustekinumab IV induction dose but delayed initiation of the SC maintenance therapy, benefit can be regained without the need for an additional IV induction dose.

Considering **Table 13** above, there are many patients who improved after LOR without receiving a dose adjustment. These analyses were limited by small numbers and are descriptive data as opposed to randomized data. Overall, the q8w dosing regimen appears favorable as compared to the q12 dosing regimen based on achieving statistical significance on clinically meaningful endpoints and fewer Crohn’s disease-related AES, suggesting lower efficacy. Given that patients are able to regain response while maintaining the q8 dose regimen and for the reasons previously described in this review, this reviewer concludes that these results do not change the overall conclusion of the q8w dosing regimen being selected for labeling as (b) (4) proposed maintenance dose regimen.

Additional Corticosteroid Endpoints

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Corticosteroid Free Remission

The proportion of all patients in the primary population (regardless of concomitant corticosteroid use at baseline) who were in clinical remission and not receiving corticosteroids for at least 90 days prior to Week 44 were greater in the ustekinumab 90 mg q12w (53/129 [41.1%], $p=0.046$) and q8w groups (58/128 [45.3%], $p=0.005$) compared with the placebo group (38/131 [29.0%]). The proportion of patients in clinical remission and not receiving steroids for at least 30 days prior week 44 were also greater in the ustekinumab groups compared with the placebo. This reviewer is unclear as to why all patients rather than just those with use of concomitant steroids at baseline were included in this analysis. This reviewer believes inclusion of the entire study population likely confounds these results. The proportion of patients who met criteria for corticosteroid-free remission was greater for the patients treated with q8 week dosing as compared to the q12w dosing regimen.

Corticosteroid Free Response

The proportion of all patients in the primary population (regardless of concomitant corticosteroid use at baseline) who were in clinical response and not receiving corticosteroids at Week 44 were significantly greater in the ustekinumab 90 mg q12w (66/129 [51.2%]), $p=0.024$) and q8w dosing regimens (65/128 [50.8%], $p=0.026$) compared with patients in the placebo dosing regimen (48/131 [36.6%]). Again, this reviewer notes the inclusion of the entire study population rather than just those on corticosteroids at baseline may confound the results of this analysis. There appears to be no advantage for using the q8w vs q12w dosing regimen for corticosteroid free response.

Elimination of Corticosteroids

One hundred eighty-one out of 397 (45.6%) patients in the primary analysis population were receiving concomitant corticosteroids at Week 0 of this maintenance study. Results from these patients are in the table below:

Table 14: Results of Patients on Corticosteroids (CS) at Baseline of the Maintenance Study

	Placebo N=58 n (%)	ustekinumab q12w N=57 n (%)	ustekinumab q8w N=59 n (%)
Clinical Remission at Week 44 (off steroids)	9 (15.5%)	17 (29.8%)	18 (30.5%)
Clinical Response at Week 44 (off steroids)	11 (19.0%)	20 (35.1%)	19 (32.2%)
Elimination of CS Use by Week 44	16 (27.6%)	24 (42.1%)	21 (35.6%)
Number of Days Without CS Use Prior to Week 44 (median)	49.5	66	25
Median Decrease in Average Daily Prednisolone Equivalent CS Dose	-10.0 mg/day	-5.0 mg/day	-10.0 mg/day

Source: Reviewer table created with Applicant data from BLA 761044 CSR 3003, attachments TEFCREM06B, TEFCREM06C, TEFCRES06, TEFCREM07 p 242-296/1619.

The proportion of patients who entered the study on CS at baseline and who were in clinical remission and off of steroids at week 44 were numerically greater than placebo for each of the two ustekinumab dosing regimens. The proportion of patients who entered the study on CS at baseline and who were in clinical response and off of steroids at week 44 were numerically greater than placebo for both dosing regimens. The q8w and q12w dosing regimens appeared to perform similarly for this endpoint for both clinical remission and clinical response.

Patients on Baseline Corticosteroids

The proportion of patients who entered the study on baseline CS who were able to eliminate CS use by week 44 were numerically greater in both ustekinumab dose groups as compared to placebo. The q12w dosing regimen appeared to perform slightly better than the q8w dosing regimen. When the timeframe of 90 days prior to week 44 was employed, the q12w dosing regimen (23/57 [40.4%]; p=0.03) and the q8w dosing regimen (20/59 [33.9%]; p=0.18) had higher proportions of CS-free patients who had eliminated CS use when compared to placebo (13/58 [22.4%]); however only the q12w dosing regimen was statistically significant. At Week 44, the median decrease in the average daily prednisone equivalent dose was equal for the placebo dosing regimen (-10.0 mg/day) and the q8w dosing regimen (-10.0 mg/day) and improved (but not significantly) for the q12 dosing regimen (-12.0 mg/day). In general,

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ustekinumab administered at both q8w and q12w dosing regimens improved the ability of patients who were on CS at baseline to come off of CS and achieve remission and response. In this subset of patients on baseline CS, the q12w dosing regimen did seem to improve the ability of previously CS dependent patients to be off of steroids 90 days prior to the study endpoint. However, this is a limited sample size and by week 44 the q8 and q12 dosing regimens performed equally in allowing patients to eliminate CS.

Clinical Efficacy by Induction Study/Induction Dose

For the following analyses, the reader is reminded that the patient population enrolled into study 3001 was patients who previously failed TNF alpha antagonist therapy and study 3002 was patients who had previously failed conventional therapy. For specific study inclusion criteria, see Section 6.1.1, Study Design.

Clinical Remission at Week 44 By Induction Study (prior failed therapy)

The proportion of patients in clinical remission at Week 44 of the maintenance study were numerically greater for both ustekinumab q8w and q12w dosing regimens compared with placebo regardless of induction study and reached statistical significance for the ustekinumab 90 mg q8w dosing regimen (45/72 [62.5%]; $p=0.02$) in study 3002 (i.e., patients who had failed conventional therapy but had not failed a TNF alpha antagonist therapy). Based on the significant result from the q8w dosing regimen in study 3002, this reviewer concludes that the q8w dosing regimen is preferable to the q12 week dosing regimen to achieve remission in the patient population who failed conventional therapy but had not yet failed or are not yet intolerant to TNF alpha antagonist therapy.

Throughout study 3003, the proportions of patients in remission from study 3001 (i.e., patients who failed prior TNF alpha antagonist therapy) decreased over time as compared to the proportion of patients in study 3002 (i.e. patients who failed conventional therapy but not TNF alpha antagonist therapy). At Week 0 of study 3003, 46/72 (64%) STELARA treated patients who failed immunomodulator therapy or corticosteroids (study 3002) and 45/72 (63%) patients were in clinical remission at Week 44 as compared to Week 0 of study 3003 where the proportion of treated patients who failed or were intolerant to TNF alpha antagonist therapy (study 3001) in clinical remission was 34/56 (61%) and at Week 44 had decreased to 23/56 (41%) patients in clinical remission. This demonstrated that patients who failed prior TNF alpha antagonist therapy lost remission over time as compared to patients who had only failed more conventional therapy.

The proportions for clinical response were similar to the proportions for clinical remission described above. The data showed clinical response was greater for both ustekinumab dosing regimens compared with the placebo dosing regimen regardless of induction study and reached statistical significance for the ustekinumab 90 mg q8w dosing regimen (49/72 [68.1%];

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p=0.03) for the patient population enrolled from induction study 3001. These results were also numerically greater for ustekinumab as compared to placebo in the TNF alpha naïve sub-population in study 3002. Based on the significant result in study 3001, this reviewer concludes that the q8w dosing regimen is preferable to the q12 week dosing regimen to achieve clinical response in those who have failed to TNF alpha antagonist therapy.

For patients from induction study 3001 who entered the maintenance study, the median change from baseline in CDAI score at Week 44 was numerically lower in both the ustekinumab 90 mg q12w and q8w dosing regimens (39.0 and 28.5, respectively) compared with the placebo group (112.0). The change from baseline in CDAI scores at Week 44 for patients in study 3002 indicated an improvement for patients in the ustekinumab 90 mg q12w dosing regimen (-18.5; p=0.06) and a significant improvement for the q8w dosing regimen (-21.0; p=0.01) against placebo (26.5). This improvement, including significance for the q8w dosing regimen was mirrored in the TNF-alpha naïve sub-population of Study 3002. Once again, it appears q8w dosing regimen is the preferred maintenance regimen for improving baseline CDAI from placebo for the study population of 3002.

By Induction Dose

Among 388 patients in the primary analysis population, 177 (45.6%) received ustekinumab 130 mg IV induction dose and 211 (54.4%) received ustekinumab 6 mg/kg IV induction dose. For patients receiving ustekinumab 130 mg IV induction dose, the proportion of patients in clinical response at Week 44 were 27/60 (45.0%), 37/59 (62.7%; p=0.07), and 37/58 (63.8%; p<0.05) for the placebo, ustekinumab 90 mg q12w, and q8w dosing regimens, respectively. For patients receiving 6 mg/kg IV induction dose, the proportions of patients in clinical response at Week 44 were 31/71 (43.7%), 38/70 (54.3%; p=0.21), and 39/70 (55.7% p=0.16) for the placebo, ustekinumab 90 mg q12w, and q8w dosing regimens, respectively. While all doses are numerically better than placebo, the only induction-maintenance dose regimen combination that achieved statistical significance over placebo at week 44 of maintenance the 130 mg induction dose followed by q8w dosing regimen.

Clinical response, while a relevant endpoint, is not as meaningful as clinical remission. Clinical remission is reflective of quiescent disease. Achieving and maintaining remission reduces the morbidity and mortality of Crohn's disease, achieving clinical response without full remission does not.

The proportion of patients in clinical remission receiving ustekinumab 130 mg IV induction dose at Week 44 were 23/60 (38.3%), 31/59 (52.5%; p=0.14), and 33/58 (56.9%; p=0.04) for the placebo, ustekinumab 90 mg q12w, and q8w dosing regimens, respectively. For patients receiving the 6 mg/kg IV induction dose, the proportions of patients in clinical remission at Week 44 were 24/71 (33.8%), 32/70 (45.7%; p=0.15), and 35/70 (50.0% p=0.05) for the placebo, ustekinumab 90 mg q12w, and q8w dosing regimens, respectively. While all doses are

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numerically better than placebo, the only induction-maintenance dose regimen combination that achieved statistical significance over placebo at Week 44 of maintenance was the 130 mg induction dose followed by q8w dosing although the 6 mg/kg dose followed by a q8 week dosing regimen was close to significant.

The change from baseline in the CDAI score to Week 44 of maintenance at each visit was evaluated separately by induction dose group (i.e., 130 mg or 6 mg/kg). At Week 0 of this maintenance study, the placebo, ustekinumab 90 mg q12w, and q8w dosing regimens showed similar median improvement in the CDAI scores from Week 0 of an induction study. At Week 44, patients in the 130 mg IV induction group who received ustekinumab 90 mg q12w or q8w dosing regimens had a significantly greater median decrease in CDAI scores (-165.0; p=0.02 and -185.0; p=0.001, respectively) from Week 0 of the induction study compared with the placebo group. At Week 44, patients in the ustekinumab 6 mg/kg IV induction dose group who received ustekinumab 90 mg q8w dosing regimen (-162.5; p=0.04) had a significantly greater median decrease in CDAI score from Week 0 of an induction study compared with placebo (-121.0) and the 90 mg q12w dosing regimen (-123.0; p=0.08) did not differentiate from placebo for this induction dose. The Applicant has proposed the 6 mg/kg induction dose and it is supported by induction study data. Additionally, the q8w maintenance dosing regimen appears to have greater effect on reducing the CDAI scores of those receiving this induction dose.

Dose/Dose Response

As noted in the Section 6.1.1, Study Design, patients in studies 3001 and 3002 were divided into 3 dose groups with 2 active dose arms of ustekinumab (130 mg IV and 6 mg/kg weight- tiered dose of 130 mg, 260mg, or 390 mg IV). As this was a single induction dose, dose adjustments after randomization did not occur. Study 3001 achieved statistical significance for both induction doses on all of the primary and key secondary endpoints. However, in other secondary endpoints including CDAI response over time and CRP reduction, each showed the weight-tiered 6 mg/kg dose had a more significant impact on these outcome measures than the 130 mg dose. Therefore, this reviewer concludes that selection of the 6 mg/kg dose as the single induction dose is justified based on the results of the efficacy measures evaluated.

As noted in the Section 6.1.1, Study Design, patients in study 3003 were divided into 3 dosing groups with 2 active dosing regimens of ustekinumab (90mg SC q12w and 90mg SC q8w). While both dosing regimens appear to result in clinical remission, over time, the maintenance dosing regimen of 90mg SC q12 weeks does not achieve statistical significance for the clinically important endpoint of sustaining clinical remission achieved at the end of induction through the end of maintenance whereas the q8w dosing regimen meets this clinically important key secondary endpoint. Additionally, the proportion of patients discontinuing the study for adverse events was double in the q12w dosing arm than the q8w dosing arm, most of which

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were Crohn's related which further supports concerns of inferior clinical benefit. Therefore, at this time this reviewer does not conclude that there appears to be comparable long term benefit for ustekinumab at both the q12w and q8w dosing regimens.

Durability of Response

Studies 3001 and 3002 were single dose studies, however, the Applicant investigated durability as one of the key secondary endpoints discussed above Section 6.1.2, Study Results, maintenance study 3003 Other Secondary Endpoints for a discussion of the results. (e.g., Clinical Remission at Week 44 Among Patients in Clinical Remission to Ustekinumab at Week 0, and other secondary endpoints sustained clinical remission over time).

Persistence of Effect

Studies 3001 and 3002 did not investigate persistence of effect over time as the treatment was not stopped or withheld, so data are not available to make conclusions on the persistence of effect. Although follow up from these studies occurred throughout week 20, patients from studies 3001 and 3002 were enrolled and randomized into the maintenance study, study 3003, where they continued to be treated with ustekinumab for a total of 52 weeks. These endpoints for study 3003 are discussed in multiple other endpoints above in Section 6.1.2, Other Endpoints.

Additional Analyses Conducted on the Individual Trial

Ustekinumab Endoscopic and Histology Substudy

The Applicant conducted an additional substudy entitled "Ustekinumab Endoscopy Substudy", of which the primary objectives were to evaluate:

- The efficacy of ustekinumab compared with placebo to induce endoscopic healing of the mucosa defined by: changes in the Simplified Endoscopic Disease Severity Score for Crohn's Disease (SES-CD) score and detection of presence/absence of mucosal ulceration supported by exploratory histologic evaluation; specifically, "mucosal healing" was defined as the complete absence of any mucosal ulcerations among patients who presented with ulceration in at least 1 ileocolonic segment at induction baseline.
- The benefit of continued ustekinumab maintenance compared with placebo on the achievement of endoscopic healing of the mucosa among patients who had a clinical response to ustekinumab induction.

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The Applicant defined endoscopic healing using endoscopic and histologic evaluations taken at timepoints at Week 8 of the two induction studies (studies 3001 and 3002) and Week 44 of the maintenance study (study 3003). It is important to note that during a pre-BLA meeting the Division communicated to the Applicant that their “definition of mucosal healing, in conjunction with available histologic data, [redacted] (b) (6) [redacted] [would] be a review issue.”³⁵

Methods

Patients from participating sites within studies 3001, 3002, and 3003 were given the option to participate in the 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).

Endoscopic Assessment

Ileocolonoscopy assessments were conducted in 5 segments: ileum, right colon, transverse colon, left colon, and rectum. A single reader at a central facility evaluated and scored all video endoscopies in a blinded manner. Two measures were used for the Applicant’s evaluation of endoscopic healing of the mucosa: changes in the Simplified Endoscopic Disease Severity Score for Crohn’s Disease (SES-CD) score^{36,37} and detection of presence/absence of mucosal ulceration. Clinically meaningful endpoints have been published in the literature for the SES-CD, namely³⁸:

- Endoscopic remission is consistent with an SES-CD score of 0-2, and
- Endoscopic response is consistent with a >50% decrease in SES-CD score

Patients with evaluable endoscopy data (i.e., at least 1 ileocolonic segment evaluated) were eligible for inclusion in the evaluation of induction and maintenance endpoints if they had either SES-CD score ≥ 3 at baseline excluding the contribution from narrowing (for evaluation of SES-CD based endpoints) or ulceration in any segment at baseline (for evaluation of mucosal healing based endpoints). SES-CD scoring can be found in the Appendix: Figures.

The endoscopy substudy was considered to be a separate experiment within the phase 3 development program for ustekinumab in Crohn’s disease. As such, control of Type 1 error was

³⁵ IND 011632 Pre-sBLA Meeting as teleconference: 5/12/2015.

³⁶ Daperno et al. 2004. Development and validation of a new, simplified endoscopic activity score for Crohn’s disease: the SES-CD. *Gastrointestinal Endoscopy* 60 (4): 505-512.

³⁷ The SES-CD is an endoscopic scoring algorithm comprised of a total of 17 points scored in 4 endoscopic findings over 5 sections of the colon. See Appendix for categories and grading.

³⁸ Vuitton et al. 2015. IOIBD technical review on endoscopic indices for Crohn’s disease trials. *Gut* 0: 1-9.

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applied independently from the Type 1 error control in the individual induction and maintenance studies. A hierarchical multiple testing procedure was used to strongly control the overall Type 1 error rate over the primary and major secondary endpoints within this substudy. The primary analysis population for endoscopy endpoints in induction was the integrated induction population from the study 3001 and 3002 induction studies, and data for ustekinumab were pooled across the induction dose groups. The primary analysis population for the endoscopic substudy of the maintenance study included the randomized population for the maintenance study, study 3003. The randomized population included ustekinumab induction responders who were randomized to ustekinumab 90 mg SC every 12 weeks (q12w), ustekinumab 90 mg SC every 8 weeks (q8w), or a placebo maintenance dosing regimen. The data for ustekinumab were pooled across maintenance dose groups. Sensitivity analyses were performed to evaluate the impact of different rules for missing data. Consistency of results was evaluated by subgroup analyses (by induction study 3001 or 3002, by induction dose 130 mg IV or 6 mg/kg IV, and by maintenance dosing regimen [90 mg SC q12w or 90 mg SC q8w]).

Histologic Assessment

In addition, biopsies were collected to support an exploratory endpoint for histologic evaluation. A single reader also scored all histologic evaluation. Histology was measured by a modified Global Histology Activity Score. The original GHAS assigns scores for 8 components: epithelial damage, architectural changes, infiltration of mononuclear cells into the lamina propria, and polymorphonuclear cells in the lamina propria (all scored 0-2); number of biopsy specimens affected (anticipating 6 biopsies per anatomic area) and number of polymorphonuclear cells in the epithelium (both scored 0-3). Lastly, the presence of erosions/ulcers and presence of granulomas are scored 1 point each for yes and 0 points for no. Two of the GHAS components were excluded: granulomas (due to their rarity and potentially sporadic nature), and the number of biopsies affected (because only up to 2 biopsies were taken from each anatomic region). At each timepoint, up to 2 biopsies per anatomic region were scored separately, and the higher scored biopsy was used as the final score for each anatomic region. Finally, an overall total score was derived based on the sum of the 3 anatomic regional scores at each timepoint. The Division consulted the Center for Devices and Radiological Health (CDRH) to comment on the selected scale and findings of the histological assessment. This consult was still pending at the time of this review. Refer to the Appendix: Figures section for a copy of the GHAS.

To evaluate whether the observed changes in endoscopic disease activity, as evaluated by the SES-CD endpoints, were reflective of changes in the underlying histologic disease activity, changes in GHAS from baseline at Week 8 of induction or Week 44 of maintenance were evaluated separately within the ustekinumab group and within the placebo group, by using paired t-tests. The treatment differences between the ustekinumab and placebo groups were also explored among patients who had histology data at both induction baseline and the post-baseline assessment time point (e.g., Week 8 of induction, Week 44 of maintenance) by using

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Student's t-tests. Three of the populations that were used for the analyses of SES-CD endpoints were used for the exploratory histologic analyses: the induction population, the randomized maintenance population, and the pooled randomized and nonrandomized maintenance population. For the induction population, subgroup analyses by induction study and by induction dose were also conducted. For the pooled randomized and nonrandomized maintenance population, subgroup analysis by maintenance dose was also conducted. To further evaluate the effect of maintenance therapy, prespecified analyses of the nonrandomized maintenance population, as well as exploratory post-hoc evaluations using pooled data from the randomized and the nonrandomized maintenance populations, were also conducted.

The Applicant presented pooled ustekinumab dose data to determine the significance of the primary and secondary endpoints. As per the Division's recommendations in the meeting minutes for the meeting held on May 12, 2015 and an Advice Letter dated July 2, 2015, the endoscopic data should have been analyzed separately in each trial first before any statistical inference was made for the pooled data from both trials. In addition, as stated in the July 2, 2015 Advice Letter, (b) (4) the clinical meaningfulness of the results. Based on the Applicant's results for the pooled data from trials and doses, a change in SES-CD score of 3 has not been established as a clinically meaningful change. Therefore, all the analyses for endoscopic substudy can only treated as exploratory.

Study Population and Demographics

Endoscopic Induction Study

The median age was 39 years and 201/252 (83.3%) patients were white. The demographic characteristics of patients randomized to placebo or ustekinumab induction were generally comparable, except for a lower proportion of women in the placebo group than in the ustekinumab group (46/97 [47.4%] and 87/155 [56.1%], respectively). Overall, the demographic characteristics of patients in the endoscopy substudy induction population were similar to those of the overall induction study population. This reviewer concludes that none of the small differences in demographics are likely to impact the results of the study.

In the endoscopy substudy induction population, the median duration of disease at baseline was 8.5 years, the median CDAI score was 311.0 points, the median CRP concentration was 8.35 mg/L, and the median IBDQ score was 116.5 points. Inclusion criteria for study 3001 and study 3002 required the presence of Crohn's disease activity in the ileum or colon, confirmed at any time in the past by radiography, histology, and/or endoscopy. Isolated ileal disease was present in 48/251 (19.1%) patients, 45 (17.9%) patients had only colonic involvement, and 158 (62.9%) patients had involvement in both areas. A total of 80/251 (31.9%) patients had perianal disease and 35/251 (13.9%) patients reported proximal gastrointestinal tract involvement. A stricturing

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phenotype was common: 91/252 (36.1%) patients had a current or prior stricture and 18/252 (7.1%) patients had some degree of stricture present at baseline. Disease characteristics of patients randomized to placebo or ustekinumab (130 mg or 6 mg/kg) induction dose were generally comparable, except for the following:

- a lower median CDAI score (301.0 and 318.0, respectively),
- lower median CRP concentration (7.49 mg/L and 9.28 mg/L, respectively—although the means with their large SDs reflect less of a difference 16.12 [24.91] and 19.87 [26.90] respectively), and
- greater proportion of patients with extra-intestinal manifestations were enrolled in the placebo group (60/97 [61.9%]) as compared to the ustekinumab groups (78/155 [50.3%]).

This reviewer concludes that these differences do not reflect a larger disease burden on the placebo group as a 17 point decrease in CDAI is not meaningful³⁹, the CRP mean differences have large, overlapping standard deviations, and 40% of those with Crohn's disease have an extraintestinal manifestation, it is not uncommon.⁴⁰ Concomitant medications for Crohn's disease at induction baseline are summarized in Table 15 below for the endoscopy substudy induction population.

³⁹ Thia et al. 2008. Defining the Optimal Response Criteria for the Crohn's Disease Activity Index for Induction Studies in Patients With Mildly to Moderately Active Crohn's Disease. *American J of Gastroenterology* 103(3123-3131).

⁴⁰ Aghazadeh et al. 2005. Inflammatory bowel disease in Iran: a review of 457 cases. *J Gastroenterol Hepatol* Nov; 20(11):1691-5.

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Table 15: Summary of Concomitant Medications for Crohn’s Disease Patients in the Endoscopy Substudy

	Placebo	Ustekinumab ^a	Total
Analysis set: Randomized subjects with eligible SES-CD score or ulcerations at baseline from the CNTO1275CRD3001 and CNTO1275CRD3002 studies	97	155	252
Subjects with 1 or more concomitant medications	72 (74.2%)	113 (72.9%)	185 (73.4%)
Immunomodulatory drugs	31 (32.0%)	45 (29.0%)	76 (30.2%)
6-MP/AZA	25 (25.8%)	36 (23.2%)	61 (24.2%)
MTX	6 (6.2%)	9 (5.8%)	15 (6.0%)
Aminosalicylates	33 (34.0%)	45 (29.0%)	78 (31.0%)
Antibiotics	6 (6.2%)	12 (7.7%)	18 (7.1%)
Corticosteroids (including budesonide)	40 (41.2%)	63 (40.6%)	103 (40.9%)
Corticosteroids P.Eq dose(excluding budesonide)(mg/day)			
N	30	52	82
Mean (SD)	17.1 (9.42)	19.5 (9.83)	18.6 (9.70)
Median	15.0	20.0	20.0
IQ range	(10.0; 20.0)	(10.0; 27.5)	(10.0; 25.0)
Range	(5; 40)	(5; 40)	(5; 40)
Budesonide dose (mg/day)			
N	10	11	21
Mean (SD)	7.2 (2.53)	7.4 (2.06)	7.3 (2.24)
Median	9.0	9.0	9.0
IQ range	(6.0; 9.0)	(6.0; 9.0)	(6.0; 9.0)
Range	(3; 9)	(3; 9)	(3; 9)

^a Ustekinumab 130 mg and tiered ustekinumab doses approximating 6 mg/kg combined.

Source: Applicant table from BLA 761044, Substudy Report: Ustekinumab Endoscopy Substudy for Phase 3 Crohn’s Disease Studies, p 34/152.

Most 185/252 (73.4%) of the patients were receiving at least 1 concomitant medication for Crohn’s disease. The most commonly used medications were corticosteroids including budesonide 103/252(40.9%), aminosaliclylates 78/252(31.0%), and immunomodulators 76/252 (30.2%). Among patients who were receiving corticosteroids (excluding budesonide), the median dose (prednisone equivalent) was 20 mg/day. A small proportion of patients 18/252 (7.1%) received antibiotics. The proportions of patients receiving each class of Crohn’s disease medication were generally comparable between patients randomized to placebo or ustekinumab induction.

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Endoscopy information at induction baseline:

- Nearly 90% of patients with evaluable endoscopy data had eligible SES-CD scores and ulceration status at baseline.
- The mean SES-CD score at baseline was 13.5 points, and 80% of patients had moderate or severe endoscopic disease severity.
 - Ulcerations were observed in the ileum only for 27.4% of patients,
 - In the colon only for 33.3%
 - In both ileum and colon for 39.3%

Overall, endoscopic disease activity was generally comparable between patients randomized to placebo or ustekinumab induction except for the following:

- The mean SES-CD score at baseline was numerically higher in the ustekinumab group (14.2 points) compared with the placebo group (12.3 points), this suggests greater endoscopic disease activity among patients randomized to ustekinumab induction. However, as the primary endpoint was mean change from baseline in SES-CD score, this difference should not have had an effect on the primary endpoint.
- The proportion of patients with moderate or severe endoscopic disease severity, as measured by the SES-CD score, was greater in the ustekinumab group (132/155 (85.1%) patients) than in the placebo group (70/97 (72.1%) patients). This appeared to be largely a factor of a lower proportion of patients randomized to placebo as compared to ustekinumab, particularly from study 3002.

Endoscopic Maintenance Study

The median age was 37.5 years and 53/70 (75.7%) patients were white. There were more female patients overall (41/70 (58.6%) female patients), which appeared to be driven by a higher proportion of females randomized to the ustekinumab arm (29/46 [63%] female) whereas the placebo arm included an equal number of females as males (12/24 [50%] female). This reviewer concludes that the small sample size of each treatment group limits the ability to make generalizable conclusions based on differences in demographics.

Disease characteristics of patients randomized to placebo or ustekinumab maintenance were generally comparable. Differences in baseline disease activity between the 2 treatment groups were as follows:

- A greater proportion of patients in the placebo group (12/24 [50.0%]) compared with the ustekinumab group (7/46 [15.2%]) had current or past strictures. This reviewer notes that strictures generally predict more aggressive disease and this skewing may have impacted endpoints down the line in favor of ustekinumab.
- Median CRP was lower in the placebo group compared with the ustekinumab group at baseline (9.82 mg/L vs 12.70 mg/L, respectively). The difference in mean CRP values

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were more pronounced as the placebo group mean CRP was 12.94 mg/L (± 11.66) and the mean CRP in the ustekinumab group was 25.85 mg/L (± 30.55). However, the standard deviations are large, this reviewer concludes that the median CRP may be more reflective of disease burden, possibly being higher in the ustekinumab group. Although this reviewer concludes that a difference of 3 mg/L in the median CRP values between the placebo and ustekinumab groups is not a clinically meaningful difference that would affect the results based on endpoints evaluating CRP.

In general, the maintenance endoscopic study enrolled more patients with ileocolonic disease (49/70 [70%]) as compared to the proportion of patients with than ileal disease (8/70 [11.4%]) or colonic disease (13/70 [18.6%]) which is in line with the prevalence of ileocolonic disease in Crohn's (most common).

Concomitant medication usage was generally comparable between patients randomized to placebo or ustekinumab maintenance. Additionally, endoscopic disease severity at induction baseline was generally comparable between patients randomized to placebo or ustekinumab in this maintenance endoscopic substudy.

Endpoints

Induction Studies (3001 and 3002)

Overall, 334/1409 (23.7%) patients in the induction studies were enrolled in the endoscopy substudy, including 142/741 (19.1%) patients from study 3001 and 192/628 (30.6%) patients in study 3002. Two-hundred fifty-two patients from both induction study population met eligibility criteria (SES-CD score ≥ 3 , [excluding the contribution of the narrowing component score], or presence of ulceration) for the induction endoscopic substudy. A greater proportion of patients in the placebo group 97/104 (93.3%) than in the ustekinumab group 155/185 (83.8%) met the eligibility criteria. The proportion of evaluable patients who met eligibility criteria was similar between the induction studies (89.9% from study 3001 and 85.3% from study 3002)

Maintenance Study (3003)

Overall, 95/397 patients in the primary randomized population of the maintenance study had enrolled in the endoscopy substudy using their baseline at induction. Seventy patients from the randomized maintenance population met eligibility criteria for the randomized maintenance endoscopic study. Eighty-three out of 95 (90%) patients in the endoscopy substudy randomized maintenance population had evaluable endoscopy data at baseline. Of those 83 patients, 24/29 patients in the placebo arm and 46/54 in both ustekinumab arms met the eligibility criteria for enrollment based on SES-CD scores or ulcerations.

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Primary Endpoint: The primary endpoint of the induction endoscopic substudy was mean change from baseline in SES-CD score at Week 8. The mean change from baseline in SES-CD score was -2.8 points in the ustekinumab group and -0.7 points in the placebo group ($p=0.012$). This reviewer acknowledges that while the difference is statistically significant, the overall difference between the two groups is 2.1. This is not a very large change in SES-CD score. Additionally, there was a high amount of missing data as 25/87 (25.8%) patients in placebo and 46/155 (28.7%) patients in the ustekinumab groups had missing data at Week 8. The reason for missing data most commonly due to no endoscopy performed or the patient had an unscorable (missing) segment of the endoscopy due to a poor bowel preparation. The amount of missing data eliminated a third of the enrolled population from the analyses and may have affected the final outcome. Additionally, a primary endpoint of “mean change from baseline” without defining what constitutes a clinically meaningful change, may not be meaningful on its own. The change should represent a clinically meaningful endpoint (i.e., change from active disease to remission, change from severe disease to mild or moderate, etc.).

When the population enrolled from each of the induction studies, 3001 and 3002, were analyzed separately, the results were consistent with the findings of the combined primary endpoint. The mean change in SES-CD score decreased by 2.5 points ($p=0.01$) in the patient population enrolled from study 3001 and decreased by 1.7 points ($p=0.23$) in the population enrolled from study 3002. Of note, the endpoint analysis based on the population enrolled from study 3002, which included patients who had failed conventional therapy but not TNF-alpha antagonists, did not reach statistical significance, suggesting that the combined result was largely driven by results from patients enrolled from study 3001, the patients who had failed TNF-alpha antagonists.

The primary endpoint for the endoscopy substudy, mean change from baseline in SES-CD score, was also evaluated by the dose that patients received during the induction study. The mean change from baseline in SES-CD score decreased by 1.8 points ($p=0.10$) for patients treated with ustekinumab 130 mg IV and decreased by 2.3 points ($p=0.009$) for ustekinumab 6 mg/kg IV. The p-values suggest a trend in favor of an induction dose of ustekinumab 6 mg/kg vs placebo when compared with the ustekinumab 130 mg dose vs placebo.

Key Secondary Endpoints

Per the prespecified multiple testing procedure, as the primary endpoint was positive, testing was allowed to continue to the major secondary endpoints.

Change from induction baseline in SES-CD score at Week 44 of maintenance

At Week 44 of maintenance, the Applicant felt a “maintenance effect” was evident in both the ustekinumab and placebo groups. The Applicant puts forth since all patients in maintenance were responders to the initial intravenous dose, the magnitude of initial improvements observed (i.e., reduction in SES-CD from induction baseline) would not be as pronounced. Loss of the initial reductions in SES-CD from induction treatment baseline was observed in both the

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ustekinumab and placebo maintenance groups. The magnitude of this decrease was numerically lower in the combined (q8w plus q12w) ustekinumab maintenance dosing regimens (from -3.6 [$\pm$ 4.8] at Week 0 of maintenance to -2.5 [$\pm$ 3.73] at Week 44 of maintenance) than in the placebo maintenance dosing regimen (from -3.4 [$\pm$ 7.85] at Week 0 of maintenance to -1.9 [$\pm$ 4.06], but the treatment difference between ustekinumab and placebo maintenance dosing regimens was not statistically significant ($p=0.176$). Seven out of 24 (29.2%) patients in the placebo dosing regimen and 10/46 (21.7%) patients in the ustekinumab combined dosing regimens had missing data at Week 44 of maintenance, primarily due to endoscopy not being performed and termination of study participation before Week 44 of maintenance. This was a significant amount of missing data for an already small patient population.

The Applicant also performed a subgroup analysis to show a reduction in the change from baseline from Week 44 of maintenance compared with Week 0 of maintenance that was apparent in each ustekinumab treatment dosing regimen. Negative numbers indicate the change from induction study baseline. The magnitude of this decrease was numerically lower among patients randomized to ustekinumab 90 mg SC q8w dosing regimen (from -4.1[$\pm$ 5.23] at Week 0 of maintenance to -3.1[$\pm$ 4.11] at Week 44 of maintenance) compared with patients randomized to ustekinumab 90 mg SC q12w dosing regimen (from -2.8 [$\pm$ 3.98] at Week 0 of maintenance to -1.6 [$\pm$ 2.83] at Week 44 of maintenance) or placebo maintenance (from -3.4 [$\pm$ 7.85] at Week 0 of maintenance to -1.9 [$\pm$ 4.06] at Week 44 of maintenance). Here a q12w dosing regimen does not appear to fare well against either placebo or a q8 dosing regimen, and the q12w dosing regimen had less patients in it at completion (17) than the q8w dosing regimen (29), so this effect may have been confounded by sample size. However, as per the statistical analysis plan (SAP), formal hypothesis testing was stopped at this endpoint; however, the subsequent secondary endpoints are discussed below.

Mucosal Healing at Week 44 of Maintenance Study

Mucosal healing was defined as the complete absence of mucosal ulcerations at the follow-up visit. During a pre-BLA held May 12th, 2015 meeting the Division communicated to the Applicant that their “definition of mucosal healing, in conjunction with available histologic data, (b) (4) [would] be a review issue.” The Division’s current position is that endoscopy that provides only an assessment of the visual appearance of the mucosa (b) (4) without a validated histologic assessment of the mucosa, would be limited to improvement of the endoscopic appearance of the mucosa.

The proportion of patients with mucosal healing was 3-fold greater in the combined ustekinumab dosing regimens (6/46 [13.0%]) than in the placebo group (1/24 ([0.2%])); however, this comparison did not meet statistical significance ($p=0.41$). At Week 44 of

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maintenance, the proportion of patients who met the definition for mucosal healing were 1/17 (5.9%) patients randomized to maintenance with the ustekinumab 90 mg SC q12w dosing regimen, 5/29 (17.2%) patients in the ustekinumab 90 mg SC q8w dosing regimen, and 1/24 (4.2%) patients in the placebo dosing regimen. Again, this reviewer concludes that even though the sample size is small, the data are suggestive of improved efficacy for the q8w dosing regimen.

Mucosal Healing at Week 8 of Induction Studies

Mucosal healing was defined as the complete absence of mucosal ulcerations at the follow-up visit.

A numerically greater proportion of patients achieved mucosal healing in the ustekinumab dose groups (14/155 [9.0%]) than in the placebo dose group (4/97 [4.1%]); however, this was not statistically significant ($p=0.14$). When broken down by induction study, for study 3001, no patient in the placebo dose group and 2/66 (3.0%) patients in the ustekinumab dose groups achieved mucosal healing at Week 8 of induction. In study 3002, 4/56 (7.1%) patients in the placebo dose group and 12/89 (13.5%) patients in the ustekinumab dose groups achieved mucosal healing at Week 8 of induction. A larger proportion of patients experiencing absence of mucosal ulcerations at Week 8 of induction in the study population of patients were from patients who had failed conventional therapy as opposed to those who had failed TNF-alpha antagonists. The proportion of patients who met the definition for mucosal healing was similar between patients who received an induction dose of ustekinumab 130 mg (6/72 [8.3%] patients) or a tiered induction dose approximating ustekinumab 6 mg/kg (8/83 [9.6%] patients) as compared to patients who received placebo (4/97 [4.1%]).

Other Endpoints

Clinically Meaningful Endoscopic Improvement at Week 8 of Induction

Clinically meaningful endoscopic improvement was defined by the Applicant as a change from induction baseline in SES-CD score ≥ 3 . At Week 8, the proportion of patients who met the definition for clinically meaningful endoscopic improvement was 74/155 [47.7%], $p=0.005$ patients in the ustekinumab dose groups and 29/97 [29.9%] patients in the placebo dose group. The proportion of patients who met this endpoint definition were similar between both study populations; however, only the patient population of study 3001, TNF-alpha antagonist failures, met statistical significance ($p=0.004$). The patient population from study 3002, patients who failed conventional therapy, did not achieve statistical significance for this endpoint ($p=0.185$). When this endpoint was analyzed based on induction dose, both doses were statistically significant: 6 mg/kg ($p=0.007$) and 130 mg ($p=0.03$).

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The Applicant provided data that showed patients who experienced their definition of a clinically meaningful endoscopic improvement at week 8 were more likely to also achieve each of these clinical endpoints:

- Clinical response (reduction from induction baseline in the CDAI score of ≥ 100 points).
- Clinical remission (a CDAI score of < 150 points).
- IBDQ response (increase from induction baseline ≥ 16 points).
- Normalized CRP (< 3 mg/L) among patients with abnormal CRP (≥ 3 mg/L) at induction baseline.
- Normalized fecal calprotectin (≤ 250 mg/kg) among patients with abnormal fecal calprotectin (> 250 mg/kg) at induction baseline.

As a change in endoscopic findings can lag behind change in CDAI, CRP is a non-specific marker, and fecal calprotectin has yet to be qualified by the FDA as a measurement of therapeutic response, additional data are needed to determine what constitutes a clinically meaningful change on the SES-CD score, the results from this study may be used to inform future studies where SES-CD is utilized as an endpoint

Clinically Meaningful Endoscopic Improvement at Week 44 of Maintenance

Clinically meaningful endoscopic improvement was defined as a change from induction baseline in SES-CD score ≥ 3 . At week 44, the proportion of patients who met the criteria for clinically meaningful endoscopic improvement were numerically greater in the ustekinumab dosing regimens (17/46 [37.0%] patients) as compared to the placebo dosing regimen (6/24 [25.0%]), but did not achieve statistical significance ($p=0.31$). Although not statistically significant, the proportion of patients treated with a maintenance dosing regimen of 90 mg q8w (12/29 [41.4%]; $p=0.21$) was numerically greater than the proportion of patients who were treated with 90 mg q12w dosing regimen (5/17 [29.4%]; $p=0.75$) or placebo (6/24 [25.0%]).

Endoscopic Response at Week 8 of Induction

Endoscopic response was defined as a reduction from induction baseline in SES-CD score $\geq 50\%$. The proportion of patients who achieved endoscopic response at Week 8 of induction was numerically greater, but not statistically significant ($p=0.25$), for the ustekinumab dose groups compared to the placebo dose group (32/155 [20.6%] vs 13/97 [13.4%]). These results appeared to be driven by patients enrolled into the maintenance study from induction study 3001. Of the patients from study 3001, who had previously failed TNF-alpha antagonist therapy, 9/66 (13.6%) patients achieved endoscopic response at Week 8 vs 0/41 patients in the placebo arm. The proportion of patients enrolled from study 3002, who had failed conventional therapy, that achieved endoscopic response was similar to placebo (ustekinumab dose groups: 23/89 [25.8%] vs placebo dose groups: 13/56 [23.2%]). Both dosing groups (130 mg and 6 mg/kg) showed improvement; neither was statistically significant as compared to placebo.

Endoscopic Response at Week 44 of Maintenance

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Endoscopic response was defined as a reduction from induction baseline in SES-CD score $\geq 50\%$. The proportion of patients who achieved endoscopic response at Week 44 of maintenance was numerically greater, but not statistically significant ($p=0.15$). The proportion of patients who met the criteria for endoscopic response was in the combined ustekinumab dosing regimens was 8/46 (17.4%) patients vs 1/24 (4.2%) in the placebo arm. Of the patients treated with the q8w maintenance dose regimen, 7/29 (24.1%, $p=0.04$) patients met the criteria for endoscopic response as compared with 1/17 (5.9%, $p=0.802$) patients treated with the q12w dosing regimen, which was similar to placebo (1/24 [4.2%]).

Endoscopic Remission at Week 8 of Induction

Endoscopic remission was defined as SES-CD score ≤ 2 . The proportion of patients with SES-CD score ≤ 2 were numerically greater in the ustekinumab dose group than in the placebo group (12/155 [7.7%] vs 4/97 [4.1%], $p=0.25$). When this endpoint was analyzed by induction study, neither study population achieved statistical significance ($p=0.52$ for study 3001 and $p=0.57$ for study 3002); however, the proportion of patients who met the definition for endoscopic remission at week 8 was numerically greater than placebo. When this endpoint was analyzed by induction dose, 130 mg (5/72 [6.9%] or 6 mg/kg (7/83 [8.4%]), neither dose achieved statistical significance either; however, both had a higher proportion of responders than placebo (4/97 [4.1%]).

Endoscopic Remission at Week 44 of Maintenance

Endoscopic remission was defined as SES-CD score ≤ 2 . The rate of endoscopic remission at Week 44 of maintenance was numerically greater in the ustekinumab group than in the placebo group (5/25 [10.9%] vs 1/24 [4.2%], $p=0.66$). The Applicant did not provide an analysis based on ustekinumab arm by dose regimen for this endpoint.

Conclusions

Overall, this reviewer concludes that the data from the endoscopic substudy support the 6 mg/kg induction dose over 130 mg fixed induction dosing, and reflects a strong case for the 90mg q8 week dosing regimen [REDACTED] (b) (4) for maintenance dosing. Additionally, while the primary endpoint was met, this reviewer had some concerns regarding the strength of the definition of that endpoint (e.g., *any* change in SES-CD from baseline). Measuring any change from baseline in the SES-CD may or may not be meaningful unless that change is associated with an important clinical endpoint (i.e. clinical remission). Additionally, the first ranked key secondary endpoint failed to meet predefined statistical criteria; therefore, formal hypothesis testing was stopped but the results of the subsequent endpoints were described. In general, this reviewer had concerns regarding the high dropout rates in the study and the amount of missing data. The Applicant stated that some endpoints would have been better assessed at 10 weeks, 12 weeks, or even 24 weeks instead of Week 8 for an improved result. However, this reviewer points out the same endpoints were assessed at Week 44 and many of the results were weaker than in the induction studies, possibly due to the

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markedly smaller sample size. The data from this study are suggestive of some benefits from ustekinumab such as clinically meaningful endoscopic improvement at Week 8 (both doses, 130 mg and 6 mg/kg), and endoscopic response at Week 44 using the q8w dosing regimen.

Histology

Of the 252 patients also had eligible SES-CD scores at baseline, 251 (99.6%) patients had evaluable histologic data at baseline. The primary population and endoscopy substudy population were not randomized or stratified by histologic disease activity; however, histologic disease activity as measured by GHAS (described at the beginning of this section) at baseline was similar between the ustekinumab and placebo groups of the endoscopy substudy population (10.4 points and 9.2 points, respectively). The Applicant performed statistical analyses using correlation coefficients endoscopy and histology at baseline, Week 8, and Week 44 to suggest a relationship between endoscopic and histological disease activity at these timepoints, see statistical review by Dr. Min Min.

Histological Improvement by Study Treatment

Induction Studies (3001 and 3002)

A significant reduction in mean GHAS score from baseline to Week 8 of induction was observed within the combined ustekinumab dose group. At baseline, the GHAS score was 10.4 points and decreased to 7.1 points at week 8 ($p < 0.001$). The change from baseline in the placebo group (9.2 points at baseline to 7.8 points at week 8; $p = 0.193$) was not statistically significant. However, the Applicant states that among patients who had evaluable histology data at both induction baseline *and* Week 8 of induction, the mean reduction from baseline in GHAS was *numerically* greater for ustekinumab, but not significant (-2.35 [n=95]) when compared with placebo (-0.97 [n=58], $p = 0.14$). This reviewer suggests the more relevant endpoint, comparing patients to themselves, would have been more relevant.

When assessed by study population, patients enrolled from study 3002, the combined ustekinumab population had no significant change when compared to the placebo population between mean GHAS scores at Weeks 0 and 8 ($p = 0.958$). The patients enrolled from study 3001, however; showed improvement in histological score for both the combined ustekinumab dose groups ($p = 0.0042$) as compared to placebo. Therefore, patients who had previous failure to TNF-alpha antagonists appeared to respond better histologically to ustekinumab.

When assessed by induction dose, both ustekinumab 130 mg ($p = 0.001$) and 6 mg/kg ($p = 0.04$) dosing resulted in significant improvements in GHAS from Week 0 baseline to Week 8 when the overall median GHAS score was compared. The placebo dose group change from Week 0 to Week 8 in overall GHAS score was not significant ($p = 0.19$). When the Applicant looked at *mean change* of GHAS, however, comparing the placebo vs the ustekinumab 130 mg dose resulted in

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a numeric improvement ($p=0.06$); however the ustekinumab 6 mg/kg dose did not reflect the same trend against placebo ($p=0.424$).

Maintenance Study (3003)

In the maintenance study, there were no meaningful differences in the change from baseline for mean GHAS among ustekinumab induction responders who were randomized to an ustekinumab maintenance dosing regimen (8.5 points at baseline to 6.8 points at Week 44) or to the placebo maintenance dosing regimen (12.9 points at baseline to 10.9 points at Week 44). However, among patients who had evaluable histology data at both induction baseline and Week 44 of maintenance, the mean reduction from baseline in GHAS was numerically greater for the combined ustekinumab dosing regimens (-1.50 points [$n=18$]) compared with placebo dosing regimen (+0.82 points [$n=11$]). While this reviewer notes the small sample size, this result may be suggestive of a long term treatment effect when the population level analysis includes the same patients at baseline and week 44.

In the subgroup analyses by maintenance dosing regimen, a trend for greater reduction in mean GHAS from baseline at Week 44 of maintenance was observed in the ustekinumab 90 mg SC q8w dosing regimen ($p=0.07$) than in the ustekinumab 90 mg SC q12w dosing regimen ($p=0.64$), which performed worse than the placebo dosing regimen ($p=0.42$).

Conclusions

This histological study had a number of confounding issues with processing, including non-blinding of the central reader. The Applicant stated in response to an IR from OSI that the Central Reader was blinded to treatment assignment and the majority of patient-level data; however, the Central Reader had access to Patient Number, Site Number, and Protocol Visit as part of the Microsoft Excel histology data file (Microsoft Excel format) provided to the Central Reader to perform data entry. Upon review this form has a donor ID number, which confounds blinding. The final clinical site inspection reports were pending at the time of this document; however, some issues were identified and will be described in the final report. In general, due to the failure of this study to meet significance for the primary endpoint of a significant reduction in mean GHAS score from baseline to Week 8 of induction when using a population analysis that includes only patients with measurable scores at both of these timepoints and the concern regarding blinding of the central reader, this reviewer recommends that the histological data (b) (4) However, the data for the induction study appears to be suggestive, but not conclusive, of histological benefit by Week 8. The data also appears to be suggestive of long term histologic benefit favoring the q8w dosing regimen, but not the q12w dosing regimen.

Alternative Remission and Response Analysis

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The Division requested that the Applicant provide an exploratory analysis of key signs and symptoms from the Crohn's Disease Activity Index as recent presentations at the third Gastroenterology Regulatory Endpoints and the Advancement of Therapeutics (GREAT 3)⁴¹ have shown their potential to represent clinically meaningful signs and symptoms for use in defining efficacy endpoints for clinical studies. In Crohn's disease, key signs and symptoms include abdominal pain and stool frequency. These 2 components of the CDAI have been shown to contribute greatly (approximately 50%) to the overall score as well as to subsequent improvements. The Applicant has provided analyses from the induction studies (3001 and 3002) and primary and key endpoints clinical remission and response involving CDAI comparing abdominal pain and stool frequency.

Alternative Clinical Remission and Response Definitions

Alternative clinical remission analyses:

- The proportions of patients with a combined abdominal pain and stool frequency score <75 points⁴² at Week 6 and Week 8 was summarized and compared between each of the ustekinumab treatment dose groups and the placebo dose group.
- The proportions of patients with both an abdominal pain mean daily score ≤ 1 and a stool frequency mean daily score ≤ 3 at Week 6 and at Week 8 were summarized and compared between each of the ustekinumab treatment dose groups and the placebo dose group.⁴³

Alternative clinical response analysis:

- The proportions of patients with a ≥ 50 point decrease from baseline in the combined abdominal pain and stool frequency score at Week 6 and Week 8 were summarized and compared between each of the ustekinumab treatment dose groups and the placebo dose group.

Currently the Division has not made a determination of the appropriate cut off values or definitions for key signs and symptoms to utilize in place of the CDAI; however, data exploration and analyses such as the above listed definitions will be helpful in informing the use of these endpoints in future trials. The Applicant's proposed cut-off value for average daily stool

⁴¹ <http://www.great3.org/> Last accessed 8/26/2016.

⁴² This scoring was a composite score is derived from two of the patient-reported components of the CDAI: stool frequency and abdominal pain. The score (referred to as the SFAP) is the sum of the stool frequency and abdominal pain scores, using the weights assigned to each component in the CDAI.

⁴³ In the CERTIFI dataset (a phase 2b trial of ustekinumab in adults with moderate-to-severe CD that explored the components of the CDAI), the Applicant performed analyses that indicated that a stool frequency ≤ 3 cutoff (retaining the abdominal pain ≤ 1 cutoff) provided a greater sensitivity than other a stool frequencies (e.g. ≤ 1.5) with minimal loss of specificity both measured from the CDAI scales but not weighted.

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frequency score of ≤ 3 to define clinical remission seems reasonable based on the number of stools per day; however, if the stools remain loose/watery stools in consistency, this may not be reflective of clinical remission. Inclusion of the Bristol Stool Form Scale (BSFS) can be a valuable inclusion to ensure that the stool consistency also returns to normal or to a consistency that is considered by patients to be a state of remission. In addition, an abdominal pain score of 1 corresponds to “mild” pain, and may not be reflective of clinical remission for many patients. As these endpoints evolve, the definition could be further informed by anchor questions for patients to help define what constitutes a state of remission.

Results from Induction Studies 3001 and 3002

Table 16: Results for Alternative Clinical Remission and Response Analyses on Randomized Subjects Excluding Those Enrolled Prior to Study Re-start Study 3001 (N=741)

	Placebo (N=247)	Ustekinumab 130 mg (N=245)	Ustekinumab 6 mg/kg* (N=249)
WEEK 8 alternative clinical remission			
Combined abdominal pain and stool frequency score <75 points			
Number (%) of Patients	37 (15.0)	60 (24.5)	74 (29.7)
p-value by CMH test**		0.0072	<0.001
Both an abdominal pain mean daily score ≤ 1 and a stool frequency mean daily score ≤ 3			
Number (%) of Patients	23 (9.3)	42 (17.1)	52 (20.9)
p-value by CMH test**		0.0086	0.0002
WEEK 8 alternative clinical response			
≥ 50 point decrease from baseline in the combined abdominal pain and stool frequency score			
Number (%) of Patients	48 (19.4)	82 (33.5)	94 (37.8)
p-value by CMH test**		0.0005	<0.001
WEEK 6 alternative clinical remission and response			
Combined abdominal pain and stool frequency score <75 points			
Number (%) of Patients	39 (15.8)	59 (24.1)	72 (28.9)
p-value by CMH test**		0.021	0.0004
Both an abdominal pain mean daily score ≤ 1 and a stool frequency mean daily score ≤ 3			
Number (%) of Patients	24 (9.7)	40 (16.3)	45 (18.1)
p-value by CMH test**		0.0282	0.0075
WEEK 6 alternative clinical response			
≥ 50 point decrease from baseline in the combined abdominal pain and stool frequency score			
Number (%) of Patients	54 (21.9)	81 (33.1)	91 (36.6)
p-value by CMH test**		0.0068	0.0003

Source: Reviewer Modified Table originally created by Dr. Min Min, Statistical Team, using data from Study 3001 in Appendix TEFDAI02, Module 2.7.3 Summary of Clinical Efficacy

Table 17: Results for Alternative Clinical Remission and Response Analyses on Randomized Subjects Excluding Those Enrolled Prior to Study Re-start and Excluding Site 1127 for Study 3002 (N=627)

	Placebo (N=209)	Ustekinumab 130 mg (N=209)	Ustekinumab 6 mg/kg* (N=209)
WEEK 8 alternative clinical remission			
Combined abdominal pain and stool frequency score <75 points			
Number (%) of Patients	67 (32.1)	86 (41.2)	111 (53.1)
p-value by CMH test**		0.0466	<0.001
Both an abdominal pain mean daily score ≤1 and a stool frequency mean daily score ≤3			
Number (%) of Patients	40 (19.1)	58 (27.8)	78 (37.3)
p-value by CMH test**		0.0297	<0.001
WEEK 8 alternative clinical response			
≥50 point decrease from baseline in the combined abdominal pain and stool frequency score			
Number (%) of Patients	68 (32.5)	83 (39.7)	93 (44.5)
p-value by CMH test**		0.1099	0.0097
WEEK 6 alternative clinical remission and response			
Combined abdominal pain and stool frequency score <75 points			
Number (%) of Patients	60 (28.7)	89 (42.6)	106 (50.7)
p-value by CMH test**		0.0024	<0.001
Both an abdominal pain mean daily score ≤1 and a stool frequency mean daily score ≤3			
Number (%) of Patients	43 (20.6)	60 (28.7)	73 (34.9)
p-value by CMH test**		0.0472	0.0008
≥50 point decrease from baseline in the combined abdominal pain and stool frequency score			
Number (%) of Patients	58 (27.8)	88 (42.1)	101 (48.3)
p-value by CMH test**		0.0013	<0.001

Source: Reviewer Modified Table originally created by Dr. Min Min, Statistical Team, using data from Study 3002 in Appendix TEFDAI03, Module 2.7.3 Summary of Clinical Efficacy

Clinical Remission

Patients were considered as meeting criteria for clinical remission if the sum of the abdominal pain and stool frequency subscores (weighted as in the standard CDAI calculation) was <75. Of note, in general weighting should not reflect the same proportions as in the CDAI as these are separate measurements without the surrounding components of the CDAI. Even if combined the relationship between abdominal pain and stool frequency may differ than in the larger scale. In both induction studies (3001 and 3002), the proportions of patients in clinical remission with this definition were significantly greater in both the 6 mg/kg and 130 mg dose groups compared with the placebo dose group. In addition, consistent with other results, the proportion of patients in clinical remission was numerically higher in the 6 mg/kg dose group than in the 130 mg dose group at each timepoint. Measured at the same timepoint (Week 8) as

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the key secondary endpoint of clinical remission in the inductions study 3001, the data show 74/249 (29.7%) and 60/245 (24.5%) for the 6 mg/kg and 130 mg doses, respectively; compared with 37/247 (15.0%) in placebo. Week 6 showed similar results (See Table 16 above). The same endpoints measured at Week 8 in study 3002 show 111/209 (53.1%) and 86/209 (41.2%) for the 6 mg/kg and 130 mg doses, respectively; compared with 67/209 (32.1%) in placebo. Week 6 showed similar results (See Table 17 above).

The second alternative definition of clinical remission required both the mean daily stool frequency and abdominal pain scores to both be below specified thresholds of abdominal pain ≤ 1 and stool frequency ≤ 3 . Similar results were observed in both studies when compared with the first alternative definition. Specifically, a greater proportion of patients in both the 6 mg/kg and 130 mg dose groups achieved remission by this definition compared with the placebo group in both studies 3001 and 3002. In addition, consistent with results utilizing the CDAI, the 6 mg/kg dose group was again numerically higher than the 130 mg dose group across the studies and the timepoints measured at the same timepoint (Week 8) as the key secondary endpoint of clinical remission in the inductions studies, the data show 52/249 (20.9%) and 42/245 (17.1%) for the 6 mg/kg and 130 mg doses, respectively; compared with 23/247 (9.3%) for the placebo at Week 8 in Study 3001. Week 6 showed similar results (See Table 16 above). The same endpoints measured at Week 8 in study 3002 show 78/209 (37.3%) and 58/209 (27.8%) for the 6 mg/kg and 130 mg doses, respectively; compared with 40/209 (19.1%) in placebo. Week 6 showed similar results (See Table 17 above).

Conclusions

This reviewer concludes that based on the exploratory results above, abdominal pain and stool frequency appear to be adequate representatives of key signs and symptoms for remission as compared to the CDAI in this study analysis. This reviewer has also determined that these data further support the 6 mg/kg tiered dosing as the most appropriate choice for induction dosing.

Clinical Response

Using the alternative definition of clinical response based on the patient-reported abdominal pain and stool frequency scores, patients were considered to be in response if the sum of the abdominal pain score and the stool frequency score (both weighted as in the standard CDAI calculation) decreased by 50 or more points relative to baseline. Using this definition, which focuses on the key Crohn's-disease related symptoms patients are experiencing, significantly greater proportions of patients in the 6 mg/kg dose group were in clinical response at Weeks 6 and 8 versus placebo in both study 3001 and study 3002. In the 130 mg dose group, the proportions of patients in clinical response were significantly greater compared with the placebo group at Weeks 6 and 8 in study 3001 and at Week 6, *but not Week 8*, in study 3002. In both studies, the proportions of patients in clinical response with this definition were numerically higher in the 6 mg/kg group vs the 130 mg group. For study 3001, Week 6 numbers,

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the timepoint used to measure the primary endpoint of clinical response with the CDAI in the induction studies, were as follows: 91/249 (36.6%) and 81/245 (33.1%) for the 6 mg/kg and 130 mg doses, respectively; compared to 54/247 (21.9%) for placebo. Week 8 numbers were similar and also significant for study 3001 (See Table 16 above). For study 3002, Week 6 numbers, the timepoint used to measure the primary endpoint of clinical response with the CDAI in the induction studies, were as follows: 101/209 (48.3%) and 88/209 (42.1%) for the 6 mg/kg and 130 mg doses, respectively; compared to 58/209 (27.8%) for placebo. Week 8 numbers were similar and also significant for the 6 mg/kg dose, but not for the 130 mg dose (See Table 17). This reviewer concludes that this again indicates the better efficacy seen in other endpoints with 6 mg/kg dose, and also this shows that the 6 mg/kg dose importantly reflects greater benefit in the key patient-experienced primary symptoms of daily abdominal pain and frequency of loose stools.

Conclusions

A significant proportion of patients also achieved clinical response at Week 6 of a 50-point reduction in CDAI exclusively from stool frequency and abdominal pain from both doses compared to placebo. As was seen with the overall clinical response (≥ 100 -point improvement in CDAI), the higher 6 mg/kg dose was slightly more efficacious, with a slightly larger treatment effect compared to placebo, compared to that seen with 130 mg dose, providing further evidence that 6 mg/kg dose is the preferable induction dose.

Additionally, efficacy seen in the overall CDAI-based remission endpoint generally mirrored each of 2 alternate stool frequency and abdominal pain remission definitions. This was true in both Phase 3 induction studies, where the 6 mg/kg dose achieved numerically higher rates than the 130 mg dose.

7 Review of Safety

7.1. Safety Review Approach

This safety of BLA 076044 was reviewed using data compiled from 3 phase 3 studies, studies 3001 and 3002, (8 week intravenous (IV) initial dose induction studies) and study 3003 (44 week subcutaneous (SC) dose maintenance study). The randomized population was used from all 3 studies (Study 3001 N = 740, Study 3002 N = 627, and Study 3003 N = 397 patients); however, in Study 3003 the non-randomized population (N= 884) was also reviewed for sections considered critical for the safety of the drug (e.g. infectious diseases, malignancy, deaths). Additionally, the

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Applicant submitted a 120 day safety update which included data from a long-term extension (LTE) study (N=605). The LTE began at Week 44 and will continue through Week 272 or until marketing authorization is obtained for ustekinumab in the treatment of Crohn’s disease in that country, or until a decision has been made not to pursue an indication in Crohn’s disease, whichever occurs first. In the LTE study, all patients continued to receive the same treatment regimen that they were receiving at Week 44 (either placebo SC or ustekinumab 90 mg SC q8w or q12w dosing regimens). After the Week 44 analyses of the study were completed, the study was unblinded at the investigative sites, and the patients who were still receiving placebo were discontinued. Dose adjustments were not permitted during the LTE study. Analysis of data and reviewer tables were generated in MedDRA Adverse Event Diagnostics (MAED) and JReview.

Key safety issues for all biologics used in inflammatory bowel disease are those of malignancy and infection (including opportunistic infection). In addition, for this particular biologic, Reversible Posterior Leukoencephalopathy Syndrome (RPLS), which is a potentially fatal rare neurological disorder that presented in a clinical database for psoriasis/psoriatic arthritis, was also tracked. Finally, incidents of major cardiovascular events (MACE), which were occurred in the trials for psoriasis and psoriatic arthritis but not found to be conclusively related to ustekinumab over placebo, were also monitored.

7.2. Review of the Safety Database

7.2.1. Overall Exposure

This table is completed for the phase 3 randomized controlled trials included in this review with the addition of the non-randomized population from study 3003.

Table 18: Exposure of Ustekinumab (Subcutaneous and Intravenous Dosing)

Clinical Trial Groups	Ustekinumab	Placebo
Phase 3 controlled trials conducted for this indication	914	535
Overall patients exposed to Ustekinumab for Crohn’s disease	1749	658

Table 19: Duration of Exposure (Intravenous Dosing)

Single IV Dose	>=6 months	>=12 months
N=1664	N=849	N=464

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7.2.2. **Relevant characteristics of the safety population:**

Intrinsic/Extrinsic factors and baseline disease characteristics taken into account when performing safety analysis for BLA 761044 were as follows:

Intrinsic Factors:

- Demographics
 - Race (white, black or African-American, Asian, and Hispanic)
 - Age (<45 vs ≥45, and <65 vs ≥65 years)
 - Weight (<69.0 kg vs ≥69 kg)
- Baseline disease characteristics
 - Extent of disease/area of GI involvement(categorized by ileum only, colon only, and ileum and colon)
 - Duration of disease (categorized by ≤5 years, >5 to ≤15 years, and >15 years)
 - Severity of disease (categorized by Crohn’s Disease Activity Index (CDAI)<300 and CDAI>300)

Extrinsic Factors:

- Baseline immunomodulator therapy (i.e., 6-mercaptopurine [6-MP], azathioprine [AZA], or methotrexate [MTX]) vs none
- Baseline oral corticosteroid therapy vs none
- TNF antagonist history (TNF failure, TNF experienced [but no failure], and TNF naïve)

Overall, no trends were observed with regard to differences between treatment groups in the proportions of patients with AEs, SAEs, infections, or who discontinued due to an AE, when evaluated by sex, race, age, and weight during induction or maintenance.

7.2.3. **Adequacy of the safety database:**

The size and adequacy of the safety database in studies 3001, 3002, and 3003 considering exposure, duration of treatment, patient demographics and disease characteristics appears adequate to assess safety of ustekinumab for the induction and maintenance of adult patients with moderately to severely active Crohn’s disease (CD) in both patients who have failed or were intolerant to immunomodulators or corticosteroids but never failed anti-TNF α treatment or patients who have failed or were intolerant to anti-TNF α treatment.

Study 3001

The majority of the patients completed the one study drug infusion and 8 week monitoring during the randomized double-blind treatment period (See Section 6.1.2, Patient Disposition). Per protocol 495 patients received IV ustekinumab; however, this number includes 17 patients

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randomized to ustekinumab dosing who were excluded from the final analysis population due to the study restarting because of instability discovered with a lot of ustekinumab dosing vials (See Section 3.1). The study was restarted at the time of this finding and these 17 patients were excluded from any analyses.

Of the patients randomized to receive ustekinumab treatment, 229/236 (97.0%) from the 130 mg dose group and 235/249 (96.6%) from the 6 mg/kg dose group continued into the maintenance trial (study 3003). There was an additional week 20 follow up for participants by which time an additional 2 patients from the 130 mg dose group and 5 patients from the 6 mg/kg dose group had withdrawn from the study. See Section 6.1.2, Patient Disposition.

All patients received the treatment to which they were assigned, with the exception of 4 patients. One patient who was randomized to the placebo dose group never received study agent. Another patient who was randomized to the placebo dose group received ustekinumab (39.6 mg) and was analyzed in the 130 mg ustekinumab dose group for PK and safety. One patient who was randomized to the 130 mg ustekinumab dose group received a dose more closely approximating the high dose (219.6 mg in a 63.5 kg patient, i.e., 3.5 mg/kg) and was therefore analyzed in the 6 mg/kg ustekinumab group for PK and safety. Lastly, a patient who was randomized to the 6 mg/kg ustekinumab dose group received a dose (3.1 mg) more closely approximating the 130 mg dose because the infusion was interrupted and drug was withdrawn due to an AE during the infusion. This patient was therefore analyzed in the 130 mg ustekinumab group for PK and safety.

Study 3002

The majority of the patients completed the one study drug infusion and 8 week monitoring during randomized double-blind treatment period (See Section 6.1.2, Patient Disposition). Per protocol 419 patients received IV ustekinumab; however, this number includes 8 patients randomized to an ustekinumab dose who were excluded from the final population due to the study restarting because of instability discovered with a specific lot of ustekinumab dosing vials (See Section 3.1) from any analyses.

Of the patients randomized to receive ustekinumab treatment, 196/200 (98.0%) from the 130 mg group dose group and 203/207 (98.1%) from the 6 mg/kg dose group continued into the maintenance trial (Study 3003). There was an additional week 20 follow up for participants by which time an additional 6 patients from the 130 mg dose group and 0 patients from the 6 mg/kg dose group had withdrawn from the study. See Section 6.1.2, Patient Disposition.

All patients received the treatment to which they were assigned with the exception of 4 patients. One patient was randomized to the placebo group but never received study agent. Another patient was randomized to the placebo group and received an ustekinumab dose approximating the low dose (130 mg); this patient was analyzed in the ustekinumab 130 mg

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group for PK and safety. In addition, 2 patients who were randomized to the ustekinumab 6 mg/kg dose group actually received doses more closely approximating the low dose (130 mg); those 2 patients were analyzed in the ustekinumab 130 mg dose group for PK and safety.

Study 3003

A total of 1,281 patients who completed the ustekinumab induction studies 3001 and 3002 were enrolled in this study 3003. Among these patients, a total of 397 patients were randomized to the primary population and an additional 884 patients were not randomized but entered into the maintenance study and were followed/analyzed as the “non-randomized” population because they were either not in clinical response to study agent or placebo, or were in clinical response to placebo. See Section 6.1.1 (Trial Design) for a description of this population.

The majority of the patients in the randomized population of the study completed either 3 or 5 SC study drug injections based on randomization to either every 8 or every 12 week dosing regimens, and weekly monitoring during the 44-week randomized double-blind treatment period. Per protocol 419 patients received IV ustekinumab; however, this number includes 8 patients randomized to ustekinumab dosing regimen who were excluded from the final population due to the study restarting because of mislabeled ustekinumab dosing vials. The study was restarted at the time of this finding and these 8 patients were excluded from any analyses.

Of the patients randomized to receive ustekinumab treatment, 103/132 from the 90mg SC q 12w dosing regimen and 99/132 from the 90mg SC q8w dosing regimen continued into the long term extension trial. An additional 20 patients from q12w dosing regimen and 19 patients from the q8w dosing regimen did not enter the long term extension trial but completed safety follow up at week 64. Nine patients from the q12w dosing regimen and 14 patients from the q8w dosing regimen withdrew from the study. See Section 6.1.2, Patient Disposition.

Of the non-randomized patients who received ustekinumab treatment in the maintenance trial, 330/761 continued into the long term extension trial. An additional 228 patients did not enter the long term extension trial but completed safety follow up at week 64. One-hundred forty-three patients withdrew from the study.

A total of 3 patients, 1 randomized patient in the ustekinumab 90 mg SC q8w dosing regimen and 2 nonrandomized patients, 1 each in the placebo induction nonresponder and ustekinumab nonresponder groups, received the wrong treatment or incorrect dose. All 3 patients missed 2 or more consecutive administrations of study agent. All patients received the treatment to which they were assigned. See Section 6.1.2, Patient Disposition. Twenty-three of 132 (17.4%) patients in the q12 dosing regimen, 26/132 (19.7%) in the q8w dosing regimen, and 35/133

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(26.3%) of randomized and enrolled patients received a scheduled administration outside of the protocol-specified window. As the number of those who received administration outside of the drug administration window was larger in placebo and similar in both ustekinumab dosing regimens, this reviewer concludes that it is not likely to have had an effect on the outcome of the safety data. A total of 75/761 (9.9%) of non-randomized patients received a scheduled administration outside of the protocol-specified window

7.3. Adequacy of Applicant's Clinical Safety Assessments

7.3.1. Issues Regarding Data Integrity and Submission Quality

During the conduct of study 3002, the Applicant was notified of significant deviations from Good Clinical Practice at 1 study site (Site 1127) and an audit was performed. Of the 2 patients randomized in study 3002 at the site, 1 patient was believed to have been falsified and all data for this patient was removed from the database. Therefore, all study population totals within this CSR exclude this 1 patient who was removed from the database. The second patient at this site, who was enrolled but not randomized, was confirmed to have consented, received study agent, and participated in the study. Nevertheless, the Applicant was unable to make a final determination of the accuracy and validity of the patient's data and the data were therefore also excluded from the efficacy analyses; however, because the patient was confirmed to have received study agent, all available data were included in the safety and PK analyses. During the course of the audit described above, it was identified that 2 additional AEs had not been recorded in the eCRF and were therefore not entered into the database for the second patient described above. These AEs are described in the Errata Section of the study 3002 clinical study report. It was also identified that 2 additional protocol deviations had not been recorded as protocol deviations on the eCRF and were therefore not entered into the database for patient 20961. This reviewer finds that as those violating GCP have been removed from the database, the falsification of data has not impacted the data available for safety review. Additionally, this reviewer agrees that the patient for whom data validity could not be confirmed be excluded from efficacy, but included in safety and PK as the Applicant could confirm the patient received doses of ustekinumab and experienced adverse events. This reviewer finds this approach to be reasonable.

7.3.2. Categorization of Adverse Events

The Applicant used Medical Dictionary for Regulatory Activities (MedDRA), version 17.0 to code SOCs and preferred terms are used to summarize AEs. The verbatim terms used in the CRF by investigators to identify AEs will be coded using the MedDRA. All reported AEs with onset during the treatment phase (i.e., treatment-emergent AEs, and AEs that have worsened since baseline) will be included in the analysis. For each AE, the percentage of patients who experience at least 1 occurrence of the given event will be summarized by treatment group.

The following analyses of AEs were used to assess the safety of patients in this study:

- The incidence and type of AEs.
- The incidence and type of SAEs.
- The incidence and type of reasonably related AEs.
- The incidence and type of infections.
- The incidence and type of infusion reactions.

The Applicant defined infusion reactions as an AE that occurs during or within 1 hour following the infusion of study agent, with the exception of laboratory abnormalities. At this time, the Agency (b) (4) currently recommends the term (b) (4) “hypersensitivity reaction” and/or “anaphylaxis” is more appropriate. The review team has recommended the Applicant (b) (4) accordingly.⁴⁴ This Guidance refers to a more accurate description of infusion reactions that defines events related to hypersensitivity within a few hours in accordance with the NIAID/FAAN criteria for anaphylaxis⁴⁵ (Sampson H et al., 2006); therefore, the Applicant was asked to perform a reanalysis for hypersensitivity reactions to include the larger time frame window.

The Applicant defined AEs as any untoward medical occurrence in a clinical study patient administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product (Definition per International Conference on Harmonisation [ICH]). This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities. Serious AEs were those that: resulted in death, were life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, are a congenital anomaly/birth defect, are a suspected transmission of an infectious agent via a medicinal product, or are medically Important.

Treatment emergent AEs and laboratory values reported during the study were summarized. Treatment-emergent AEs were coded in accordance with MedDRA, version 17.0, using the lower-level term (LLT) as the description most closely related to the investigator's terminology, a preferred term describing a group of closely related LLTs, and the system organ

⁴⁴ Guidance for Industry: Immunogenicity Assessment for Therapeutic Protein Products, dated August 2014.

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm338856.pdf>

⁴⁵ Sampson et al. 2006. Second symposium on the definition and management of anaphylaxis: summary report-- Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol.* Feb;117(2):391-7.

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class (SOC), which is the broad category including related preferred terms. This reviewer has recoded the following terms in order to better assess the impact of the event on safety.

Table 20: Recoded Terms

Applicant's AE Code (number of events recoded)	Reviewer's Recoded Term
Study 3001	
Acne condyloma (1)	Acne
Acne pustular (1)	Acne
Abdominal discomfort (2)	Abdominal Pain
Abdominal pain upper (8)	Abdominal Pain
Abdominal pain lower (3)	Abdominal Pain
Abdominal tenderness (2)	Abdominal Pain
Gastroenteritis viral (5)	Gastroenteritis
Gastrointestinal infection (1)	Gastroenteritis
Oropharyngeal candidiasis (1)	Oral candidiasis
Paresthesia oral (3)	Paresthesia
Rash maculo-papular (1)	Rash
Rash pruritic (1)	Rash
Urinary tract infection enterococcal (1)	Urinary tract infection
Viral upper respiratory tract infection (1)	Upper respiratory infection
Vision blurred (2)	Visual impairment
Vulvovaginal candidiasis (2)	Vulvovaginal mycotic infection
Study 3002	
Abdominal pain upper (4)	Abdominal Pain
Abdominal pain lower (3)	Abdominal Pain
Abdominal tenderness (1)	Abdominal Pain
Gastroenteritis viral (1)	Gastroenteritis
Rash erythematous (1)	Rash
Rash maculo-papular (1)	Rash
Rash papular (1)	Rash
Rash pruritic (2)	Rash
Elevation in body temperature (1)	Pyrexia
Viral upper respiratory tract infection (2)	Upper respiratory infection
Vision blurred (1)	Visual impairment
Visual acuity reduced (1)	Visual impairment
3003	
Abdominal pain upper (9)	Abdominal Pain
Abdominal pain lower (7)	Abdominal Pain

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Gastroenteritis viral infection (2)	Gastroenteritis
Gastroenteritis viral (17)	Gastroenteritis
Gastrointestinal bacterial infection (1)	Gastroenteritis
Gastroenteritis norovirus (1)	Gastroenteritis
Injection site swelling(1)	Injection site edema
Paresthesia oral (3)	Paresthesia
Rash erythematous (1)	Rash
Rash macular (2)	Rash
Rash maculo-papular (1)	Rash
Rash pruritic (5)	Rash
Viral upper respiratory tract infection (1)	Upper respiratory infection
Visual field defect (1)	Visual impairment
Vision blurred (1)	Visual impairment
Vulvovaginal candidiasis (3)	Vulvovaginal mycotic infection

7.3.3. Routine Clinical Tests

The time and events schedule for clinical laboratory data to assess safety are reasonable and adequate for the population studied. For the induction trials, clinical lab tests were measured at weeks 0, 3, 6, and 8. For the maintenance trials, they were measured at weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, and 44. Labs were processed by a central laboratory.

Normal clinical laboratory tests were defined as the following:

Normal lab values:

- a. Hemoglobin $\geq$ 8.5 g/dL
- b. WBCs $\geq$ 3.5 x 10³/ μ L
- c. Neutrophils $\geq$ 1.5 x 10³/ μ L
- d. Platelets $\geq$ 100 x 10³/ μ L
- e. Serum creatinine < 1.7 mg/dL
- f. AST and ALT concentrations must be within 2 times the ULN range for the laboratory conducting the test
- g. Direct (conjugated) bilirubin < 1.0 mg/dL

This reviewer concludes the normal laboratory values are reasonable.

The time and events schedule for studies 3001, 3002 and 3003 are below:

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Table 21: Time and Events Schedule for Induction Studies 3001 and 3002

TIME AND EVENTS SCHEDULE

Table 1 Protocol NTO1275CRD3001							
Study Procedures ^c	Screening ^a	Induction Period ^b					
	-5Weeks	Week 0	Week 3	Week 6	Week 8	Early Termination ^d	Safety Follow-up ^d
Screening/Administrative							
Informed consent	X						
Inclusion/exclusion criteria	X	X					
Medical history and demographics	X						
Chest radiograph ^e	X						
QuantiFERON-TB Gold In-Tube test ^f	X						
Stool studies to evaluate for enteric pathogens ^g	X						
Training on diary card completion	X						
Study Agent Administration							
Randomization		X					
Administer study agent		X					
Safety Assessments							
Detailed physical examination	X					X	X
Weight	X	X	X	X	X	X	
Height	X						
Vital signs ^h	X	X ⁱ				X	X
Baseline 12-lead ECG	X						
Serum pregnancy test	X						
Urine pregnancy test		X ^j				X	X
TB evaluation ^k /other infection assessment		X	X	X	X	X	X
Efficacy Assessments							
Collect and review diary cards		X	X	X	X	X	
CDAI assessments ^l		X	X	X	X	X	
Fistula exam		X	X	X	X	X	
Stool sample (fecal lactoferrin and calprotectin)	X			X		X	
C-reactive protein (CRP)	X	X	X	X	X	X	
Pyoderma gangrenosum assessment		X	X	X	X	X	
Video ileocolonoscopy ^m with biopsies for RNA analysis and histology	X					X	

Table 1 Protocol NTO1275CRD3001							
Study Procedures ^c	Screening ^a	Induction Period ^b					
	-5Weeks	Week 0	Week 3	Week 6	Week 8	Early Termination ^d	Safety Follow-up ^d
Inflammatory Bowel Disease Questionnaire (IBDQ)							
Inflammatory Bowel Disease Questionnaire (IBDQ)		X				X	
36-Item Short-form Health Survey (SF-36)							
36-Item Short-form Health Survey (SF-36)		X				X	
Health economics							
Work Limitations Questionnaire (WLO)		X				X	
Productivity Visual Analog Scale (VAS)		X				X	
Time Lost from Work		X				X	
Clinical Laboratory Assessments							
Hematology and chemistry	X	X ^a	X	X	X	X	
Pharmacokinetics/Immunogenicity							
Ustekinumab serum concentration		X ^c	X	X	X	X	X
Antibodies to ustekinumab		X		X	X	X	X
Pharmacodynamics							
Serum sample collection		X	X	X		X	
Whole blood sample collection for RNA analysis ^f		X ^g		X			
Pharmacogenomics							
Whole blood sample collection for DNA analysis ^h		X ^g					
Ongoing Subject Review							
Concomitant therapy	X	X	X	X	X	X	X
AEs	X	X	X	X	X	X	X
Crohn's disease-related hospitalizations and surgeries		X	X	X	X	X	X
Footnotes:							
^a The screening period should be a minimum of 7 days to allow for collection of CDAI data. Subjects who are rescreened do not need to have a minimum of 7 days provided they have enough data to support CDAI calculation.							
^b The visit windows will be ± 4 days for each visit.							
^c All assessments are to be completed prior to study agent administration, unless otherwise specified. It is recommended that patient reported outcome (PRO) assessments be completed first.							
^d If a subject ends study participation prior to Week 8, the Early Termination Visit should be completed. If a subject will not enter the maintenance study, but is still participating in the induction study, the subject should complete all scheduled visits and complete the final safety follow up visit approximately 20 weeks after study agent administration at Week 0.							
^e May be taken within 3 months prior to the Week 0 visit.							

Table 1 Protocol CNTO1275CRD3001

^f In countries in which the QuantiFERON-TB Gold test is not considered approved/registered, a tuberculin skin test is additionally required. The QuantiFERON-TB Gold In-Tube test is not required at screening for subjects with a history of latent TB and appropriate treatment as described in Inclusion Criterion 7d.

^g Stool studies for enteric pathogens may be performed at either the central or local laboratory and must include a stool culture and *Clostridium difficile* toxin assay. These must have been performed during the current episode of disease exacerbation and within 4 months prior to Week 0. Additional testing, such as ova and parasite or *E. coli* O157:H7 assessments may be performed at the investigator's clinical discretion.

^h Temperature, pulse/heart rate, and blood pressure.

ⁱ At Week 0, vital signs obtained prior to infusion, approximately every 30 minutes during infusion, and twice (approximately 30-minute intervals) after the completion of infusion.

^j Must be performed prior to study agent administration at Week 0 in females of childbearing potential.

^k If TB is suspected at any time during the study, a chest x-ray, QuantiFERON-TB Gold In-Tube test, and/or a tuberculin skin test (in countries in which the QuantiFERON-TB Gold test is not considered approved/registered) should be performed.

^l For calculation of CDAI at Week 0, the hematocrit value obtained during screening will be used.

^m For sites selected to perform video ileocolonoscopy: Because these procedures must not interfere with the collection of CDAI data, the video ileocolonoscopy examination will be performed at least 8 days before or at the Week 0 visit and at least 8 days before or at the Week 8 visit. If performed on the day of these visits, the 7 days prior to the initiation of the colonoscopy preparation should be utilized to calculate CDAI scores for these visits.

ⁿ Laboratory tests at Week 0 are not required if screening laboratory tests were performed within 2 weeks before the Week 0 visit.

^o Blood should be drawn before the infusion begins and approximately 60 minutes after completion of the infusion.

^p Whole blood for RNA analysis will be collected from all subjects in the study.

^q Sample may be collected at another timepoint if not collected at Week 0.

^r Whole blood for DNA will be collected from subjects who consent to participate in pharmacogenomic assessments.

Figure 37: Time and Events Schedule Maintenance Study 3003

Table 1. Protocol CNTO1275CRD3003 – Maintenance Treatment Phase

Study Procedures: ^{a,b}	Week 0 ^c	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36 ^d	Week 40 ^e	Week 44 ^d	Early Term ^{rs}	Safety F/U ^s
Screening/Administrative														
Informed consent	X													
Inclusion/exclusion criteria	X													
Study Agent Administration														
Randomization ^t	X													
Administer study agent	X ^g		X	X	X	X	X	X	X	X	X			
Safety Assessments														
Detailed physical examination												X	X	X
Weight	X ^a	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs ¹	X ^j	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Pregnancy test ^k	X		X	X	X	X	X	X	X	X	X	X	X	X
TB evaluation ^l /other infection assessment	X ^a	X	X	X	X	X	X	X	X	X	X	X	X	X
Study agent injection-site evaluation	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy Assessments														
Collect and review diary cards	X ^b	X	X	X	X	X	X	X	X	X	X	X	X	X
CDAI assessments ^m	X ^a	X	X	X	X	X	X	X	X	X	X	X	X	X
Fistula exam	X ^a	X	X	X	X	X	X	X	X	X	X	X	X	X
Stool sample (fecal lactoferrin and calprotectin)	X ^a		X				X					X	X	
CRP	X ^a	X	X	X	X	X	X	X	X	X	X	X	X	X
Pyoderma gangrenosum assessment	X ^a	X	X	X	X	X	X	X	X	X	X	X	X	X
Video ileocolonoscopy ⁿ with biopsies for RNA analysis and histology	X ^b											X	X	
IBDQ	X ^a					X						X	X	
SF-36	X ^a					X						X	X	
Health Economics														
Productivity VAS	X ^b					X						X	X	
WLQ	X ^b					X						X	X	
Time Lost from Work	X ^b					X						X	X	
Clinical Laboratory Assessments														
Hematology and chemistry	X ^b	X	X	X	X	X	X	X	X	X	X	X	X	
Pharmacokinetics/Immunogenicity														
Ustekinumab serum concentration ^p	X ^a	X	X	X	X	X	X	X	X	X	X	X	X	X
Antibodies to ustekinumab	X ^a			X			X			X		X	X	X

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Study Procedures: ^{a, b}	Week 0 ^c	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36 ^e	Week 40 ^e	Week 44 ^d	Early Term ^{z, s}	Safety F/U [*]
Pharmacodynamics														
Serum sample collection			X				X					X	X	
Whole blood sample collection for RNA analysis ^q			X		X		X					X		
Ongoing Subject Review														
Concomitant therapy	X ^h	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Crohn's disease related hospitalizations and surgeries	X ^h	X	X	X	X	X	X	X	X	X	X	X	X	X
Footnotes:														
a The visit windows will be ± 10 days for each visit.														
b All assessments are to be completed prior to study agent administration, unless otherwise specified. It is recommended that patient reported outcome (PRO) assessments be completed first.														
c Week 0 visit should be within 4 days of the Week 8 visit in study CNTO1275CRD3001 or CNTO1275CRD3002. At the discretion of the investigator, the window may be extended to 8 days to allow appropriate treatment and/or recovery of nonserious infections.														
d All subjects will be assessed at Week 44 to determine eligibility for entry into the long-term extension. Study agent administration at Week 44 will be considered part of the long-term extension and is captured in the Time and Events Schedule for the long-term extension (Table 2).														
e Subjects who discontinue study agent administration (but have not terminated study participation) or who do not enter the study extension will have a final follow-up safety visit approximately 20 weeks after the last administration of study agent.														
f Subjects in clinical response to ustekinumab induction dosing.														
g Subjects in clinical response following induction will receive SC study agent and subjects not in clinical response will receive both SC and IV study agent.														
h Data from study procedure performed at Week 8 of induction study CNTO1275CRD3001 or CNTO1275CRD3002 will be used for Week 0 of this study.														
i Temperature, pulse/heart rate, and blood pressure. Vital signs should be obtained prior to and approximately 30 minutes post study agent injections.														
j For subjects receiving IV infusion at Week 0, vital signs should be obtained prior to infusion, approximately every 30 minutes during the infusion, and twice (approximately 30 minute intervals) after the completion of the infusion.														
k Must be performed prior to each study agent administration in females of childbearing potential.														
l If TB is suspected at any time during the study, a chest x-ray, QuantiFERON-TB Gold In-Tube test, and/or a tuberculin skin test (in countries in which the QuantiFERON-TB Gold test is not considered approved/registered) should be performed.														
m For calculation of CDAI at Week 0, the hematocrit value obtained during Week 6 of induction study CNTO1275CRD3001 or CNTO1275CRD3002 will be used.														
n Data from study procedure performed at Week 6 of induction study CNTO1275CRD3001 or CNTO1275CRD3002 will be used for Week 0 of this study.														
o For sites selected to perform video ileocolonosopies: Because these procedures must not interfere with the collection of CDAI data, the video ileocolonoscopy evaluation will be performed at least 8 days before or at the Week 44 visit. If performed on the day of this visit, the 7 days prior to the initiation of the colonoscopy preparation should be utilized to calculate the CDAI score for this visit.														
p For subjects receiving IV infusion at Week 0, a sample should be drawn approximately 60 minutes after completion of the infusion. At all other study agent administration visits blood samples should be collected prior to study agent injection.														
q Whole blood for RNA analysis will be collected from all subjects in the study.														
r When early termination coincides with a scheduled visit, perform activities identified for early termination.														
s Subjects who discontinue study agent on or after Week 36 should complete the Week 44 visit (in addition to a final safety visit).														

Source: Applicant BLA TIME AND EVENTS SCHEDULE modules 5.3.5.1 for Protocols from BLA 761044, Studies 3001, 3002, and 3003.

7.4. Safety Results

Deaths

There were no deaths during the double-blind phases of the phase 3 studies 3001, 3002, or 3003. However, 6 deaths have been reported at the time of this review. Five deaths occurred during the long term extension (LTE) study and were reported in the integrated summary of safety provided with the Applicant's submission (3 cardiovascular, 1 infectious, 1 renal failure, and 1 suicide) and one additional death was provided in the 120 day safety update (infectious). This reviewer has reviewed all of the deaths and does not find conclusive evidence that any of the deaths reported can be clearly attributed to the study drug due to co-morbid, confounding, or other confounding factors noted in the brief narratives below:

- Septic shock in a 33-year-old woman with a history of Factor V Leiden mutation, who developed sepsis believed to be secondary to an infected seroma from a hernia repair. The patient was admitted 3 days after drainage of the seroma with reaccumulation of the seroma. The patient developed intracranial thrombus after an attempt at drainage of the seroma. The patient finally succumbed to ventricular fibrillation during a procedure to insert a Sheldon catheter for renal replacement. She had initially received ustekinumab IV induction dosing and then went on to receive ustekinumab 90 mg SC q8w dosing regimen as maintenance therapy for 22 months in the LTE after the end of the maintenance study.
- Cardiorespiratory arrest in a 56-year-old man with a known history of coronary artery disease, hyperlipidemia, and hypertension. He had initially received placebo IV induction and then went on to receive ustekinumab 90 mg SC q12w dosing regimen as maintenance therapy. This patient withdrew 4 months into the LTE for lack of efficacy with worsening Crohn's disease and passed away 5 months after the maintenance trial ended.
- Chronic renal failure in a 72-year-old woman with a history of chronic renal disease who was admitted to the hospital for acute worsening of chronic renal failure secondary to dehydration, refused dialysis, and died in hospice. She had initially received ustekinumab IV induction and then went on to receive ustekinumab 90 mg SC q8w dosing regimen as maintenance therapy as maintenance therapy for 15 months in the LTE after the end of the maintenance study.
- Acute myocardial infarction (MI) in a 46-year-old male, with known cardiovascular risk factors including smoking, hyperlipidemia, and hypertension who died of a MI approximately 10 days after experiencing unstable angina. Autopsy showed coronary atherosclerosis and signs of acute left heart failure. He had initially received

ustekinumab IV induction and then went on to receive ustekinumab 90 mg SC q12w dosing regimen as maintenance therapy for 21 months in the LTE after the end of the maintenance study.

- Sudden death in a 61-year-old man with a history of tobacco use who was found deceased of presumed ventricular arrhythmia although no autopsy was performed. He had initially received ustekinumab IV induction then went on to receive placebo SC as maintenance therapy and then dose adjusted to ustekinumab 90 mg SC q8w dosing regimen 11 months in the LTE after the end of the maintenance study prior to death.
- Self-asphyxia (by hanging) in a 24-year-old man who had no known past medical history other than Crohn’s disease. The patient committed suicide at home shortly after being incarcerated for a day for driving under the influence of alcohol. He had initially received ustekinumab IV induction and then went on to receive placebo SC as maintenance therapy and then dose adjusted to ustekinumab 90 mg SC q8w dosing regimen and was in the LTE study 14 months prior to his death.

7.4.2. Serious Adverse Events

Study 3001

For study 3001, the number of patients with 1 or more serious adverse events (SAE) through Week 8 is presented below in Table 22. The proportion of patients who had 1 or more SAEs was 15/245 (6.1%) patients in the placebo group compared with 12/246 (4.9%) patients in the 130 mg ustekinumab dose group and 18/249 (7.2%) in the 6 mg/kg ustekinumab dose group during Study 3001. Except for Crohn’s disease, no SAE occurred in more than 1 patient in either ustekinumab dose group. In the placebo group, 2 patients experienced both SAEs related to Crohn’s disease and diarrhea.

Table 22: Patients Who Experienced 1 or More Serious Adverse Events through Week 8 in Study 3001

Dictionary-Derived Term	Placebo		UST 130		UST 6 mg/kg	
	N=245		N=246		N=249	
	Patient Count	%	Patient Count	%	Patient Count	%
Cardiac Disorders						
Atrial fibrillation	0	0.0	0	0.0	1	0.4
Cardiac failure	0	0.0	0	0.0	1	0.4
Intracardiac thrombus	1	0.4	0	0.0	0	0.0
Gastrointestinal Disorders						
Abdominal pain	0	0.0	0	0.0	1	0.4
Colonic fistula	0	0.0	0	0.0	1	0.4

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Crohn's disease	9	3.7	7	2.8	5	2.0
Dental caries	1	0.4	0	0.0	0	0.0
Diarrhea	2	0.8	0	0.0	0	0.0
Gastric ulcer hemorrhage	0	0.0	0	0.0	1	0.4
Large intestine perforation	1	0.4	0	0.0	0	0.0
Small intestinal obstruction	0	0.0	0	0.0	1	0.4
General disorders and administration site conditions						
Pyrexia	1	0.4	0	0.0	0	0.0
Hepatobiliary disorders						
Cholangitis	0	0.0	0	0.0	1	0.4
Immune system disorders						
Hypersensitivity	0	0.0	0	0.0	1	0.4
Infections and infestations						
Abscess intestinal	0	0.0	0	0.0	1	0.4
Anal abscess	1	0.4	0	0.0	0	0.0
Clostridial infection	0	0.0	0	0.0	1	0.4
Escherichia sepsis	0	0.0	0	0.0	1	0.4
Gastroenteritis	0	0.0	1	0.4	0	0.0
Infected fistula	1	0.4	0	0.0	0	0.0
Intervertebral discitis	0	0.0	0	0.0	1	0.4
Meningitis listeria	0	0.0	0	0.0	1	0.4
Pelvic abscess	0	0.0	1	0.4	0	0.0
Perineal abscess	0	0.0	0	0.0	1	0.4
Peritonitis	0	0.0	0	0.0	1	0.4
Pneumonia	1	0.4	0	0.0	0	0.0
Postoperative abscess	1	0.4	0	0.0	0	0.0
Vulval abscess	0	0.0	1	0.4	0	0.0
Injury, poisoning and procedural complications						
Road traffic accident	0	0.0	0	0.0	1	0.4
Investigations						
Blood electrolytes abnormal	0	0.0	1	0.4	0	0.0
Metabolism and nutrition disorders						
Dehydration	0	0.0	1	0.4	0	0.0
Hypocalcaemia	0	0.0	1	0.4	0	0.0
Hypokalemia	1	0.4	1	0.4	0	0.0
Hypomagnesaemia	0	0.0	1	0.4	0	0.0
Malnutrition	1	0.4	0	0.0	0	0.0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
Multiple myeloma	0	0.0	0	0.0	1	0.4
Renal and urinary disorders						
Nephrolithiasis	0	0.0	1	0.4	0	0.0
Reproductive system and breast disorders						
Female genital tract fistula	0	0.0	0	0.0	1	0.4
Respiratory, thoracic and mediastinal disorders						
Asthma	0	0.0	1	0.4	0	0.0
Pulmonary embolism	0	0.0	1	0.4	0	0.0
Vascular disorders						
Lymphocele	0	0.0	0	0.0	1	0.4

Phlebitis superficial	0	0.0	1	0.4	0	0.0

Source: Reviewer created table using MAED based on Applicant dataset "adae": from BLA 761044, Section 5.3.5.1 Study 3001.

Of note, for serious adverse events, gastrointestinal disorders had the highest proportion of patients who experienced an SAE: 13/245 (5.3%) patients in the placebo dose group, 7/246 (2.8%) patients in the 130 mg ustekinumab dose group, and 9/249 (3.6%) patients in the 6 mg/kg ustekinumab dose group. These proportions were numerically similar across treatment groups, and highest in the placebo dose group. Within gastrointestinal disorders, however, Crohn's disease was reported in the highest proportion of patients, and was the only SAE that occurred in more than one patient among the ustekinumab dose groups. Diarrhea occurred in two patients in the placebo group. The high number of Crohn's disease-related SAEs appears to be more reflective of the underlying disease rather than a safety concern and occurred in a higher proportion of patients in the placebo arm. However, a higher proportion of SAEs in the Infections and Infestations SOC were reported at a higher proportion in patients in the 6 mg/kg ustekinumab dose group (7/249 patients, 2.8%) than in the placebo (4/245 patients, 1.6%) and 130 mg ustekinumab (3 patients, 1.2%) dose groups. The higher proportion of patients experiencing SAEs in this SOC is balanced out when considering the proportions of serious infections and infestations that occurred in study 3002, where the lowest proportion of patients experiencing serious infections was in the 6 mg/kg dose group (Table 23 on study 3002 below). Given that the occurrence of serious infections was not consistently observed to be higher in the 6 mg/kg ustekinumab dose group across the two induction trials, this reviewer is not concerned regarding the predominance of serious infection in the 6 mg/kg dose group in study 3001.

Reasonably related adverse events were defined as any event with a relationship to study agent of "very likely," "probable," or "possible" on the AE page of the eCRF or if the relationship to study agent was missing. The Applicant determined that there were six patients who experienced SAEs that were thought to be treatment related: 2/245 (0.8%) patients in the placebo group and 4/249 (1.6%) patients in the 6 mg/kg ustekinumab dose group. This reviewer identified an additional patient with Escherichia (E. coli) sepsis in the 6 mg/kg dose group bringing that proportion to 5/249 (2.0%). The reasonably related SAEs included infected fistula and viral pneumonia in the placebo dose group, and intestinal abscess, listeria meningitis, colonic fistula, and cholangitis, and E. coli sepsis in the 6 mg/kg ustekinumab dose group. In this reviewer's opinion after reviewing the CRFs, the events in the placebo dose group were not reasonably related to the study drug as the patients did not receive the drug. In the 6 mg/kg dosing arm, the colonic fistula and intestinal abscess may have been related to treatment failure rather than ustekinumab. The patients with cholangitis and E. coli sepsis were additionally on steroids, which further suppress the immune system, and it is difficult to determine causality. The patient with E. coli sepsis was also determined to have had a past diagnosis of monoclonal IgG kappa gammopathy of undetermined significance (MGUS) which

additionally may have confounded the SAE. The patient with listeria meningitis may have been more prone to developing the infection because he/she received ustekinumab. Serious infections are known to be associated with ustekinumab treatment based on the approved labelling for the other indications. This patient is more fully discussed in the section on opportunistic infections in Section 7.5.1, Infections below.

Additionally, the Applicant reports 9 SAEs in 5 patients after Week 8 who did not continue into the maintenance study, 4 SAEs occurred in 1 patient in the placebo dose group: two serious infections (postoperative abscess, dental caries), and the same patient also had an SAE of intracardiac thrombus and subsequent pulmonary embolism. The remaining SAEs included 2 events of Crohn’s disease in 2 patients in the placebo dose group, asthma and pulmonary embolism (PE) in 1 patient in the 130 mg ustekinumab dose group, who had a history of cardiac surgery and atrial septal defect, and developed a PE 3 months after the dose of intravenous ustekinumab. This patient did not continue into maintenance study due to lack of efficacy of ustekinumab. Another patient in the 6 mg/kg ustekinumab dose group developed multiple myeloma. This is the same patient who had a history of monoclonal IgG kappa gammopathy of undetermined significance (MGUS) and did not enter maintenance because he/she was retrospectively determined to be ineligible for the trial.

Study 3002

For study 3002, the number of patients with 1 or more SAEs through Week 8 is presented below in Table 23. The proportion of patients who had 1 or more SAEs was 12/208 (5.8%) patients in the placebo dose group compared with 10/212 (4.7%) patients in the 130 mg ustekinumab dose group and 6/207 (2.9%) patients in the 6 mg/kg ustekinumab dose group during study 3002. Except for Crohn’s disease-related SAEs, no SAE occurred in more than 1 patient in any dose group.

Table 23: Patients Who Experienced 1 or More Serious Adverse Events through Week 8 in Study 3002

Dictionary-Derived Term	Placebo		UST 130		UST 6 mg/kg	
	N=208		N=212		N=207	
	Patient Count	%	Patient Count	%	Patient Count	%
Blood and lymphatic system disorders						
Anemia	1	0.5	1	0.5	0	0.0
Pancytopenia	1	0.5	0	0.0	0	0.0
Cardiac disorders						
Atrial fibrillation	1	0.5	0	0.0	0	0.0
Gastrointestinal disorders						

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Crohn's disease	5	2.4	5	2.4	2	1.0
Small intestinal obstruction	1	0.5	1	0.5	2	1.0
Colitis	0	0.0	0	0.0	1	0.5
Diarrhea	0	0.0	1	0.5	0	0.0
Intestinal obstruction	1	0.5	0	0.0	0	0.0
Localized intraabdominal fluid collection	0	0.0	1	0.5	0	0.0
Small intestinal perforation	1	0.5	0	0.0	0	0.0
General disorders and administration site conditions						
Impaired healing	0	0.0	1	0.5	0	0.0
Non-cardiac chest pain	0	0.0	1	0.5	0	0.0
Hepatobiliary disorders						
Bile duct stone	1	0.5	0	0.0	0	0.0
Infections and infestations						
Anal abscess	3	1.4	2	0.9	0	0.0
Gastroenteritis	0	0.0	0	0.0	1	0.5
Genital herpes	1	0.5	0	0.0	0	0.0
Pneumonia	1	0.5	0	0.0	0	0.0
Injury, poisoning and procedural complications						
Incisional hernia	0	0.0	1	0.5	0	0.0
Nervous system disorders						
Headache	1	0.5	0	0.0	0	0.0
Reproductive system and breast disorders						
Dysmenorrhea	1	0.5	0	0.0	0	0.0
Respiratory, thoracic and mediastinal disorders						
Pneumothorax spontaneous	0	0.0	1	0.5	0	0.0
Pulmonary granuloma	0	0.0	1	0.5	1	0.5

Source: Reviewer created table using MAED based on Applicant dataset "adae": from BLA 761044, Section 5.3.5.1 Study 3002.

Of note, for serious adverse events, the highest proportion occurred in the gastrointestinal disorder SOC: 8/208 (3.8%) patients in the placebo dose group, 8/212 (3.8%) patients in the 130 mg ustekinumab dose group, and 5/207 (2.4%) patients in the 6 mg/kg ustekinumab dose group. These percentages were numerically similar across treatment dose groups, and highest in the placebo dose group. Crohn's disease and its sequelae (i.e., small intestinal obstruction, and anal abscess) were the only SAEs reported in more than 1 patient in any treatment dose group. Crohn's disease was reported as an SAE in 5/208 (2.4%) patients in the placebo dose group and 5/212 (2.4%) and 2/207 (1.0%) patients in the 130 mg and 6 mg/kg ustekinumab dose groups, respectively. As placebo and the 130 mg dose groups had greater than twice the proportion of Crohn's disease SAEs than the 6 mg/kg dose group, this reviewer concludes this

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may have been due to inferior treatment effect in the 130 mg dose group as compared to the 6 mg/kg dose group in this study population. However, the numbers are small overall. It appears slightly more patients had SAEs in both the placebo and 130 mg dose groups than in the 6 mg/kg dose group.

SAEs of note that occurred in the ustekinumab 130 mg dose group included events of noncardiac chest pain (1 patient) that occurred one month after dosing during an episode of vigorous exercise along with shortness of breath and brief syncope (2-3 minutes). The patient was evaluated, found to have a normal ECG, and released from emergency care without treatment. In another patient, spontaneous pneumothorax was reported on Study Day 4 (1 patient). The event resolved with surgical intervention including a thoracoscopy and wedge resection, followed by reinflation of the lung. This did not appear related to the study drug and the patient recovered and continued on into the maintenance study. A third patient experienced impaired wound healing after an incisional hernia repair with contents of the small bowel resected. The patient was noted to have an enterocutaneous fistula to the abdominal wall upon hernia repair. A re-appearance of an enterocutaneous fistula through the wound occurred 3 weeks later (one month after the IV dose). This patient was also on steroids and withdrew consent for the study. There were no notable SAEs in the 6 mg/kg ustekinumab dose group. Two patients within the placebo dose group also had SAEs of note; 1 patient had pancytopenia and another patient experienced rapid atrial fibrillation during a serious event of pneumonia.

Reasonably related adverse events were defined as any event with a relationship to study agent of “very likely,” “probable,” or “possible” on the AE page of the eCRF or if the relationship to study agent was missing. The Applicant reported the following SAEs that were designated as reasonably related: 1/208 (0.5%) patient in the placebo dose group, 2/212 (0.9%) patients in the 130 mg dose group, and 0/207 patients in 6 mg/kg ustekinumab dose groups, respectively. The Applicant identified reasonably related SAEs included one patient with pancytopenia in the placebo dose group (this patient was unblinded during the study and eventually withdrew consent), and diarrhea and anal abscess in another patient the 130 mg dose group. In this reviewer’s opinion after reviewing the CRFs, the placebo dosing events were not reasonably related to the study drug as the patients did not receive the drug. In the 130 mg dose group, the diarrhea appeared to be related to either a food-borne illness or a flare of Crohn’s disease (of which the patient had many sequelae in the following month including bowel obstruction, anemia, and finally, Crohn’s flare). The patient with the anal abscess underwent perianal fistula closure. This patient was concomitantly on azathioprine and mesalamine and withdrew consent following surgery. In this reviewer’s opinion, both SAEs in the ustekinumab arm may have resulted from treatment failure as the events are reflective of signs/symptoms and complications of Crohn’s disease, rather than indicative of a safety concern related to ustekinumab. This reviewer did not identify any further potentially related SAEs in study 3002.

Additionally, the Applicant reports 6 SAEs in 6 patients after Week 8. Of the 6 SAEs, 4 were serious infections (anal abscess [2 patients in the placebo dose group, one of whom withdrew consent from the study due to lack of efficacy, the other was unblinded and did not continue with the randomized maintenance population], genital herpes [1 patient in the placebo dose group who did not continue in maintenance and experienced multiple Crohn’s disease flares during the study] and localized intraabdominal fluid collection [1 patient in the ustekinumab 130 mg dose group]) which occurred 3.5 months after receiving ustekinumab as sequelae of a surgery for pelvic abscess thought to be related to Crohn’s disease flare. The remaining 2 SAEs were headache (1 patient in the placebo dose group who discontinued after Week 8 and did not enroll into the maintenance trial for lack of efficacy) and pulmonary granuloma (1 patient in the ustekinumab 6 mg/kg dose group). The pulmonary granuloma occurred 3.5 months after the ustekinumab dose. This patient underwent multiple diagnostic techniques: bronchoscopy with lymph node biopsy, PET-CT, and mediastinoscopy with biopsy, however; the as the granuloma remained stable at last follow up nearly 2 years post ustekinumab dose, the patient was being monitored without change in status of the granuloma.

Study 3003

In the maintenance trial, the overall proportion of patients experiencing 1 or more SAEs was comparable between the 3 dosing regimens with 28/133 (21%) in the placebo regimen, compared with 25/132 (18.9%) in the ustekinumab 90 mg q12w dosing regimen and 19/131 (14.5%) in the ustekinumab q8w dosing regimen. However, the proportion of patients with SAEs was the lowest in the q8 week dosing regimen. This was in part, influenced by the majority of SAEs in each dosing regimen occurring with Crohn’s related illness, with the most Crohn’s related illnesses in the placebo dosing regimen, followed by the q12w dosing regimen, then the q8w dosing regimen. Please refer to Table 24 below for a summary of SAEs.

Table 24: Patients Who Experienced 1 or More Serious Adverse Events through Week 44 in Maintenance Study 3003

Dictionary-Derived Term	90 mg Q12		90 mg Q8 W		Placebo SC	
	N=132		N=131		N=133	
	Subject Count	%	Subject Count	%	Subject Count	%
Gastrointestinal disorders						
Crohn's disease	8	6.1	6	4.6	10	7.5
Small intestinal obstruction	1	0.8	1	0.8	1	0.8
Anal fistula	0	0.0	0	0.0	2	1.5
Large intestinal stenosis	0	0.0	2	1.5	0	0.0
Abdominal hernia	0	0.0	1	0.8	0	0.0
Abdominal pain	0	0.0	1	0.8	0	0.0

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Enterovesical fistula	0	0.0	0	0.0	1	0.8
Gastrointestinal hemorrhage	0	0.0	1	0.8	0	0.0
Large intestinal obstruction	0	0.0	1	0.8	0	0.0
Large intestine perforation	0	0.0	0	0.0	1	0.8
General disorders and administration site conditions						
Asthenia	0	0.0	0	0.0	1	0.8
Hepatobiliary disorders						
Cholecystitis	1	0.8	0	0.0	0	0.0
Infections and infestations						
Pneumonia	0	0.0	2	0.8	2	1.5
Anal abscess	1	0.8	0	0.0	1	0.8
Appendicitis	2	1.5	0	0.0	0	0.0
Abdominal infection	1	0.8	0	0.0	0	0.0
Bacteremia	1	0.8	0	0.0	0	0.0
Gastroenteritis	3	2.3	0	0.0	0	0.0
Influenza	0	0.0	0	0.0	1	0.8
Ophthalmic herpes zoster	0	0.0	1	0.8	0	0.0
Peritonitis	1	0.8	0	0.0	0	0.0
Pneumonia pneumococcal	0	0.0	1	0.8	0	0.0
Postoperative wound infection	1	0.8	0	0.0	0	0.0
Viral infection	0	0.0	1	0.8	0	0.0
Injury, poisoning and procedural complications						
Allergic transfusion reaction	1	0.8	0	0.0	0	0.0
Musculoskeletal and connective tissue disorders						
Arthralgia	0	0.0	0	0.0	1	0.8
Fibromyalgia	0	0.0	0	0.0	1	0.8
Lumbar spinal stenosis	0	0.0	0	0.0	1	0.8
Rotator cuff syndrome	1	0.8	0	0.0	0	0.0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
Meningioma	0	0.0	0	0.0	1	0.8
Ovarian adenoma	0	0.0	1	0.8	0	0.0
Nervous system disorders						
Headache	0	0.0	0	0.0	1	0.8
Migraine	0	0.0	1	0.8	0	0.0
Psychiatric disorders						
Depression	0	0.0	0	0.0	1	0.8

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Suicidal ideation	1	0.8	0	0.0	0	0.0
Renal and urinary disorders						
Nephrolithiasis	0	0.0	0	0.0	1	0.8
Social circumstances						
Substance abuser	0	0.0	0	0.0	1	0.8
Vascular disorders						
Deep vein thrombosis	1	0.8	0	0.0	0	0.0
Essential hypertension	1	0.8	0	0.0	0	0.0

Source: Reviewer created table using MAED based on Applicant dataset "adae": from BLA 761044, Section 5.3.5.1 Study 3003.

From this reviewer's analysis, the number of patients experiencing SAEs in the three dosing regimens was lowest in the 90mg SC q8w dosing regimen and was distributed as follows: placebo 28/133 (21.1%), q12w 25/132 (18.9%), and q8w 19/131 (14.5%). Again, note that the most common serious adverse event is Crohn's disease related events, of which the proportion was highest in the placebo dosing regimen (10/133 [7.5%]), followed by the q12 (8/132 [6.1%]), then the q8 (6/131 [4.6%]) dosing regimens. The trend between the three dosing regimens may indicate a greater therapeutic effect of the q8 week dosing regimen. Infections and infestations occurred most commonly in the q12w dosing regimen, and were driven by gastroenteritis. Gastrointestinal infection causing gastroenteritis could occur more often in the setting of inflamed bowel. However, this was not seen in the placebo or in the q8w dosing regimens. Therefore, it is unclear as to why it occurred more frequently in the q12 dosing regimen. See Section 7.5.1 on Infections for further discussion.

As the most common serious treatment related event is Crohn's disease related events, of which the proportion was highest in placebo, followed by the q12, then the q8 dosing regimens. The trend between the three dosing regimens may indicate a greater therapeutic effect of the q8 week dosing regimen. Infections and infestations occurred most in the q12w dosing regimen, and were driven by gastroenteritis which did not occur in the placebo or q8 week dosing regimens. Gastrointestinal infection causing gastroenteritis could occur more often in the setting of inflamed gastrointestinal tract; however, this was not seen in the placebo dosing regimen which also may have had more inflamed gastrointestinal tract. Therefore, it is unclear as to why it occurred more frequently in the q12w dosing regimen. See Section 7.5.1 on Infections for further discussion.

Appendicitis occurred twice in the q12w dosing regimen and not in any other dosing regimen. This reviewer notes that this can be an early sign of Crohn's disease (although some believe it is

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likely diagnostic bias)⁴⁶, but there does not appear to be a clear relationship between ustekinumab and appendicitis based on the limited population that experienced this event. Likewise, large intestinal stenosis occurred in two patients in the q8w dosing regimen and not in the q12w or placebo dosing regimens. This reviewer concludes neither event appears to be related at this time to ustekinumab based on the occurrence of appendicitis in two patients and given that intestinal stenosis is a known complication of Crohn's disease.

Of the serious infections that occurred in more than twice the proportion of patients in the q12w dosing as in the placebo or q8w dosing regimens. Infections could be a combination of lack of therapeutic effect, as patients with Crohn's disease can be immunosuppressed, and the immunosuppression is compounded by the study drug. Serious infections are currently included in the approved label for ustekinumab for the psoriasis and psoriatic arthritis indications.

Ovarian carcinoma occurred in one patient in the q8w dosing regimen during this study. Ovarian carcinoma is not currently included in the labeling as it has not occurred at a higher frequency with ustekinumab use. This reviewer notes that incidence is not higher than that in the general population using the National Institutes of Health Surveillance, Epidemiology, and End Results database on cancer SEER database⁴⁷. (See Section 7.5.3 on Malignancy below for further discussion). Overall, this reviewer concludes that the current labeling adequately describes serious infections and malignancy and none of these events below from study 3003 warrants inclusion in the label with the addition of a few noted serious infections. See Section 9 on Labeling Recommendations for further discussion.

Reasonably related adverse events were defined as any event with a relationship to study agent of "very likely," "probable," or "possible" on the AE page of the eCRF or if the relationship to study agent was missing. This reviewer identified 2/133 (1.5%) in placebo (patient's SAE occurred after receiving dosing adjustments for loss of response to active drug), 4/132 (3.0%) in q12w, and 5/131 (3.8%) in q8w dosing regimens.

The patients in the placebo regimen experienced influenza and depression. The patients with depression and influenza were initially randomized to placebo but received a 90mg SC q8 dosing regimen after he/she met criteria for loss of response. This patient received the dose of ustekinumab on 10/26/12 and was hospitalized on 11/29/12 with new psychiatric manifestations with depressive features. This patient was discharged from the hospital on 12/3/12 and discontinued from the study due to the depression. The patient who contracted influenza and was hospitalized did so 1 week after receiving a single 90mg SC dose of ustekinumab. As ustekinumab is an immunosuppressant, patients are vulnerable to infectious

⁴⁶ Kaplan et al. 2007. The risk of developing Crohn's disease after an appendectomy: a population-based cohort study in Sweden and Denmark

⁴⁷ <http://seer.cancer.gov/> Website last accessed 8/5/2016.

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diseases as is noted in the currently approved label. This patient recovered, continued ustekinumab for the duration of the maintenance study, and enrolled in the LTE study.

In the 90mgSC q12w dosing regimen serious AEs that were reasonably related were: gastroenteritis (x2), abdominal infection, and suicidal ideation. One patient with gastroenteritis had an endoscopy that was “suggestive” of viral gastroenteritis but no confirmed organism was available. The other patient was diagnosed with *Campylobacter jejuni* gastritis after an endoscopy during hospitalization for fever, abdominal pain, diarrhea, and acute renal insufficiency. Both patient with gastroenteritis recovered, finished the study, and went on to enter the LTE. The patient with the abdominal infection appeared to have it as a result of worsening Crohn’s disease with structuring and ulceration. Serious infections are already listed in the approved label of ustekinumab. The patient with suicidal ideation had a history of depression for years before starting ustekinumab. He/she was hospitalized on 6/15/2012 after 2 maintenance doses of ustekinumab with complaints of depression and suicidal ideation worsened that had worsened over the past 2 months. The patient’s depression medications were adjusted and the patient felt better. This patient had multiple episodes of recurring Crohn’s disease and one more episode of recurring depression and eventually withdrew from the study. This reviewer believes it is difficult to conclude that the suicidal ideations were a result of ustekinumab as the patient had a previous history of the disease; however, it is a possible that the drug initiated worsening depression.

In the 90mgSC q8w dosing regimen serious AEs that were reasonably related were: pneumonia (x3), viral infection, ophthalmic herpes zoster. One patient with pneumonia was hospitalized with vomiting, fever and hemoptysis. CT indicated pneumonia as well as active Crohn’s disease. Sputum was positive for *S. pneumonia* the patient was treated with multiple antibiotics and discharged in a week. This patient did not continue the study due to the adverse event. A second patient developed lower left lobar pneumonia while in the hospital recovering from surgery for an abdominal stricture. This patient had already completed the study receiving their last dose a month prior to the development of the pneumonia. The third patient with pneumonia was hospitalized 3 days after their final study dose of ustekinumab for acute onset of dyspnea on exertion, mild congestion, and a non-productive cough with reports of having fever, chills, and fatigue for 2 weeks. Chest radiograph showed bilateral lower lobe pneumonia and the patient was discharged home the next day on oral antibiotics. This patient continued on ustekinumab in the LTE. Another patient experienced a “viral infection” consisting of headache, neck stiffness, and sinus congestion during a hospitalization for a Crohn’s flare that occurred 5 days after his/her dose of ustekinumab. This patient was discharged after resolution of the Crohn’s flare and continued the study as well as entered the LTE. The final patient in this dosing regimen developed ophthalmic herpes zoster 6 days after a dose of ustekinumab and is discussed further below in the section on serious infections. This patient completed treatment with prednisolone acetate eye drops and valacyclovir before going on to complete the maintenance study and went on to enter the LTE. Serious infections are already listed in the

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approved label of ustekinumab.

7.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Study 3001

In study 3001, 14/247 (5.7%) patients in the placebo group discontinued due to an AE compared with 3/246 (1.2%) patients in the 130 mg and 7/249 (2.8%) in the 6 mg/kg ustekinumab dose groups. Crohn's disease was the most common event that led to discontinuation in 11/14 patients in the placebo arm and 2/3 patients in the 130 mg treatment dose group. However, only 1/7 patients withdrew from the 6 mg/kg dose group due to worsening Crohn's disease. When combined with the second induction study (Study 3002), the proportion of patients who discontinued due to an AE are 13/19 (68.4%) patients in the placebo dose group, 4/7 (57.1%) in the 130 mg dose, and 1/8 (12.5%) in the 6 mg/kg dose group. While the numbers are small, the data suggest improved efficacy in the 6 mg/kg dose group as there were proportionately fewer discontinuations due to Crohn's disease in the 6 mg/kg dose group as compared to the 130 mg dose group or placebo.

Of those patients who discontinued for other reasons, there was one patient in the placebo dose group who developed an infected fistula, one patient with diabetes that led to complications with the patient's foot, and another patient discontinued for pregnancy. The infected fistula could be considered a complication of Crohn's disease, while the others are unlikely to be related to Crohn's disease.

In the 130 mg ustekinumab dose group, other than the 2 patients who discontinued for Crohn's disease, one patient discontinued for pyrexia related to the ustekinumab infusion. This patient was initially randomized to the 6 mg/kg dose group, however, the patient had a fever of 101.8 F prior to infusion of ustekinumab which increased to 103.7 F during infusion. The infusion was halted due to the increase in temperature. The total dose received approximated the 130 mg dose; therefore this patient was analyzed in the 130 mg drug dose group. It is difficult to determine whether this was a fever related to drug infusion or the natural course of an underlying illness as the patient was febrile prior to the infusion.

In the 6 mg/kg dose group, other than the one patient who discontinued for Crohn's disease, the 6 remaining patients discontinued for the following reasons: colonic fistula, inguinal hernia, listeria meningitis, perineal abscess, elevated immunoglobulin E, and leukocytic vasculitis. This reviewer concludes that the colonic fistula and perineal abscess could possibly be Crohn's related events since fistula and abscess are associated complications of Crohn's disease. The inguinal hernia is not likely to be related to ustekinumab infusion. The patient with elevated IgE

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also had a history of allergic bronchopulmonary aspergillosis before study entry and had an IgE level drawn nearly 2 months after study drug infusion for potential management of his allergic bronchopulmonary aspergillosis. This patient was discontinued as it was determined further steroid treatment that would be required for his/her bronchopulmonary condition would confound the results of the ustekinumab treatment. It is this reviewer's opinion that the study drug is unlikely the cause for the elevation of IgE. In contrast, listeria meningitis is rare and likely an infection related to immunosuppression from receiving the drug. The patient fully recovered with amoxicillin treatment. The patient with leukocytoclastic vasculitis received the study drug on 11/27/2012 and presented to clinic on 12/12/12 with bilateral lower limb erythema and rash. The patient suffered a similar reaction during prior therapy with infliximab and certolizumab but the diagnosis was only confirmed as vasculitis by punch biopsy after receiving certolizumab in 1/2007. The patient withdrew from the study. This patient possibly experienced a hypersensitivity reaction to ustekinumab; however, given the prior history of vasculitis with other therapies and the rare but potential association with inflammatory bowel disease described in the literature through case reports, it is difficult to establish definite causality with ustekinumab.⁴⁸ See Section 7.5.2 below on Hypersensitivity reactions for further discussion.

Study 3002

In Study 3002, overall 5/208 (2.4%) patients discontinued placebo dose group, due to an AE compared with 4/212 (1.9%) patients in the 130 mg and 1/207 (0.4%) in the 6 mg/kg ustekinumab dose groups. An AE of Crohn's disease was the most common event that led to discontinuation overall in 2/5 patients in the placebo dose group, and 2/4 patients in the 130 mg treatment dose groups, combined numbers for the induction trials for this category of AE can be seen in the section on study 3001 above. Of those patients who discontinued for reasons other than for Crohn's disease-related AEs, in the 130 mg the ustekinumab dose group, one patient (1029-20618) discontinued because of a SAE of chest discomfort during infusion, with associated pyrexia, flushing, pruritus and urticarial. Treatment included discontinuation of the infusion, loratadine, and ranitidine and all symptoms lasted less than one hour and resolved the same day. This patient is considered by the reviewer to have experienced a hypersensitivity reaction and is further discussed in the Section 7.5.2 below on hypersensitivity reactions. Another patient reported an anal abscess and after repair of a perianal fistula with diverting ostomy and withdrew from the study. This reviewer concludes that the majority of discontinuations in the 130 mg dose arm were reflective of treatment failure.

In the 6 mg/kg dose group reasons for discontinuations other than Crohn's disease include one patient with a skin rash who withdrew at the request of the investigator as the rash occurred 2

⁴⁸ Hagen JW, Swoger JM and LM Grandinetti. 2015. Cutaneous Manifestations of Crohn's Disease. *Dermatologic Clinics* 33(3): 417-431.

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days after infusion with peripheral edema around the actual infusion. The patient had a history of drug reaction to etanercept, which appeared similar in presentation. This reviewer concludes that this reaction may have been a hypersensitivity reaction to ustekinumab.

In the placebo dose group, other than the 2 patients who discontinued for Crohn's disease flares, 1 patient each) discontinued for small intestinal obstruction and anal abscess (also possibly related to Crohn's disease) as well as hepatitis C. This reviewer concludes that the majority of discontinuations in the placebo arms were due to treatment failure, and the hepatitis C was likely unrelated.

Maintenance Study 3003

In the placebo dosing regimen, 8/133 (6%) patients discontinued due to an AE compared with 10/132 (7%) patients in the 90mg SC q12w and 4/131 (3.1%) in the 90mg SC q8w dosing regimens. Crohn's disease was the most common event that led to discontinuation overall with 3/8 patients in placebo, 3/10 patients in the q12w dosing regimen, and 1/4 patients in the q8w dosing regimen. Other reasons for discontinuation included one patient each in the placebo dosing regimen with anal fistula, enterovesical fistula, large intestine perforation, tuberculosis, and pregnancy. The other reasons for discontinuation in the ustekinumab q12w dosing regimen included one patient each with: anal fistula, intestinal fistula, anal abscess, furuncle, pregnancy, thyroiditis, and rash. The patient who had a rash received a dose of IV ustekinumab on April 13, 2013 and presented with a maculopapular erythematous rash on the right upper extremity in clinic on April 15, 2013. The patient received diphenhydramine and the rash resolved. The patient was discharged from clinic with a 5 day course of methylprednisolone and the patient withdrew on study day 117. The other reasons for discontinuation in the q8w dosing regimen included one patient with large intestinal stenosis and two patients with pregnancy. Many of the gastrointestinal-related reasons for discontinuation could have been related to Crohn's disease (i.e., fistulas, stenosis, perforation), as these events are known to be associated complications of poorly controlled Crohn's disease. Since many of the gastrointestinal-related reasons for discontinuation are likely reflective of the underlying Crohn's disease, this reviewer combined the gastrointestinal-related reasons for discontinuation with the AEs designated as due to Crohn's disease complications. The proportion of patients who discontinued for Crohn's related AEs increases in each dosing regimen were 6/8 (75%) in the placebo regimen, 6/10 (60%) in the q12 dosing regimen and 1/3 (33%) q8 dosing regimen. While the numbers are small, proportionally, there were greater Crohn's related discontinuations, which appear to be more reflective of loss of efficacy, occurred in the placebo and q12w dosing regimens as compared to the q8w dosing regimen, further supporting the q8 week maintenance regimen as the preferred regimen.

7.4.4. Significant Adverse Events

Please refer to Categorization of Adverse Events in Section 7.3.2 for the categorization of

adverse events employed by the Applicant.

Study 3001

The proportion of adverse events considered to be severe intensity through week 8 of study 3001 occurred in 17/245 (6.9%) patients who experienced 27 severe adverse events in the placebo dose group, 17/246 (6.9%) patients who experienced 23 severe adverse events in the 130 mg dose group, and 27/249 (10.8%) patients who experienced 37 severe adverse events in the 6 mg/kg dose group. As in other adverse event analyses, the gastrointestinal disorders comprised the largest SOC grouping of adverse events for each dose group, with Crohn's disease related severe events as the most frequently reported with 9 events in placebo and 4 in the 130 mg dose group. However, the 6 mg/kg dose group had only 2 severe Crohn's disease events recorded. This reviewer concludes that this illustrates the trend of lower efficacy in the 130 mg dose group. Otherwise, the 6 mg/kg dose group appeared to have a higher proportion of severe intensity adverse events due to a larger number of overall gastrointestinal and infectious events than either placebo or the 130 mg dose group.

The number of infections was second highest out of the SOC classes, with 15 severe events: 2 events, (one event of pneumonia and one of an infected fistula) in the placebo dose group, 5 events (gastroenteritis [x2], ophthalmic herpes zoster, oral herpes, and pelvic abscess) in the 130 mg dose group, and 8 events (gastroenteritis, intestinal abscess, anal abscess, anal fistula infection, clostridial infection, E. coli sepsis, listeria meningitis, and perineal abscess) in the 6 mg/kg dose group. There appear to be more infections in the ustekinumab dose groups than in the placebo dose group. Ustekinumab is already labeled for serious infection risk in the approved label.

For further discussion on the infections, please see Section 7.5.1, Infections .

Study 3002

The proportion of adverse events considered to be severe intensity through week 8 of study 3002 occurred in 14/208 (6.7%) patients who experienced 18 severe adverse events in the placebo dose group, 12/212 (5.7%) patients who experienced 17 severe adverse events in the 130 mg dose group, and 11/207 (5.3%) patients who experienced 17 severe adverse events in the 6 mg/kg dose group. As in other adverse event analyses, the gastrointestinal disorders comprised the largest SOC grouping of adverse events for each dose group, with Crohn's disease related severe events the most frequently reported with 3 events in placebo, 4 in the 130 mg dose group, and 2 in the 6 mg/kg dose group. There were twice as many severe events in the 130 mg dose group as compared to the 6 mg/kg dose group, which further supports this reviewer's conclusion of improved efficacy in the 6 mg/kg dose. However, there were 4 events of severe intensity abdominal pain in patients in the 6 mg/kg dose group, as opposed to 1 in

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placebo and none in the 130 mg dose group.

The number of infections was second highest out of the SOC classes, with 5 severe events: one event of pneumonia in the placebo dose group, 3 events (bronchitis, anal abscess, and otitis media) in the 130 mg dose group, and 2 events (groin abscess and urinary tract infection) in the 6 mg/kg dose group. There do not appear to be meaningful differences or clear trends among the severe infection rates between dose groups. For further discussion on the infections, please see Section 7.5.1, Infections.

Study 3003

The proportion of adverse events considered to be severe intensity through week 44 of study 3003 occurred in 32/133 (24.1%) patients who experienced 55 severe adverse events in the placebo dosing regimen, 28/132 (21.2%) patients who experienced 40 severe adverse events in the q12w dosing regimen, and 30/131 (22.9%) patients who experienced 42 severe adverse events in the q8w dosing regimen. As in other adverse event analyses, the gastrointestinal disorders comprised the largest SOC grouping of adverse events for each dosing regimen, with Crohn's disease related severe events the most frequently reported. The proportion of severe Crohn's disease related events was comparable across the dosing regimens: 9/133 (6.8%) in placebo, 8/132 (6.1%) in the q12w dosing regimen and 8/131 (6.1%) in the q8w dosing regimen.

Also similar to other adverse event analyses, the infections and infestations class was the second highest SOC. Again, the numbers are comparable across the dosing regimens. For further discussion on infections, please see Section 7.5.1.

One patient developed ovarian adenocarcinoma previously discussed in the Section 7.4.2 on Serious Adverse Events.

Of note, patient 1018-10162 is not listed in the table below and had a severe hypersensitivity reaction, which this reviewer concludes was not related to ustekinumab. This patient had a history of chronic anemia and chronic iron deficiency and regularly received blood and iron transfusions for both. Her last dose of ustekinumab q12w was on 10/31/2012. The patient was hospitalized on 11/12/2012 and again on 11/17/2012. The patient was reported to have an "allergic transfusion reaction" listed occurred after a blood and iron transfusion and included symptoms of generalized rash, fatigue, anorexia, malaise, intense pruritus, and facial swelling. Treatment included prednisone, fluconazole, hydroxyzine, and triamcinolone ointment at discharge. The patient continued to be evaluated for continuing symptoms and did not continue in the study.

Table 25: Severe Adverse Events in ≥3% Patients and Higher than Placebo: Study 3003*

Body or System Organ Class	Preferred Term	Placebo N=133 n(%)	90mg SC Q12w N=132 n(%)	90mg SC Q8w N=131 n(%)
Gastrointestinal Disorders	Abdominal pain	5 (3.8%)	5 (3.8%)	3 (2.3%)
Infections and Infestations	Appendicitis	0	2 (1.5%)	0
	Abdominal Infection	0	1 (0.8%)	0
	Bacteremia	0	1 (0.8%)	0
	Clostridium difficile	0	0	1 (0.8%)
	Gastroenteritis	1 (0.8%)	2 (1.5%)	1 (0.8%)
	Ophthalmic herpes zoster	0	0	1 (0.8%)
	Peritonitis	0	1 (0.8%)	0
	Pneumonia	2 (1.5%)	0	2 (1.5%)
	Cystitis	0	1 (0.8%)	1 (0.8%)
	Upper respiratory infection	0	0	2 (1.5%)
	Sinusitis	0	0	1 (0.8%)
	Viral Infection	0	0	1 (0.8%)
	Varicella	0	0	1 (0.8%)
Neoplasms benign, malignant, and unspecified	Ovarian adenoma	0	0	1 (0.8%)

** Infections and Malignancies are currently reported as increased risks for patients using ustekinumab in the approved label, therefore, this reviewer included them in this table regardless of the incidence for reference unless the placebo arm had a higher rate.
 Source: Reviewer created table using Applicant's data from data set "adae" Module 5.3.5.1, BLA 761044, Study 3003.*

7.4.5. Treatment Emergent Adverse Events and Adverse Reactions

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Overall, amongst the 740 patients treated with a single IV induction dose of ustekinumab or placebo at Week 0, the proportion of patients who had at least 1 treatment-emergent adverse event (TEAE) were similar across the treatment groups: 159/245 (64.9%) patients in the placebo group compared with 159/246 (64.6%) patients and 164/249 (65.9%) patients in the 130 mg and 6 mg/kg ustekinumab dose groups, respectively.

Below is a table of events constructed for TEAEs in $\geq 3\%$ of patients receiving ustekinumab. Ustekinumab dose groups higher than placebo are highlighted.

Table 26: Treatment Emergent Adverse Events Reported in $\geq 3\%$ of Ustekinumab Treated Patients with a Higher Incidence in Either Ustekinumab Arm than Placebo in Study 3001

Event	Placebo N=245 n(%)	Ustekinumab 130 mg N=246 n(%)	Ustekinumab 6 mg/kg N=249 n(%)
Arthralgia	18 (7.3)	26 (10.6)	15 (6.0)
Nausea	18 (7.3)	20 (8.1)	13 (5.2)
Abdominal Pain	16 (6.5)	15 (6.1)	19 (7.6)
Vomiting	9 (3.7)	9 (3.7)	11 (4.4)
URI (upper respiratory infection)	9 (3.7)	12 (4.9)	10 (4.0)
Cough	7 (2.9)	8 (3.3)	0

Source: Reviewer's analysis using Applicant's data, BLA 761044, Study 3001 dataset "adae", module 5.3.5.1.

Ustekinumab is already approved for other indications (psoriasis, psoriatic arthritis) and many of these adverse events are already described in the label (e.g. Nasopharyngitis, URI, headache, arthralgia, and nausea) under the other indications. In the CD 3001 trial, arthralgia, nausea, URI, and cough occurred at higher proportions in the 130 mg dose group compared to placebo. However this dose does not appear to be as effective as the 6 mg/kg dose (see efficacy Section 6.1.2 above for discussion). Higher proportions than placebo of abdominal pain, vomiting, and URI are seen with the 6 mg/kg dose. AEs not previously described in the label include abdominal pain and vomiting. As the majority of these are already described in the approved label for other indications, this reviewer recommends combining overall incidences of these events with the other induction study (study 3002) and describing the combined findings of treatment emergent adverse events reported in $\geq 3\%$ of ustekinumab treated patients with a higher incidence in the final approved dose of ustekinumab than placebo.

Study 3002

Overall, amongst the 647 patients treated with a single IV induction dose of ustekinumab or placebo at Week 0, the proportions of patients who reported at least 1 TEAE were similar across the treatment groups: 113/208 (54.3%) of patients in the placebo group compared with 106/212 (50.0%) and 115/207 (55.6%) in the 130 mg and 6 mg/kg ustekinumab dose groups, respectively.

Below is a table of events constructed for TEAEs in $\geq 3\%$ of patients receiving ustekinumab. Ustekinumab dose groups higher than placebo are highlighted.

Table 27: Treatment Emergent Adverse Events Reported in $\geq 3\%$ of Ustekinumab Treated Patients with a Higher Incidence in Either Ustekinumab Arm than Placebo in Study 3002

Event	Placebo N=208 n(%)	Ustekinumab 130 mg N=212 n(%)	Ustekinumab 6 mg/kg N=207 n(%)
Headache	14 (6.7)	20 (9.4)	10 (4.8)
Nausea	5 (2.4)	20 (8.1)	11 (5.3)
Nasopharyngitis	10 (4.8)	10 (4.7)	14 (6.8)
Abdominal Pain	10 (4.8)	7 (3.3)	13 (6.2)
Pyrexia	10 (4.8)	6 (2.8)	11 (5.3)
Vomiting	3 (1.4)	5 (2.4)	9 (4.3)

Source: Reviewer's analysis using Applicant's data, BLA 761044, Study 3002 dataset, module 5.3.5.1.

Ustekinumab is already approved for other indications (plaque psoriasis, psoriatic arthritis). There is a higher incidence of nausea in the 130 mg dosing arm than in the 6 mg/kg dosing arm. Nausea, nasopharyngitis, abdominal pain, pyrexia, and vomiting were reported in a higher proportion of patients in the 6 mg/kg dosing compared to the placebo arm, and headache, nausea, and vomiting were reported in a higher proportion of patients in the 130 mg dosing arm than placebo; therefore, this reviewer concludes combining overall incidences of these events with the other induction study (study 3002) and describing the combined findings of treatment emergent adverse events reported in $\geq 3\%$ of ustekinumab treated patients with a higher incidence in the final approved dose of ustekinumab than placebo. See Labeling Recommendations in Section 9 below for a discussion of recommended labeling revisions.

Study 3003

After the single IV induction dose, eligible patients (responders) were randomized into the maintenance study and received one of three dosing regimens: placebo, 90mg subcutaneous injection every 12 weeks, or 90mg of subcutaneous injection every 8 weeks. Overall, amongst

the 396 patients treated with a single SC induction dose of ustekinumab or placebo at the onset of the maintenance trial, the proportions of patients who had at least 1 treatment-emergent adverse event (TEAE) were similar across the dose arms. The proportion of patients by dosing regimen who experienced at least one TEAE were 42/133 (31.6%) patients in the placebo dosing regimen, 34/132 (25.8%) patients in the q12w dosing regimen, and 39/131 (29.8%) patients in the q8w dosing regimen.

Below is a table of events constructed for TEAEs in $\geq 5\%$ of patients receiving ustekinumab. Ustekinumab dosing regimens higher than placebo are highlighted. Adverse events that meet these criteria where one or both dosing regimens appear more than a single patient higher than placebo are highlighted.

Table 28: Treatment Emergent Adverse Events Reported in $\geq 3\%$ of Ustekinumab Treated Patients with a Higher Incidence in Either Ustekinumab Arm than Placebo in Study 3003

Event	Placebo N=133 n()	Ustekinumab q12w N=132 n()	Ustekinumab q8w N=131 n()
Arthralgia	19 (14.3)	22 (16.7)	18 (13.7)
Headache	15 (11.3)	15 (11.4)	16 (12.2)
Nasopharyngitis	10 (7.5)	17 (12.9)	14 (10.7)
Pyrexia	10 (7.5)	11 (8.3)	5 (3.8)
Diarrhea	7 (5.3)	11 (8.3)	5 (3.8)
Fatigue	6 (4.5)	8 (6.1)	6 (4.6)
Nausea	9 (6.8)	10 (7.6)	4 (3.1)
Influenza	5 (3.8)	8 (6.1)	5 (3.8)
Cough	3(2.3)	4 (3.0)	7 (5.3)
Rash**	7 (5.3)	5 (3.8)	9 (6.9)
Injection site erythema	0	1 (0.8)	7 (5.3)
Gastroenteritis***	6 (4.5)	11 (8.3)	8 (6.1)
Bronchitis	4 (3.0)	1 (0.8)	6 (4.6)

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Vulvovaginal Mycotic Infection	1 (0.8)	1 (0.8)	6 (4.6)
Pruritus	3 (2.3)	2 (1.5)	5 (3.8)
Migraine	3 (2.3)	1 (0.8)	5 (3.8)
Pain In Extremity	0	0	5 (3.8)
Sinusitis	2 (1.5)	6 (4.5)	4 (3.1)
Urinary Tract Infection (UTI)	3 (2.3)	8 (6.1)	5 (3.8)

Source: Reviewer's analysis using Applicant's data, BLA 761044, Study 3003 dataset "adae", module 5.3.5.1.

7.4.6. Laboratory Findings

Study 3001

Hematology Parameters

Laboratory assessments for hematology parameters, including complete blood counts with differentials, were performed at weeks 0, 3, 6, and 8 in this trial. The mean values were comparable across the dosing arms during the 8-week double-blind treatment period. Abnormal changes defined by hemoglobin < 8.5 g/dL, white blood cell count (WBCs) < 3.5 x 10³/μL, neutrophils < 1.5 x 10³/μL or platelets < 100 x 10³/μL occurring in more than 1 patient on more than 1 occasion in any treatment dose group through Week 8 included the following: decreased hematocrit in 2/245 (0.8%) patients in the placebo dose group and 0/246 and 2/249 (0.8%) patients in the 130 mg and 6 mg/kg ustekinumab dose groups, respectively, and decreased lymphocytes in 13/245 (5.3%) patients in the placebo dose group and 7/246 (2.9%) and 10/249 (4.0%) patients in the 130 mg and 6 mg/kg ustekinumab dose groups, respectively. Although these changes were the only significant findings in the hematology labs, no trends were identified between the placebo and the ustekinumab dosing arms. Decreased lymphocytes are reflected in all of the studies and across all of the arms, placebo included. As the proportion of patients with changes in hematology parameters was either similar to or higher in the placebo arm as compared to the ustekinumab dose groups in all instances of hematology lab abnormalities, this reviewer concludes that these changes were unlikely to be related to the study drug.

Serum Chemistry Parameters

Laboratory assessments for serum transaminase, chemistry, bilirubin, total protein, albumin, and alkaline phosphatase were performed at weeks 0, 3, 6, and 8 in this trial. No clinically meaningful trends were identified between the ustekinumab dosing arms and placebo dose

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groups in serum chemistry lab values. The only markedly abnormal change in chemistry laboratory values that was observed in more than 1 patient on more than 1 occasion in any treatment dose group through Week 8 was decreased albumin in 2/249 (0.8%) patients in the placebo dose group and no patients in the ustekinumab dose groups. This reviewer notes that low albumin is often observed in patients with Crohn's disease whose disease is not well controlled.

Study 3002

Hematology Parameters

Laboratory assessments for hematology parameters, including complete blood counts with differentials, were performed at weeks 0, 3, 6, and 8 in this trial. The mean values were comparable across the dosing arms during the 8-week double-blind treatment period. The only abnormal changes occurring in more than 1 patient on more than 1 occasion in any treatment dose group through Week 8 were decreased lymphocytes in 12/208 (5.9%) patients in the placebo dose group compared with 6/212 (2.8%) and 2/207 (1.0%) patients in the 130 mg and 6 mg/kg ustekinumab dose groups, respectively. Decreased lymphocytes were reflected in all of the studies and across all of the arms, placebo included. As the proportion of patients with changes in hematology parameters was either similar to or higher in the placebo arm compared to the ustekinumab dose groups in all instances of hematology lab abnormalities, this reviewer concludes that these changes were unlikely to be related to the study drug.

Serum Chemistry Parameters

Laboratory assessments for serum transaminase, chemistry, bilirubin, total protein, albumin, and alkaline phosphatase values were performed at weeks 0, 3, 6, and 8 in this trial. No clinically meaningful trends were identified between the ustekinumab dosing arms and placebo dose groups in serum chemistry lab values. There were no markedly abnormal changes in chemistry laboratory values observed in more than 1 patient on more than 1 occasion in any treatment dose group through Week 8.

Study 3003

Hematology Parameters

Laboratory assessments for hematology parameters including complete blood counts with differentials were performed at weeks 0, 8, 24, and 44 in this trial. The mean values were comparable across the dosing arms during the 44-week double-blind treatment period. The most frequent markedly abnormal post baseline hematology laboratory value occurring more than 1 time for more than 1 patient was a decrease in lymphocytes, and the proportions of patients across treatment groups for both randomized and all treated patients were comparable. In randomized patients, a decrease in lymphocytes occurred in 28/133 (21.5%) patients in placebo, 21/132 (15.9%) patients in q12w dosing, and 26/131 (19.8%) patients in the

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q8w dosing arm; however, although this was the only significant finding in hematology labs, the decreases were not clinically relevant and the proportion of patients with decreased lymphocytes was highest in the placebo arm. Therefore, this reviewer concludes that a decrease in lymphocytes is unlikely to be related to the study drug.

Serum Chemistry Parameters

Serum transaminases, chemistries, bilirubins, total protein, albumin, and alkaline phosphatase were measured at weeks 0, 8, 24, and 44 in this trial. No clinically meaningful trends were identified between the ustekinumab dosing arms and placebo groups in serum chemistry lab values.

7.4.7. Vital Signs

Overall, the adverse events including abnormal vital signs were too few to draw any trends or conclusions from comparing the ustekinumab dosing arms to placebo.

Induction Study 3001

Overall, there were no significant differences in vital signs in patients who received ustekinumab vs patients who received placebo. Hypersensitivity reactions that included changes in vital signs occurred in 2/246 (0.8%) patients in the 130 mg dose group. Overall pyrexia occurred in the placebo dose group in 15/245 (6.1%) patients, in the 130 mg week dose group in 14/246 (5.7%), and 6 mg/kg dose group 15/249 (6.0%) of patients. Blood pressure increased in one patient in the placebo arm 1/245(0.4%) and defined hypertension 1/249 (0.4%) and hypotension 1/249 (0.4%) occurred in 1 patient each in the 6 mg/kg dose group. Tachycardia occurred in 1/245 (0.4%) in the placebo arm and 1/249 (0.4%) in the 6 mg/kg ustekinumab arm. None of these were considered to be SAEs.

Induction Study 3002

Overall, there were no significant differences in vital signs in patients who received ustekinumab vs patients who received placebo. Hypersensitivity reactions that occurred did not include meaningful changes in blood pressure, heart rate or changes body temperature. Overall pyrexia occurred in the placebo dose group in 10/208 (4.8%) patients, in the 130 mg week dose group in 6/212 (2.8%) patients, and 6 mg/kg dosing 11/207 (5.3%) patients. Blood pressure increased in 1/208 (0.5%) patients in the placebo arm, in 130 mg dose group in 2/212 (0.9%) patients, and in the 6 mg/kg dose group in 1/207 (0.5%) patients. Defined hypertension occurred in 1/208 (0.5%) patients in placebo and 2/207 (1.0%) patients in the 6 mg/kg dose group. Tachycardia occurred in 2/207 patients in the 6 mg/kg dose group. None of these were SAEs.

Maintenance Study 3003

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There were no significant differences in vital signs in patients who received ustekinumab vs patients who received placebo. Hypersensitivity reactions that occurred did not include meaningful changes in blood pressure, heart rate or body temperature. Overall pyrexia occurred in the placebo dosing regimen in 10/133 (7.5%) patients, in the q 12 week dosing regimen in 11/132 (8.3%) patients, and q8 week dosing in 8/131 (6.1%) patients. Diastolic blood pressure increased in 1/132 (0.8%) patients in the q12 week dosing regimen and defined hypertension occurred in 3/132 (2.3%) patients in the every 12 weeks dosing regimen and 2/131(1.5%) patients in q8 week dosing regimen. One of these patients in the q12 week dosing regimen developed essential idiopathic hypertension on study day 362. The patient was 69 years old and had a history of hypertension, coronary artery disease, and ischemic heart disease. Tachycardia occurred in 2/132 (1.5%) patients in the q 12 week dosing regimen.

7.4.8. **Electrocardiograms (ECGs)**

ECG monitoring was only performed during studies at screening. Ustekinumab is currently approved for the treatment of psoriasis and psoriatic arthritis and not known to have anti-arrhythmic properties. There was one patient in the non-randomized population of Study 3003 who experienced a serious adverse cardiac safety event and is described below.

Maintenance Study 3003

Patient 3412-20429 in the non-randomized patient population with a history of arrhythmia who experienced atrial fibrillation while on ustekinumab q12w dosing. Treatment with digitoxin and potassium citrate/potassium hydrogen carbonate (Kalinor effervescent) was provided. The patient stabilized, was discharged, and continued in the trial and the long term extension.

7.4.9. **QT**

EKGs/QT were assessed in phase 1 studies and no current warnings or precautions are described in the currently approved label.

7.4.10. **Immunogenicity**

Please refer to the Clinical Pharmacology Review by Dr. Christine Hon for complete details.

Immunogenicity:

For induction studies 3001 and 3002, antibodies to ustekinumab were drawn at weeks 0, 3, 6, 8, an early termination visit and week 20 safety follow up visit, if necessary, for patients who either withdrew from the study or did not continue on into the maintenance study. According to the Applicant's protocol, blood should be drawn before the infusion begins and

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approximately 60 minutes after completion of the infusion.

Study 3001

Two patients tested positive for antibodies to ustekinumab through the end of the study. Neither of the 2 patients who were positive for antibodies to ustekinumab experienced hypersensitivity reactions during their participation in the study. Patient 10766 was randomized to the 130 mg group and had a titer of 1:6400 at Week 6 and was not on concomitant immunomodulators at baseline. While this patient did not have a hypersensitivity reaction, this patient did experience a severe flare of Crohn's disease during the induction phase and was considered as a non-responder to induction therapy. The presence of anti-drug antibodies may have contributed to the decreased efficacy of the drug in this patient. This patient was included in the non-randomized population of the maintenance trial and the LTE subsequently. Patient 10351 was in the placebo induction group, yet tested positive for antibodies at week 6 with a titer of 1:51200. This reason is unknown to the Applicant. This patient was not on any other immunomodulators therapy and had no quantifiable serum ustekinumab levels. This patient went on to complete the maintenance study.

Study 3002

One patient (#20823) in the 130 mg dose group was positive for antibodies to ustekinumab through the Week 20 safety follow up visit, and had a titer of 1:200. This patient was not taking concomitant immunomodulators at baseline, and did not report signs and symptoms of a hypersensitivity reaction during participation in the study. However, this patient withdrew for lack of efficacy after the induction study and did not participate in the maintenance study due to Crohn's flare. The finding of decreased efficacy in the presence of anti-drug antibodies further supports that the presence of ADA to Stelara may have an impact on the effectiveness of the drug.

Study 3003

Fourteen patients out of 397 were positive for antibodies to ustekinumab in the randomized treated patient population through week 44 in the maintenance trial. Of these 14 patients, 4 were in the q12w dosing regimen, 3 were in the q8w dosing regimen, and 7 were in the placebo group. Seven out of these 14 patients were positive for neutralizing antibodies. Patients randomized to placebo had received one dose of IV ustekinumab during the induction phase, which explains the presence of anti-drug antibodies in these patients during the maintenance phase. Dosing intervals did not appear to have an effect on development of antibodies. None of these patients experienced injection site reactions. No relationship between the development of antibodies to ustekinumab and injection-site reactions was identified in this trial.

The antibody to serum concentration relationship will be discussed in detail in the clinical pharmacology review by Drs J Eun Lee and Christine Hon. In summary, the majority of patients positive for antibodies (13 vs. 5) had lower mean serum concentrations than those patients

who did not develop antibodies. Additionally, individual patients with neutralizing antibodies appeared to have a greater effect on lowering the ustekinumab concentration than those patients not positive for neutralizing antibodies. However, this did not appear to have a significant effect on either efficacy as measured by the primary endpoint of clinical remission in maintenance study 3003 or safety related events (i.e. hypersensitivity).

Two hundred and eighty-seven of the 397 randomized patients did not have a dose adjustment for loss of response (LOR) (See Section 6.1.1 on Study Design, Maintenance Study 3003) and had appropriate samples for assessing antibodies to ustekinumab. Nine of the 14 ADA+ patients were ADA positive but did not lose clinical response through Week 44 of the maintenance study. Of the 9 patients, (4 in the placebo group (these patients had received a single IV induction dose of ustekinumab), 3 in the ustekinumab 90 mg SC q12w group, and 2 in the ustekinumab 90 mg SC q8w group) the majority (7 of 9) exhibited titers at or below 1:800.

One hundred and nine of the 397 randomized patients did meet LOR criteria (described in Section 6.1.1 on Study Design) through Week 44. Five of the 14 ADA+ patients met LOR criteria and had a dose adjustment: 3/51 (5.9%) patients in the placebo group (these patients had received ustekinumab induction treatment), 1/29 (3.4%) patient in the ustekinumab 90 mg SC q12w group, and 1/29 (3.4%) patient in the ustekinumab 90 mg SC q8w group. All of the patients who were positive for antibodies to ustekinumab exhibited titers at or below 1:400.

As the majority of patients (9/14) who were ADA+ did not meet LOR criteria during the maintenance trial, and given the small sample size, it is difficult to determine whether development of ADA+ is related to loss of efficacy. This reviewer concludes that there does not appear to be a relationship between development of antibodies and efficacy in this trial, although those who develop antibodies do appear to have mean lower concentrations of ustekinumab than those who do not develop antibodies.

7.5. Analysis of Submission-Specific Safety Issues

Drug specific safety issues discussed below include: infections, hypersensitivity reactions, malignancy, reversible posterior leukoencephalopathy syndrome, and major adverse cardiac events (MACE).

7.5.1. Infections

Infections and serious infections are known to be an adverse reaction for the class of biologic therapeutics due to immunosuppressive properties of the therapy. The approved ustekinumab product label describes infections that occurred in the psoriasis and psoriatic arthritis populations, specifically:

- In the psoriasis program: serious infections included diverticulitis, cellulitis, pneumonia,

appendicitis, cholecystitis, sepsis, osteomyelitis, viral infections, gastroenteritis and urinary tract infections.

- Psoriatic arthritis program: serious infections included cholecystitis.

Induction Study 3001

The proportions of patients with treatment-emergent AEs that were reported as infections were similar across the treatment groups; however, serious infections were higher in the 6 mg/kg group. However, when combined with the serious infection rates across both induction studies (i.e. study 3001 and study 3002), the overall rates of serious infection between the two treatment arms of ustekinumab appear similar.

Table 29: Table of Infections For Induction Study 3001

Event	Placebo N=245 n(%)	Ustekinumab 130 mg N=246 n(%)	Ustekinumab 6 mg/kg N=249 n(%)
Infections (SOC)	58 (23.7)	57 (23.2)	64 (25.7)
Serious Infections	3 (1.2)	3 (1.2)	7 (2.8)
Infections requiring antimicrobial treatment	31 (12.7)	26 (10.6)	29 (11.6)

Source: reviewer’s analysis using Applicant’s data, BLA 761044, study 3001 dataset, module 5.3.5.1.

No one specific type of infection occurred in ≥5% of patients in any treatment dose group. As noted above, 13 patients had serious infections: 3/245 (1.2%) patients in the placebo dose group and 3/246 (1.2%) patients and 7/249 (2.8%) patients in the 130 mg and 6 mg/kg ustekinumab dose groups, respectively. A total of 14 serious infections were reported, 7 of which may be considered manifestations of underlying Crohn’s disease (i.e., vulval, pelvic, perineal, intestinal, and anal abscesses, infected fistula, peritonitis). Serious infections unrelated to Crohn’s disease include viral pneumonia (1 patient in the placebo dose group), viral gastroenteritis (1 patient in the 130 mg ustekinumab dose group), and 1 case each of Escherichia coli sepsis, intervertebral discitis, Listeria meningitis, Clostridium difficile infection, and cholangitis in the 6 mg/kg ustekinumab dose group. Listeria meningitis was the only serious infection that was considered to be an opportunistic infection. None of the treatment-emergent serious infections occurred in more than 1 patient in any treatment dose group.

The patient with listeria meningitis (patient 3302-10290) withdrew consent and did not continue in the study. This patient was dependent on corticosteroids at baseline, which may have further suppressed the immune system. This patient received a dose of 6 mg/kg IV

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ustekinumab on June 28, 2012 and on July 17, 2013, developed vomiting, headache, and photophobia. This patient fully recovered. This reviewer recommends that this infection warrants reporting in Section 5 of the label.

Induction Study 3002

The proportions of patients with treatment-emergent infections was lower in both ustekinumab doses than in placebo during study 3002. While the overall proportion of infections was higher in the 6 mg/kg dose group as compared to the 130 mg dose group, the proportion of serious infections were lowest in the 6 mg/kg dose group, while the 130 mg and placebo dose groups were both three times higher than the 6 mg/kg dose group. When combined with the serious infection rates in dosing arms in study 3001, the overall rates of serious infection between the two treatment arms of ustekinumab appear similar.

Table 30: Table of Infections in Induction Study 3002

Event	Placebo N=208 n(%)	Ustekinumab 130 mg N=212 n(%)	Ustekinumab 6 mg/kg N=207 n(%)
Infections (SOC)	48 (23.1)	31 (14.6)	45 (21.7)
Serious Infections	3 (1.4)	3 (1.4)	1 (0.5)
Infections requiring antimicrobial treatment	24 (11.5)	13 (6.1)	23 (11.1)

source: reviewer's analysis using Applicant's data, BLA 761044, study 3002 dataset, module 5.3.5.1.

Nasopharyngitis was the only infection occurring in 5% or more of patients in any treatment dose group, with 10/208 (4.8%) patients in the placebo dose group, 8/212 (3.8%) patients in the ustekinumab 130 mg dose group, and 13/207 (6.3%) patients in the ustekinumab 6 mg/kg dose group. A total of 7 serious infections were reported, 4 of which may be considered manifestations of underlying Crohn's disease (i.e., 3 anal abscesses and 1 intestinal perforation). Serious infections unrelated to Crohn's disease included: pneumonia (1 patient in the placebo dose group), diarrhea (1 patient in the 130 mg ustekinumab dose group), and gastroenteritis (1 patient in the ustekinumab 6 mg/kg dose group). Stool testing was negative for bacterial etiologies (including *C. difficile*) in both the diarrhea and gastroenteritis events. Anal abscess was the only type of treatment-emergent serious infection that occurred in more than 1 patient in any treatment dose group (1 patient in the placebo dose group and 2 patients in the 130 mg ustekinumab dose group) and could be related to the underlying Crohn's disease and not the study drug. Finally, one patient in the placebo dose group experienced an opportunistic infection of esophageal candidiasis. This patient was also receiving treatment

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with concomitant medications, glucocorticoids and methotrexate (MTX). Given that this patient was in the placebo dose group and receiving concomitant therapy with immunosuppressive properties, this reviewer concludes that the esophageal candidiasis was unrelated to ustekinumab.

Maintenance Study 3003

In the maintenance study, the proportions of patients with treatment-emergent infections similar across groups; however, the proportion of patients with serious infections in the every 12 week dosing regimen was 2.5 times that of either placebo or every 8 week dosing regimens.

Table 31: Table of Infections: Study 3003

Event	Placebo N=133 n(%)	Ustekinumab 90mg SC q12w N=132 n(%)	Ustekinumab 90mg SC q8w N=131 n(%)
Infections (SOC)	66 (49.6)	61 (46.2)	63 (48.1)
Serious Infections	3 (2.3%)	7 (5.3%)	3 (2.3%)
Infections requiring antimicrobial treatment	34 (25.6)	34 (25.8)	38(29.0)

Source: Reviewer's analysis using Applicant's data, BLA 761044, Study 3003 dataset, module 5.3.5.1.

Nasopharyngitis and upper respiratory tract infection were the most frequently reported AEs of all infections among randomized patients, with 10/133 (7.5%), 17/132 (12.9%), and 13/131 (9.9%) of patients with an AE of nasopharyngitis and 21/133 (15.8%), 9/132 (6.8%), and 13/131 (9.9%) with an AE of upper respiratory tract infection in the placebo, ustekinumab 90 mg q12w, and q8w dosing regimens, respectively. Table 32 below shows other notable AEs of infection:

Table 32: Infections of Note with Incidence >3% in a Study Drug Arm: Study 3003

Infection	Placebo N=133 n(%)	Ustekinumab 90mg SC q12w N=132 n(%)	Ustekinumab 90mg SC q8w N=131 n(%)
Nasopharyngitis	10 (7.5%)	17 (12.9%)	13 (9.9%)
Upper Respiratory Tract Infection	21 (15.8%)	9 (6.8%)	13 (9.9%)
Influenza	4 (3.0%)	8 (6.1%)	5 (3.8%)

Urinary Tract Infection	3 (2.3%)	8 (6.1%)	4 (3.1%)
Sinusitis	2 (1.5%)	6 (4.5%)	4 (3.1%)
Gastroenteritis	6 (4.5%)	11 (8.3%)	8 (6.1%)
Bronchitis	4 (3.0%)	1 (0.8%)	6 (4.6%)
Vulvovaginal Mycotic Infection	1 (0.8%)	1 (0.8%)	4 (3.1%)

Other noted AEs of infection included influenza, urinary tract infection, sinusitis, gastroenteritis, bronchitis, and vulvovaginal mycotic infection. It should be noted that infections listed with rates higher in placebo are unlikely to be related to the drug. When compared to placebo, nasopharyngitis, influenza, and urinary tract infection were most frequent in the q12w dosing regimen. Vulvovaginal mycotic infection and bronchitis were most frequent in the q8w dosing regimen. Both sinusitis and gastroenteritis were more frequent in both ustekinumab dosing regimens than placebo. Crohn's patients experience an increased rate of opportunistic fungal infection as compared to the normal populace; however, this reviewer suggests that the fourfold increase in this infection in the q8w dosing regimen vs the placebo warrants inclusion in the label. Additionally, sinusitis should also be included in the label (gastroenteritis is already included among other indications but should also be added to the Crohn's disease section). The most frequently occurring infections requiring antimicrobial treatment were urinary tract infection, upper respiratory tract infection, and bronchitis.

As noted above, 13 patients experienced 13 serious infections: 3/133 (2.3%) patients in the placebo dosing regimen, 7/132 (5.3%) and 3/131 (2.3%) patients in the q12w and q8w ustekinumab dosing regimens, respectively. Within the total of 13 serious infections that were reported, 2 (one in placebo, one in q12w dosing regimen) may be considered manifestations of underlying Crohn's disease (e.g. anal abscesses). Serious infections unrelated to Crohn's disease include pneumonia (2 patients in the placebo dosing regimen, 1 in the q8w dosing regimen), gastroenteritis (3 patients in the q12w dosing regimen), and 2 cases of appendicitis in the q12w dosing regimen. Of the remaining 5 serious infections, there was 1 case each of post-operative wound infection, abdominal infection, and bacteremia in the q12w dosing regimen and 1 case each of viral infection and ophthalmic herpes in the q8 week dosing regimen. There were two serious infections of note, the synopses are below:

- **Ophthalmic herpes zoster** in patient 1016-21010 (ustekinumab 6 mg/kg IV induction and 90 mg q8w maintenance). This 31-year-old man had a SAE of ophthalmic herpes zoster in a single dermatome (onset Study Day 121). The patient had a history of varicella in the past and was not taking corticosteroids at diagnosis. There were no visual changes reported. Treatment included prednisolone acetate eye drops and valacyclovir. The patient made a full recovery and continued in the study.
- **Bacteremia** in patient 1007-10176 (ustekinumab 130 mg IV induction [non-responder] and received 90 mg q8w *nonrandomized* maintenance trial). This 34-year-old man had a

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SAE of bacteremia with concurrent ascending cholangitis (onset Study Day 62). The event occurred while tapering doses of corticosteroids, he was not taking other immunosuppressive agents. He presented to the emergency room on study day 62 (after 1 IV dose and 1 SC doses of ustekinumab) with fever, chills, and hypotension. A blood culture was positive for *Klebsiella pneumoniae*. Treatment included IV fluids, steroids, norepinephrine, vasopressin, and piperacillin/tazobactam (Zosyn) and levofloxacin. The ustekinumab dosing was not interrupted as he was in between the q8 week dosing. The patient fully recovered and continued in the nonrandomized portion of the study.

The Applicant proposes to include the addition to events of abscess, gastroenteritis, and pneumonia, this reviewer concludes that the case of ophthalmic herpes should be included in the label. See Section 9 on Labeling Recommendations below for a discussion of labeling recommendations. Crohn's patients can be known to translocate gut bacteria to the bloodstream and therefore the *Klebsiella* bacteremia infection associated with cholangitis is unlikely related to ustekinumab therapy.

Through Week 44 of this study, there was 1 event of presumed active primary TB reported in a patient who was randomized to ustekinumab 130 mg IV as induction treatment and then received placebo maintenance treatment. Patient 3605-20285 (a 32-year-old Hungarian male) had previously received a Bacilli Calmette Guerin (BCG) vaccination and at screening, had a negative chest radiograph and negative QuantiFERON test. The patient experienced flu like symptoms with fever, chills, sore throat, cough and yellowish sputum approximately 10 months after exposure to a single IV ustekinumab dose. QuantiFERON test results were negative, as however, chest radiograph and CT scan results were reported as consistent with TB. The patient was empirically treated with triple anti-TB therapy with resolution of symptoms. The patient discontinued study agent administration.

There were no opportunistic infections in the primary randomized population. In the nonrandomized population, there was one opportunistic infection: a nonserious event of esophageal candidiasis in a 31-year-old female patient (3417-20377) who was a nonresponder to ustekinumab induction and subsequently received ustekinumab 90 mg q8w as maintenance treatment. Approximately 2 weeks after the last ustekinumab dose at week 24, the patient discontinued study agent due to "worsening Crohn's disease" and on November 30, 2013 was treated with infliximab. A gastroscopy on December 2, 2013 showed multiple white plaque-like depositions along the esophagus, and diffuse redness and swelling of the gastric body and antrum consistent with marked candidal esophagitis. Other concomitant medication included pantoprazole. As opportunistic infections are not uncommon in Crohn's disease (for example, a patient in the placebo arm of study 3002 developed esophageal candidiasis) and academic

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papers have shown a relative risk of 2 for developing an opportunistic infection with anti-TNF α therapy.⁴⁹ This patient had been treated with TNF blockers and given that this occurred in only one patient, this reviewer concludes there is insufficient evidence based on this single case to warrant inclusion in the label. In addition, an increased risk for fungal infections is described in the product label.

7.5.2. Hypersensitivity

Hypersensitivity reactions, including anaphylaxis, are known to be associated adverse reactions with the administration of therapeutic proteins that have the potential for immune responses. Hypersensitivity reactions are described in the approved label for ustekinumab. However, the current label does not encompass all signs and symptoms associated with hypersensitivity events that were reported during in study 3001 or 3002. It should be noted that previous approved dosing of ustekinumab for other indications did not include an intravenous formulation. The Applicant defined hypersensitivity events as infusion reactions of any AE that occurred during or within 1 hour of the administration of the study agent infusion, with the exception of laboratory abnormalities. The FDA Guidance for Industry: Immunogenicity Assessment for Therapeutic Protein Products⁵⁰ refers to a more accurate description of infusion reactions that defines events related to hypersensitivity within a few hours in accordance with the NIAID/FAAN criteria for anaphylaxis. During review of this BLA, the review team requested that the Applicant recategorize hypersensitivity events according to the criteria in the Guidance (Information Request, dated May 10, 2016). The Applicant's response was confirmed by this reviewer's analysis.

Induction Study 3001

Overall in study 3001, 5/245 (2.0%) patients experienced signs and symptoms suggestive of hypersensitivity reactions in the placebo dose group, compared with 11/246 (4.5%) patients and 9/249 (3.6%) patients in the 130 mg and 6 mg/kg ustekinumab treatment dose groups, respectively. When ustekinumab treatment dose groups are combined, the total is 20/495 (4.0%) patients, double in the placebo dosing dose group. Hypersensitivity reactions reported by more than 1 patient are listed in the table below:

⁴⁹ Ford AC and L Peyrin Biroulet. 2013. Opportunistic infections with anti-tumor necrosis factor- α therapy in inflammatory bowel disease: meta-analysis of randomized controlled trials. *Am J Gastroenterol.* Aug;108(8):1268-76.

⁵⁰ Guidance for Industry: Immunogenicity Assessment for Therapeutic Protein Products, dated August 2014. <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm338856.pdf>
Sampson et al. 2006. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol.* Feb;117(2):391-7.

Table 33: Hypersensitivity Events: Occurred in More than 1 Patient Receiving Ustekinumab within a Few Hours of Administration in Study 3001

Event	Placebo N=245 n(%)	Ustekinumab 130 mg N=246 n(%)	Ustekinumab 6 mg/kg N=249 n(%)
Dysguesia	0	0	2 (0.4)
Headache	1 (0.4)	2 (0.8)	0
Nausea	1 (0.4)	0	3 (1.2)
Oral paresthesia	0	1 (0.4)	1 (0.4)
Pyrexia	0	3 (1.2)	0
Visual Impairment	0	1 (0.4)	1 (0.4)

Source: reviewer’s analysis using data from BLA 761044, study 3001 dataset “adae”, module 5.3.5.1.

None of these reactions were reported as serious and no events of anaphylaxis occurred in study 3001. This reviewer recommends adding hypersensitivity reactions that occurred in more than one patient receiving ustekinumab to the label as the safety profile for the intravenous formulation has not previously been described in the label. See Labeling Recommendations, Section 9 below for a discussion of the labeling recommendations.

Induction Study 3002

Overall in study 3002, 6/208 (2.9%) patients experienced signs and symptoms suggestive of hypersensitivity reactions in the placebo dose group, compared with 4/212 (1.9%) and 4/208 (1.9%) patients in the 130 mg and 6 mg/kg ustekinumab treatment dose groups, respectively. When the ustekinumab treatment dose groups are combined, the total is 8/420 (1.9%) patients, and remains at a lower proportion as compared to the placebo dose group. No individual hypersensitivity reactions were reported by more than 1 patient.

Hypersensitivity reactions of note identified by the reviewer:

- As noted previously, one patient who was randomized to ustekinumab 6 mg/kg, experienced infusion site extravasation, chest discomfort, flushing, urticaria, and increased body temperature, which resulted in termination of the infusion. Treatment included discontinuation of the infusion, loratadine, and ranitidine. All symptoms lasted less than one hour and resolved the same day. However, this patient received a total dose of 195mg and thus the Applicant included the patient’s analysis in the 130 mg dose group. This reviewer concludes that this patient received a dose over 130 mg and should remain for safety analysis in the 6 mg/kg dose group.

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- A second patient in the 6 mg/kg arm was discontinued from the trial by the investigator for a skin rash that appeared a few days after the dose, however, this patient experienced mild peripheral edema at the time of the infusion. This patient also had a history of hypersensitivity manifested as leukocytoclastic vasculitis to etanercept.

Maintenance Study 3003

Overall, 1/396 patient (#20753) experienced signs and symptoms suggestive of hypersensitivity reactions in the Study 3003. This patient was a *non-responder* to the 130 mg IV ustekinumab induction dose identified based on the Applicant response to an IR sent May 10, 2016. As a non-responder to ustekinumab, this patient was able to participate in maintenance study 3003 in the *non-randomized* population. As this population was still blinded, this patient received an IV dose of placebo (to correlate with the IV dose of ustekinumab patients who were not in response to placebo induction dosing) followed by a 90mg SC dose to start SC the maintenance dosing regimen to be continued throughout maintenance at the same visit. This patient experienced a reaction to the ustekinumab SC dosing followed by placebo infusion when seen for Week 0 maintenance visit in study 3003. The SC dose was received at 12:45pm, placebo infusion at 1:45pm (ending at 2:35pm). At this time, the patient experienced tightness of the throat, shortness of breath, and flushing. The patient was treated with IV hydrocortisone and chlorpheniramine and symptoms resolved by 3:00pm. This patient remained in the trial after this event, however, was discontinued at a later date due to lack of efficacy. The patient did not receive another dose of the study drug. This reviewer concludes that this event meets clinical criteria for anaphylaxis based on respiratory (dyspnea) and skin involvement (flushing). Hypersensitivity, injection site erythema, and warning of anaphylactoid reactions are already in the label for ustekinumab.

Injection site reactions also occurred with the subcutaneous dose. These were experienced by 0/133 patients in placebo, 3/132 (2.3%) patients receiving dosing every 12 weeks, and 9/131 (6.9%) patients receiving dosing every 8 weeks. Injection site reactions were the most common, and the only injection site reaction experienced by more than one person in any treatment dosing regimen was erythema at the injection site, experienced by 1/132 (0.8%) patients in the q12w dosing regimen and 7/131 (4.6%) of patients in the q8w dosing regimen. Injection site reactions appear to be more common with more frequent dosing. Patients receiving placebo dosing also experienced injection site reactions, however these patients included patient from each trial arm as in order to maintain the blind, all patients received placebo injections. By dosing regimen, placebo injections caused injection site reactions most frequently in patients receiving q8 week dosing [4/131 (3.1%) patients], q12 week dosing (1/132 [0.8%] patients) and placebo (1/131 [0.8%] patients). Again, those receiving actual study drug every 8 weeks reacted more often to injections than those who were receiving the drug at longer intervals or receiving placebo.

7.5.3. Malignancy

Induction Studies 3001/3002

One patient (#3421-10675) in the 6 mg/kg dose group developed multiple myeloma during the safety follow up period, diagnosed 199 days after receiving ustekinumab for the induction study. This patient had a history of monoclonal IgG kappa gammopathy of undetermined significance (MGUS) and did not enter maintenance because he/she was retrospectively determined to be ineligible for the trial. This patient received appropriate treatment for the disease, including chemotherapy. Given the patient's medical history, it is unclear if ustekinumab could have induced the malignancy.

Another patient (#1127-20961) in the placebo arm, with a history of sun exposure and long-term immunosuppression, underwent a routine skin cancer examination on July 30, 2014, on the same day as the Week 8 visit. A biopsy taken from the forehead during the exam was identified to be basal cell carcinoma (BCC). Histopathology showed acanthosis with basilar hyperplasia and showed few small nests of neoplastic hyperchromatic cells invading the superficial and mid-dermis. Areas of dermal fibrosis surrounded hyperchromatic cells. A surgical resection was planned. The BCC was assessed as not related to study drug.

Maintenance Study 3003

In study 3003, basal cell carcinoma was reported in two randomized patients, 1 patient in the placebo dosing regimen (1009-10269) and 1 patient in the ustekinumab 90 mg q8w dosing regimen (1072-20295).

Eight additional malignancies were reported among 4 patients in the nonrandomized population:

- Six nonmelanoma skin cancers (NMSC) were reported in 3 patients:
 - One patient with basal cell carcinoma (1117-20913) who received IV induction dose of 130 mg followed by the 90mg SC q8w dosing regimen. This patient completed the study and was diagnosed shortly following the end of the maintenance trial.
 - One patient with 2 squamous cell carcinomas (1078-10778). This patient received the induction dose of 130 mg IV and then one SC dose of 90mg prior to discontinuation for malignancy in the ustekinumab dosing regimens.
 - 2 basal cell carcinomas and one squamous cell carcinoma in a patient (1022-20231) who never received ustekinumab.
- Two other malignancies occurred during the maintenance study in 1 patient (1013-11005) who was a placebo IV induction nonresponder and received ustekinumab 90 mg q12w during maintenance. This patient was found to have a metastatic adenocarcinoma

of the small bowel and also found to have an incidental carcinoid tumor after resection. This patient discontinued the study.

120 Day Safety Follow Up

In the 120 day follow up safety report, the Applicant noted 6 NMSCs, which were previously reported during study 3003, and 2 additional malignancies in patients continuing on ustekinumab. The total number of patient years of follow-up between Week 44 and October 1, 2015 for all ustekinumab patients was 797.95 years. The rate of malignancies was 1.00 per 100 patient years of follow-up (8 malignancies/797.95 patient years of follow-up).

The 6 NMSCs were all previously reported in study 3003. The two additional malignancies are described below.

- Chronic myeloid leukemia in a 50-year old woman with no previous history of immunosuppressive use, who received ustekinumab 6 mg/kg IV induction→placebo maintenance→ustekinumab 90 mg SC q8w as dose adjustment upon loss of response.
- Seminoma in a 31-year old man with a history of immunomodulator use at study entry, who received 6 mg/kg IV induction→ustekinumab 90 mg SC q12w maintenance →ustekinumab 90 mg SC q8w as dose adjustment upon loss of response.

Based on the randomized patients, there does not appear to be an increased risk for malignancy to the ustekinumab population over placebo based on data reviewed up to 44 weeks and the non-randomized population appears to have additional skin cancers in both the placebo and ustekinumab dosing regimens. While the one patient who reported two abdominal malignancies while on ustekinumab therapy is concerning, it is difficult to make definite conclusions on causality based on one patient. The 120 day safety update generates additional data to warrant long term follow up in the post-marketing period.

The Applicant states that to assess the incidence of malignancies in the ustekinumab studies compared with the expected incidence in the general US population, standardized incidence ratios (SIR) were evaluated using the National Institutes of Health SEER database. The SIR is the ratio of the observed number of patients with 1 or more malignancies to the expected number of patients with 1 or more malignancies in the general US population adjusting for age, sex, and race. **When the SIR is greater than 1, the observed number of patients is higher than the expected number of cases.** In the Crohn's disease studies, the SIR in the combined ustekinumab dosing regimen was **1.22** (95% CI, 0.25, 3.56) compared with an SIR of 0.00 (95% CI, 0.00, 3.56) in the placebo dosing regimen. However, the confidence interval overlaps normal incidence and only one year of data were available. This reviewer recommends collecting more data to help determine whether there is a potential for increased risk of malignancy in patients treated with ustekinumab long-term. This may be

conducted in the post-marketing period to gain a better understanding of the potential relationship between ustekinumab therapy and the risk for malignancy.

7.5.4. Reversible Posterior Leukoencephalopathy Syndrome

Reversible Posterior Leukoencephalopathy Syndrome (RPLS) is a rare neurological disorder that can present with headache, seizures, confusion and visual disturbances. RPLS can be fatal. RPLS was noted in clinical trial safety database for psoriasis in a patient who had received approximately 12 doses of ustekinumab over approximately 2 years. Ustekinumab was halted and the patient recovered. No cases of RPLS were observed in studies 3001, 3002, or 3003. However, there was one case of demyelination and is described below.

- A 58-year-old female patient received placebo IV induction, was found to be a non-responder, and subsequently received ustekinumab 130 mg IV at Week 0 of maintenance, followed by a single dose of ustekinumab 90 mg SC 8 weeks later. The patient experienced dizziness and numbness and tingling of her mouth starting approximately 2 months after entering the maintenance study. She also experienced double vision and other visual symptoms. An MRI was performed and reported as a negative MRI of the brain for focal/acute abnormality. Periventricular altered T2 signal including callosal lesions and multiple areas of altered T2 signal in the white matter tracts of both hemispheres were noted. The findings could represent microvascular disease and previous small vessel insults however demyelinating disease is the diagnosis of exclusion. A non-serious event of “other demyelinating diseases of central nervous system” was reported and led to study discontinuation.

For the above case with previous concerns of RPLS in another clinical trial, this reviewer recommends inclusion of demyelinating disease in the label.

7.5.5. Major Adverse Cardiac Events (MACE)

As per the clinical review of BLA 125261, by Dr. Brenda Carr, dated September 13, 2014, an imbalance in serious cardiovascular (CV) events was noted in a phase 2 psoriasis clinical trial that showed: 3 myocardial infarction (MI) or stroke in the ustekinumab dosing regimen compared to none in the placebo dosing regimen. The Applicant considered that the imbalance might be attributable to the 4:1 randomization of ustekinumab and placebo treatment, respectively. A similar numeric imbalance in CV was not noted in the controlled portion of the ustekinumab psoriasis phase 3 program (2:1 randomization). (b) (4)

The Division of Dermatology and Dental Products requested that the Applicant to perform an extensive review of:

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- major adverse cardiovascular events (MACE), defined as cardiovascular (CV) death, nonfatal myocardial infarction [MI], and nonfatal stroke.
- Other nonfatal thrombotic events, defined as unstable angina, venous thromboembolic disease (deep vein thrombosis [DVT] pulmonary embolism [PE], and other peripheral venous thrombosis) and peripheral arterial thrombosis.
- Other nonfatal cardiovascular (CV) events, defined as heart failure (HF) and arrhythmia requiring intervention.

The Applicant used their clinical trial databases, irrespective of indication, the Psoriasis Longitudinal Assessment and Registry (PSOLAR), and postmarketing reports and concluded that, “Based on the results of these comprehensive analyses...the benefit/risk profile for STELARA remains positive as there is no consistent evidence of increased cardiovascular risk with ustekinumab.”

Dr. Carr concluded the benefit/risk profile remained favorable and recommended no labeling changes based on the CV analyses and acknowledge and support the Applicant’s commitment to continue their pharmacovigilance efforts. The following recommended comments for incorporation were provided for a regulatory letter for conveyance to the sponsor:

“We have completed our review and, at this time, have no recommendations for any changes to labeling regarding cardiovascular risk.”

Since this review, the Applicant has provided additional assessment of MACE in clinical trials, including Crohn’s disease (CD). In the CD trials for ustekinumab a proportion of the study population had risks for cardiovascular disease:

- Study 3001: At baseline, 294/741 (39.7%) patients had at least 1 cardiovascular risk factor, including hyperlipidemia, hypertension, diabetes mellitus, family history of early coronary artery disease, or current smoking status, and 67 (9.0%) patients had 2 or more cardiovascular risk factors.
- Study 3002: At baseline, 272/629 (43.2%) patients had at least 1 cardiovascular risk factor, including hyperlipidemia, hypertension, diabetes mellitus, family history of early coronary artery disease, or current smoking status, and 63 (10.0%) patients had 2 or more cardiovascular risk factors.
- Study 3003: 141/369 (38.3%) patients had at least 1 cardiovascular risk factor and 7.1% had 2 or more risk factors including hypertension, family history of coronary artery disease, and were current smokers.

In the CD studies with ustekinumab, there were no MACE events in the induction trials. In the maintenance study 3003, there were zero nonadjudicated MACE reported through Week 44 in study 3003. There was, however, 1 event of a subarachnoid hemorrhage due to aneurysm rupture which was adjudicated as a nonfatal stroke in a nonresponder to ustekinumab

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induction who subsequently received ustekinumab 90 mg SC q8w as maintenance treatment in study 3003. With the addition of data between Week 44 and October 1, 2015, reported March 8, 2016, there were 2 nonadjudicated MACE (1 in a ustekinumab-treated patient and 1 in a placebo-only treated patient) described below:

- One fatal MI in 46-year old man who received ustekinumab (6 mg/kg IV induction→ustekinumab 90 mg SC q12w maintenance). The patient had a medical history of untreated hypertension and hyperlipidemia, and smoking.
- One nonfatal MI in a 58-year old female, who was receiving treatment for hypertension and had a history of untreated hyperlipidemia, who received only placebo in both the induction and maintenance studies.

Given that one of the cases above is associated with cardiovascular risks, and the other patient received placebo, it is difficult to establish causality of these events to ustekinumab.

Below are cases of adjudicated MACE that took place with additional data between Week 44 and October 1, 2015. All serious adverse events possibly consistent with MACE (including cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) were retrospectively adjudicated by an independent, blinded adjudication process performed by the (b) (4) as described in the committee manual. Analyses of cumulative serious MACE rates were based on the following adjudicated events:

- Cardiorespiratory arrest in a 56-year-old man with a known history of coronary artery disease and hypertension. He had initially received placebo IV induction and then went on to receive ustekinumab 90 mg SC q12w as maintenance therapy.
- Acute myocardial infarction (MI) in a 46-year-old male, with known cardiovascular risk factors including smoking, hyperlipidemia, and hypertension died of a MI approximately 10 days after experiencing unstable angina. He had initially received ustekinumab IV induction and then went on to receive ustekinumab 90 mg SC q12w as maintenance therapy.
- Sudden death in a 61-year-old man with a history of tobacco use who was found deceased of presumed ventricular arrhythmia although no autopsy was performed. He had initially received ustekinumab IV induction then went on to receive placebo SC as maintenance therapy and then dose adjusted to ustekinumab 90 mg SC q8w.

The placebo to ustekinumab randomization ratio was 2:1. Currently there are 4 cases in which the patients (all with cardiovascular risk factors) were randomized to receive some form of ustekinumab and 1 case who received only placebo. Some of the patients randomized to ustekinumab received only one dose and received placebo as well. This reviewer has analyzed these cases and concludes that there is no conclusive data that would justify additions to the label or dedicated monitoring apart from typical post marketing surveillance.

7.6. Safety Analyses by Demographic Subdosing regimens

Overall, in studies 3001, 3002 and 3003, no trends were observed with regard to differences between treatment dosing regimens in the proportions of patients with AEs, SAEs, infections, or who discontinued due to an AE, when evaluated by sex, race, age, weight or disease characteristics during induction or maintenance.

Weight

Weight was a pre-specified endpoint used to evaluate if comparatively greater drug exposure observed in lower-weight patients affected safety, treatment emergent AEs, SAEs, and serious infection rates through Week 44. There were no differences found in the number of treatment emergent AEs, SAEs, or serious infection rates in either the induction or the maintenance trials. This reviewer concludes that that weight, while there may be concerns for efficacy in the lowest weight tier, weight did not appear to impact safety in these trials for ustekinumab.

Additionally, no trends were observed with regard to differences in the proportions of patients with a AEs, SAEs, infections, or who discontinued due to an AE, when evaluated by the patient's disease severity, disease duration, or extent of disease during induction or maintenance.

7.7. Specific Safety Studies/Clinical Trials

No specific safety studies were conducted for this application.

7.8. Additional Safety Explorations

7.8.1. Human Carcinogenicity or Tumor Development

See Section 7.5.3 on Malignancy.

7.8.2. Human Reproduction and Pregnancy

No studies of ustekinumab were conducted in pregnant or lactating women. The ustekinumab protocols mandated the use of effective contraception during the studies. Discontinuation of study agent was mandated in the event a patient became pregnant. Overall in all 3 studies there were 22 cases of pregnancy. At the time the databases closed, there had been 8 live births without adverse event or congenital anomaly, 3 spontaneous abortions, 4 elective abortions, 2 premature births, one fetal demise and 4 pregnancies pending.

7.8.3. Pediatrics and Assessment of Effects on Growth

The clinical trials included in this submission were conducted in adults and therefore pediatric

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assessment of effects on growth were not conducted in these clinical trials. There is an agreed upon iPSP that was approved by the Pediatric Equity in Research Committee (PeRC) July 15, 2015 and an agreement letter was sent to the Applicant on November 11, 2015.

7.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

These categories are not applicable to this application.

7.9. Safety in the Postmarket Setting

7.9.1. Safety Concerns Identified Through Postmarket Experience

Postmarketing safety events are included in the current label and recent periodic safety update reports for the psoriasis and psoriatic arthritis indications for ustekinumab. These events include safety concerns that are previously discussed in this review including: cutaneous squamous cell carcinomas, hypersensitivity, anaphylaxis, and reverse posterior leukomyelodystrophy syndrome.

7.9.2. Expectations on Safety in the Postmarket Setting

Specific safety concerns of malignancy and serious infection are discussed in the Section 11, Postmarketing Requirements and Commitments.

7.10. Additional Safety Issues From Other Disciplines

The clinical pharmacology, pharmacometrics, and genomics and targeted therapy teams recommend that the Applicant conduct a clinical trial to assess whether ustekinumab alters the metabolism or pharmacokinetics of cytochrome P450 (CYP) substrates in CD patients treated with ustekinumab (e.g., using a cocktail of relevant CYP probe drugs). This recommendation is based on the current understanding that CD patients have elevated levels of proinflammatory cytokines which can suppress the expression of some CYP enzymes and the CYP enzyme expression could be normalized upon the disease improvement following the ustekinumab treatment. See the combined Pharmacology review by Drs Christine Han, Jee Eun Lee, and Anuradha Ramamoorthy for further details.

7.11. Integrated Assessment of Safety

Overall, the safety profile reported in the phase 3 trials for initial and maintenance dosing of ustekinumab in studies 3001, 3002, and 3003 are not substantially different than the safety profile previously reported for ustekinumab for the treatment of psoriasis and psoriatic arthritis. The safety database for the studies includes data from 1367 patients with moderately to severely active Crohn's disease (CD) from two initial 8 week studies, 3001 for patients who failed or were intolerant to TNF α antagonists (N=740) and 3002 for patients who failed or were

intolerant to conventional therapy such as corticosteroids and immunomodulators, but not TNF α antagonists (N=627). These two initial studies evaluated 2 intravenous ustekinumab doses (130 mg IV and a 6 mg/kg weight tiered IV dose) against placebo. Responders to the primary endpoint in these studies, (i.e. patients in clinical response, defined as a reduction from baseline in the Crohn's Disease Activity Index [CDAI] score of ≥ 100 points) continued on re-randomized into Study 3003, a 44 week maintenance dosing study (N=396). Non responders were able to continue into a "non-randomized" patient population, which was followed in the maintenance trial (N=884) but not included in the efficacy analyses. Eligible patients for Study 3003 were re-randomized to receive either 90mg SC every 8, 90 mg SC every 12 weeks, or a placebo dosing regimen. For the purpose of this review, safety data was primarily analyzed using the randomized study population only. The non-randomized populations was reviewed for safety and known adverse events in the approved label of ustekinumab (i.e. infection, malignancy, reversible posterior leukoencephalopathy syndrome [RPLS]). The Applicant recorded an additional safety endpoint at week 20 for the initial studies 3001 and 3002 and an additional 64 week safety follow up for study 3003. Patients were able to enroll in a long term extension (LTE) trial to go until week 272 or marketing approval is obtained.

Deaths

There were no deaths reported in the 3 randomized phase 3 studies. However, 6 deaths have been reported at the time of this review; five deaths have occurred during the (LTE) study (3 cardiovascular, 1 infectious, 1 renal failure, and 1 suicide) and one (infectious) for a patient outside of the long term extension trial that had been on ustekinumab but did not enroll in the LTE study. Upon review, none of the deaths can be clearly attributed to the study drug due to co-morbid, confounding, or other confounding factors noted in the review.

Adverse Events

In general, adverse events from the two induction trials will be summarized below in an integrated fashion; however, since the maintenance study evaluated a different formulation of the drug (SC in maintenance vs IV induction) and dosing was chronic in the maintenance rather than a single induction dose, the maintenance study data will not be integrated. Ustekinumab was originally approved in 2009 with a REMS to evaluate and mitigate the potential risks of serious infections and malignancy, and reversible posterior leukoencephalopathy syndrome (RPLS) associated with ustekinumab. No cases of RPLS were identified in the CD studies.

Serious infections occurred at a higher proportion in the initial 6 mg/kg IV dose group 8/456 (1.75%) than in the placebo dose group 6/453 (1.3%) and included such infections as listeria meningitis and *E coli* sepsis. Serious infections are currently in the warnings and precautions section of the label and should be monitored as a post-marketing requirement for patients with CD given their underlying immunocompromised state in addition to receiving ustekinumab. For the maintenance dosing regimens, serious infections also occurred at double the proportion in the q12w dosing regimen (7/132 [5.3%]) than placebo (3/133 [2.3%]) or the q8w dosing

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regimen (3/131 [2.3%]). The most common serious infection was gastroenteritis (x3 in the q12w dosing arm). Other serious infectious included ophthalmic herpes (q8w dosing regimen) and in the *non-randomized* population there was one case of reactivated tuberculosis in a patient during the maintenance trial who had received an initial dose of 130 mg IV followed by a placebo maintenance dosing regimen.

Malignancies were rare in the short 8 week single initial dose studies of 3001 and 3002 with one patient who received placebo developing basal cell carcinoma and another patient with a history of elevated immunoglobulins developing multiple myeloma. The patient with multiple myeloma was retroactively determined ineligible to participate in the trial and it is not clear that ustekinumab played a role in this patient's development of the disease. In the maintenance study 3003 of 44 weeks they were more common. Basal cell carcinoma was reported in two randomized patients, 1 in the placebo dosing regimen and 1 in the ustekinumab 90 mg q8w dosing regimen. However, when including the randomized and long term extension trials an additional eight additional malignancies were reported among 4 patients in the nonrandomized population:

- Basal cell carcinoma (one patient on q8 week dosing regimen and one patient who developed 2 basal cell carcinomas in the placebo arm)
- Squamous cell carcinoma (x2 in one patient who received an initial dose of 130 mg and only one 90mg SC dose before being discontinued for cancer and one that developed in a patient on placebo for induction and maintenance)
- Metastatic adenocarcinoma of the small bowel and carcinoid tumor in the same patient on the q 12w dosing regimen

In the long term extension trial one patient developed chronic myeloid leukemia who received ustekinumab 6 mg/kg IV induction dose → randomized to placebo for maintenance → then moved to ustekinumab 90 mg SC q8w dosing regimen for loss of response to placebo and a final patient developed seminoma who received 6 mg/kg IV induction dose → ustekinumab 90 mg SC q12w maintenance dosing regimen → ustekinumab 90 mg SC q8w dosing regimen with a dose adjustment for loss of response. Malignancies are in the warnings and precautions section of the currently approved label and given the predisposition of CD patients for skin cancers and certain forms of lymphoma on biologic therapy, and should be monitored as a post-marketing requirement.

Hypersensitivity is another adverse event of special interest to biologic therapy in the current warnings and precautions section of the approved ustekinumab label. In the initial dose IV trials, hypersensitivity reactions the following proportions of patients experienced hypersensitivity reactions in the combined placebo groups 11/453 (2.4%), 130 mg dose groups 15/458 (3.3%) and 6 mg/kg dose groups 13/247 (2.8%) with both dose groups exhibiting a higher proportion of hypersensitivity reactions than placebo. In the initial dose IV studies, two serious hypersensitivity reactions occurred. One patient on the 6 mg/kg IV dose experienced

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infusion site extravasation, chest discomfort, flushing, urticaria, and increased body temperature, which resulted in termination of the infusion. Treatment included discontinuation of the infusion, loratadine, and ranitidine. All symptoms lasted less than one hour and resolved the same day. This patient continued in the trial. A second patient in the 6 mg/kg dose group was discontinued from the trial by the investigator for a skin rash that appeared a few days after the dose. This patient also had a history of hypersensitivity manifested as leukocytoclastic vasculitis to etanercept.

In the maintenance trials, one patient experienced tightness of the throat, shortness of breath, and flushing after receiving a SC dose of ustekinumab. The patient was treated with IV hydrocortisone and chlorpheniramine and symptoms resolved within 25 minutes. This patient initially remained in the trial but then dropped out for lack of efficacy before receiving another dose of ustekinumab.

Overall, hypersensitivity events were more common in the ustekinumab dosing arms than in the placebo dosing arms and serious hypersensitivity reactions should be monitored in the post marketing setting.

Serious Adverse Events

Serious adverse events (SAEs) from the two induction trials will be summarized below in an integrated fashion; however, since the maintenance study evaluated a different formulation of the drug (SC in maintenance vs IV induction) and dosing was chronic in the maintenance rather than a single induction dose, the maintenance study data will not be integrated.

Overall the proportions of SAEs in initial dose studies 3001 and 3002 were the highest in placebo with the ustekinumab dose arms being similar. The proportion of patients who had 1 or more SAEs was 27/453 (6.0%) patients in the placebo dosing regimen compared with 22/458 (4.8%) patients in the 130 mg ustekinumab dosing regimen and 24/456 (5.3%) patients in the 6 mg/kg ustekinumab dosing regimen.

In both studies 3001 and 3002, except for Crohn's disease, no SAE occurred in more than 1 patient in either ustekinumab dose dosing regimen. Seven of the 44 patients (16%) experienced at least one serious adverse event (SAE) (categorized as an event related to death or hospitalization) and no same SAE was reported in more than 1 patient. None of the SAEs were considered related to treatment and included: idiopathic thrombocytic purpura; pulmonary embolism following surgery for a known hemangioma; diabetes mellitus; grade 3 prolapse of the rectum, bladder and cervix, and requiring surgical correction for uterine prolapse; renal stone removal; surgery for osteoarthritis to place a knee prosthetic; and traumatic pneumothorax.

In the maintenance trial, the overall proportion of patients experiencing 1 or more SAEs was comparable between the 3 dosing regimens with 28/133 (21%) in the placebo dosing regimen,

compared with 25/132 (18.9%) in the ustekinumab 90 mg q12w dosing regimen and 19/131 (14.5%) in the ustekinumab q8w dosing regimen. However, the proportion of patients with SAEs was the lowest in the q8 week dosing regimen. This was in part, influenced by the majority of SAEs in each arm occurring with Crohn's related illness, with the most Crohn's related illnesses of which the proportion was highest in the placebo dosing regimen (10/133 [7.5%]), followed by the q12 (8/132 [6.1%]), then the q8 (6/131 [4.6%]) dosing regimen. The trend between the three dosing regimens may indicate a greater therapeutic effect of the q8 week dosing arm. Other than Crohn's related SAEs, reasonably related SAEs in the q12w dosing regimen included: gastroenteritis (x2), abdominal infection, and suicidal ideation; and in the q8w dosing regimen included: pneumonia (x3), viral infection, ophthalmic herpes zoster.

Adverse Events $\geq$ 3% and Higher than Placebo

During the CD induction trials, there was a $\geq$ 3% of the patient population and higher incidence of abdominal pain, pyrexia, nasopharyngitis, arthralgia, nausea, and vomiting reported for patients treated with the initial IV 6 mg/kg dose as compared to placebo. During the maintenance trial, patients treated with the subcutaneous dose regimen reported a $\geq$ 3% of the patient population and higher incidence of headache, nasopharyngitis, rash, gastroenteritis, cough, injection site erythema, bronchitis, vulvovaginal mycotic infection, pruritus, migraine, pain in extremity, sinusitis and urinary tract infection in the 90mg SC every 8 week dosing regimen as compared to placebo. Many of these adverse events are already reported in the approved label.

Conclusions

Overall, no new or unexpected safety issues were identified during the CD trials and the safety profile demonstrated for ustekinumab was consistent with the known safety profile reported in approved labeling for the other approved indications. Ustekinumab is currently approved for psoriasis and psoriatic arthritis, however, there is no IV formulation for these indications and the SC dosing for these indications is lower than that proposed for CD. The safety profile for ustekinumab also appears generally consistent with the safety profile for other biologics used to treat CD.

The safety profile between maintenance dosing regimens was remarkable for double the number of patients discontinuing the study for adverse events in the every 12 week dosing regimen than in the every 8 week dosing regimen. The majority of these events were CD related, indicating inadequate treatment effect of the every 12 week dosing regimen as compared to the every 8 week dosing regimen. As the rate of serious infections is also higher in the q12w dosing regimen than the q8 week or placebo dosing regimens, there appears to be a favorable safety and tolerability profile for the maintenance dose regimen of every 8 weeks compared to the every 12 week dosing regimen.

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Biologic therapies, often used in the treatment of CD, are associated with increase in risks of serious infection and malignancy. Given the observations of serious infection and malignancy in these trials long-term observational postmarketing studies are recommended to evaluate the long-term risk of developing serious adverse events that may have a longer latency period.

8 Advisory Committee Meeting and Other External Consultations

Not Applicable.

9 Labeling Recommendations

9.1. Prescribing Information

For this BLA the Applicant proposes adding data for safety and efficacy for the indication of moderately to severely active Crohn's disease (CD) who have 1) failed or were intolerant to immunomodulators or corticosteroids but never failed (b) (4) or 2) failed or were intolerant to (b) (4) from three phase 3 studies 3001, 3002, and 3003 to the label. This reviewer agrees with this addition, and proposes to revise the ustekinumab label to incorporate information from this BLA application in the following sections: 5, 6 and 14 in the following manner:

Section 5 – This reviewer recommends:

- 5.1: Adding the serious or clinically significant infections of listeria meningitis and ophthalmic herpes.
- 5.2: Removing theoretical from section 5.2 and (b) (4) of a Bacillus Calmette-Guerin (BCG) vaccine (b) (4)
- 5.5: Modifying section 5.5 to note hypersensitivity reactions

• **Section 6** – This reviewer recommends:

- 6.1: The Applicant revise the numbers for the safety data to include only the number of patients included in the final randomized population that met the criteria specified instead of all patients initially randomized into the induction and maintenance studies. Specifically, 58 patients were noted by the statistical team not to meet the inclusion criteria specified by the sponsor for moderately to severely active Crohn's disease (i.e. (Crohn's Disease Activity Index (CDAI) ≥ 220 and ≤ 450).

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When reporting most common adverse events in Crohn's disease, this reviewer revised the section to include only the doses recommended for approval (e.g. weight tiered 6 mg/kg IV for induction and 90mg SC q 8 weeks). In addition to the already proposed adverse events by the Applicant, this reviewer added gastroenteritis to the induction dose adverse events and urinary tract infection, vulvovaginal mycotic infections, (b) (4), and bronchitis to the maintenance dose adverse events.

For consistency with other biologics to treat inflammatory bowel disease, a section on serious infections was added, a section describing the two hypersensitivity cases, including one anaphylaxis case was also added.

Section 14 – This reviewer recommends:

- 14.3 The Applicant revise the numbers for the efficacy data to include only the number of patients included in the final randomized population that met the criteria specified for the final efficacy analysis instead of all patients initially randomized into the induction and maintenance studies. Specifically, 58 patients were noted by the statistical team not to meet the inclusion criteria specified by the sponsor for moderately to severely active Crohn's disease (i.e. (Crohn's Disease Activity Index (CDAI) ≥ 220 and ≤ 450), 1 patient was excluded from a site that did not follow Good Clinical Practices, and 40 patients randomized prior to the studies being halted a stability issue was identified with a batch of the IV drug.

In the Applicant's description of efficacy for the induction studies in Table (b) (4) Induction of Clinical Response and Remission in CD-1 and CD-2, this reviewer recommends the Applicant revise the endpoints in this table according to pre-specified hierarchical order (i.e. primary, followed by key secondary in the order in which they were tested). This reviewer also recommended the Applicant make other minor additions to the table (b) (4)

In the Applicant's description of the efficacy in the label for maintenance study 3003 in Table (b) (4) Maintenance of Clinical Response and Remission in CD-3 (Week 44; 52 weeks from initiation of the induction dose), this reviewer recommended the Applicant revise the table to reflect only pre-specified primary and key secondary endpoints in the hierarchical order that they were tested and remove (b) (4) other endpoints added to the table. (b) (4) Additionally for the text of study 3003, this reviewer recommends the Applicant remove mention of (b) (4) data from the non-randomized patients from the text.

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(b) (4)

Labeling negotiations are ongoing at the time of this review. For final labeling agreements, see the approved label for ustekinumab.

9.2. Patient Labeling

Please refer to the review by the Division of Medical Policy Programs by Dr. Nyedra Booker dated August 9, 2016.

9.3. Nonprescription Labeling

Not Applicable.

10 Risk Evaluation and Mitigation Strategies (REMS)

Safety Issue(s) that Warrant Consideration of a REMS

A REMS already exists for the approved indications of STELARA to evaluate and mitigate the potential risks of serious infections and malignancy, and reversible posterior leukoencephalopathy syndrome (RPLS) associated with STELARA® by alerting and warning healthcare providers about the risks. DRISK has determined that the new BLA for the Crohn's disease indication will not require a REMS modification to the existing Stelara REMS. Refer to REMS review by Jacqueline Sheppard, dated August 1, 2016.

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10.2. Conditions of Use to Address Safety Issue(s)

Not applicable.

10.3. Recommendations on REMS

Not applicable, see Section 10.1.

11 Postmarketing Requirements and Commitments

The PMR/PMC language below is proposed language. At the time of this review the language is being negotiated. Refer to the approval letter for the final PMR language.

Required Pediatric Assessments:

The Applicant currently has an agreed upon iPSP with the Agency. The pediatric study requirement for ages 0 to <2years of age (b) (4) is waived and pediatric study requirements for ages ≥2 through 17 years will be completed. The required pediatric study is:

(b) (4) clinical study of ustekinumab in pediatric patients (2 to 17 years old) with moderately to severely active CD despite (b) (4) conventional therapy will be conducted. (b) (4)

(b) (4)

(b) (4)

(b) (4) Conduct a long-term, postmarketing, (b) (4) observational, (b) (4) study of ustekinumab versus other agents (b) (4). The study's primary outcome is malignancy. Secondary outcomes include, but are not limited to, (b) (4) opportunistic infections (i.e. tuberculosis [TB]), (b) (4). Specify concise case definitions and validation (b) (4) for both primary and secondary outcomes. Justify the choice of appropriate comparator population(s) and estimated background rate(s) relative to ustekinumab-exposed patients; clearly define the primary comparator population for the primary objective. Design the study around a testable hypothesis to assess, with sufficient sample size and power, a clinically meaningful increase in malignancy risk above the comparator background rate, with a pre-specified statistical analysis method. For the ustekinumab-exposed and comparator(s), the study drug initiation period should be clearly defined, including any exclusion and inclusion criteria. Ensure adequate number of patients with at least (b) (4) months of ustekinumab exposure at the end of the study. (b) (4) follow for a period of at least (b) (4) years.

Active Risk Identification and Analysis (ARIA) Sufficiency

The Division of Epidemiology I (DEPI) evaluated the sufficiency of ARIA to track the risks of serious infection and malignancy in the Crohn's disease (CD) population treated with ustekinumab. Regarding serious infection, DEPI agrees surveillance for serious infections, with a focus on serious bacterial infections should be conducted as ustekinumab is now being used to treat a new patient population in CD and has a new formulation (intravenous) for use in the CD patient population. DEPI has determined that ARIA may not perform well for opportunistic infections, such as TB and Candidiasis due to poor performance of the algorithms. Therefore, as there is a need to assess these types of opportunistic infections in CD, it should be considered as part of a PMR or PMC for this BLA.

Regarding serious malignancy, ARIA currently relies heavily on information submitted by private healthcare providers on behalf of patients with commercial health insurance. Because of instability in the U.S. marketplace for health care and health insurance, ARIA cannot satisfy the regulatory need (b) (4) of ustekinumab surveillance for malignancy. Therefore, DEPI deemed ARIA not sufficient for identifying (1) malignancy outcomes long after first ustekinumab exposure or (2) malignancy outcomes in patients maintained continuously on ustekinumab for long periods both of which need to be assessed in the CD population. Therefore, malignancy should be considered as part of a PMR or PMC for this BLA.

12 Appendices

12.1. References

Refer to footnotes.

12.2. Financial Disclosure

Templates and detailed tables and analyses of financial disclosures are below.

Table 34: Financial Interest Form for Covered Clinical Study 3001

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>570</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>17</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>16</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator: <u>1</u> Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>17</u>		

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Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

In the Table 34 above, 17 investigators disclosed financial arrangements with the Applicant. Sixteen of these arrangements were either payments attributed to research and educational support (5) or speaking/consulting fees (11). The highest enrolling of these sites was Dr. (b) (6), who enrolled (b) (4) patients. This investigator received a research grant and did not directly receive payment from the Applicant for consulting or speaking fees and investigation of this site by OSI did not reveal any protocol violations and determined study appeared to have been conducted adequately, and the data generated by this site may be used in support of the respective indication. An additional investigator, Dr. (b) (6) disclosed significant equity interest, as his spouse owned (b) (6) shares of stock in the Applicant's company that is held in a trust. This investigator was not determined to have a high enroller site. This reviewer believes that given the randomized, double-blind, placebo-controlled, parallel-dosing regimen, design of this trial which enrolled patients from multiple sites data was pooled, this reviewer does not conclude that the financial disclosures had an effect on the outcome of the trial. (See Table 35 below for detailed disclosures).

Table 35: Investigators with Financial Disclosure Forms 3454/3455 for Study 3001

Investigator	Site #	Number of Patients Enrolled	Category of Disclosure (e.g. equity, significant payments of other sorts, etc.)	Description of Disclosure (e.g. "speaker fees", "research grant", "stocks owned", etc.)	Rationale or Steps taken to Minimize Bias
(b) (6)		(b) (6)	reported a payment from Janssen Research & Development and/or Johnson & Johnson in excess of \$25,000	Research support for exact science and compensation from exact sciences as site P1 for a clinical trial	Stelara Crohn's (CNT01275CRD3001) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b) (6) site enrolled (b) (6) out of the total 762 patients in the trial.
(b) (6)		(b) (6)	reported a payment from Janssen Research, LLC. & Development and/or Johnson & Johnson in excess of \$25,000	for speaking and consultation over a two year time period.	Stelara Crohn's (CNT01275CRD3001) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b) (6) site enrolled (b) (6) out of the total 762 patients in the trial.
(b) (6)		(b) (6)	reported a payment from Janssen Research & Development and/or Johnson & Johnson in excess of \$25,000	for grant support for (b) (6) research grant.	Stelara Crohn's (CNT01275CRD3001) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b) (6) site enrolled (b) (6) out of the total 762 patients in the trial.

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(b) (6)	reported a payment from Janssen Research & Development and/or Johnson & Johnson in excess of \$25,000	for educational grants.	Stelara Crohn's (CNTO1275CRD3001) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b) (6) site enrolled (b) (6) out of the total 762 patients in the trial.
	reported a payment from Janssen Research & Development and/or Johnson & Johnson in excess of \$25,000	for speaker's bureau.	Stelara Crohn's (CNTO1275CRD3001) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b) (6) site enrolled (b) (6) out of the total 762 patients in the trial.
	reported a payment from Janssen Research & Development, LLC and/or Johnson & Johnson in excess of \$25,000	for Janssen funding for (b) (6) fellowship support.	Stelara Crohn's (CNTO1275CRD3001) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b) (6) site enrolled (b) (6) out of the total 762 patients in the trial.

(b) (6)	reported a payment from Janssen Research & Development, LLC and/or Johnson & Johnson in excess of \$25,000	for speaker's bureau \$49,500.	Stelara Crohn's (CNTO1275CRD3001) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b) (6) site enrolled (b) (6) out of the total 762 patients in the trial.
	reported a payment from Janssen Research & Development, LLC and/or Johnson & Johnson in excess of \$25,000	for speaking and advisory board.	Stelara Crohn's (CNTO1275CRD3001) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b) (6) site enrolled (b) (6) out of the total 762 patients in the trial.
	reported a significant equity interest in Janssen Research & Development, LLC and/or Johnson & Johnson, parent company of the sponsor of the trial.	Spouse's trust own (b) (6) approximately (b) (6) shares of Johnson & Johnson.	Stelara Crohn's (CNTO1275CRD3001) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b) (6) site enrolled (b) (6) out of the total 762 patients in the trial.

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(b) (6)	reported a payment from Janssen Research & Development and/or Johnson & Johnson in excess of \$25,000	for honoraria for speaking engagement.	Stelara Crohn's (CNTO1275CRD3001) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b) (6) site enrolled (b) (6) out of the total 762 patients in the trial.
	reported a payment from Janssen Research & Development and/or Johnson & Johnson in excess of \$25,000	for Advisory board, honoraria.	Stelara Crohn's (CNTO1275CRD3001) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b) (6) site enrolled (b) (6) out of the total 762 patients in the trial.
	reported a payment from Janssen Research & Development and/or Johnson & Johnson in excess of \$25,000	for Research grant provided by Janssen Canada \$175,000.	Stelara Crohn's (CNTO1275CRD3001) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b) (6) site enrolled (b) (6) out of the total 762 patients in the trial.

(b) (6)	reported a payment from Janssen Research & Development and/or Johnson & Johnson in excess of \$25,000	for speaking honoraria.	Stelara Crohn's (CNTO1275CRD3001) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b) (6) site enrolled (b) (6) out of the total 762 patients in the trial.
	reported a payment from Janssen Research & Development and/or Johnson & Johnson in excess of \$25,000	for speaker's bureau / honorarium.	Stelara Crohn's (CNTO1275CRD3001) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b) (6) site enrolled (b) (6) out of the total 762 patients in the trial.
	reported a payment from Janssen Research & Development and/or Johnson & Johnson in excess of \$25,000	for speaking and advisory board honoraria.	Stelara Crohn's (CNTO1275CRD3001) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b) (6) site enrolled (b) (6) out of the total 762 patients in the trial.

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 Stelara (ustekinumab)

(b) (6)	reported a payment from Janssen Research & Development and/or Johnson & Johnson in excess of \$25,000	for consulting agreement	Stelara Crohn's (CNT01275CRD3001) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b) (6) site enrolled (b) (6) out of the 762 patients in the trial.
	reported a payment from Janssen Research & Development and/or Johnson & Johnson in excess of \$25,000	For consultancy services	Stelara Crohn's (CNT01275CRD3001) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b) (6) site enrolled (b) (6) out of the total 762 patients in the trial.

Source: Applicant's response to IR dated 8/17/2016 for Study 3001.

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Table 36: Financial Interest Form for Covered Clinical Study 3002

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>885</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>14</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):		

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Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>12</u> Proprietary interest in the product tested held by investigator: <u>1</u> Significant equity interest held by investigator: <u>1</u> Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>17</u>		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

In Table 36 above, 14 investigators disclosed financial arrangements with the Applicant. Twelve of these arrangements were payments attributed to speaking/consulting fees. The highest enrolling of these sites was Dr. (b) (6) who enrolled (b) (6) patients who received consulting fees from the Applicant. Investigation of this site by OSI did not reveal any protocol violations and determined study appeared to have been conducted adequately, and the data generated by this site may be used in support of the respective indication. An additional investigator, Dr. (b) (6) disclosed significant equity interest, as his spouse owned 1200 shares of stock in the Applicant's company that is held in a trust and another investigator, Dr. (b) (6) disclosed proprietary interest in a patented colorectal cancer birthday card. Neither of these investigators were determined to have a high enroller sites. This reviewer believes that given the randomized, double-blind, placebo-controlled, parallel-dosing regimen, design of this trial which enrolled patients from multiple sites data was pooled, this reviewer does not conclude that the financial disclosures had an effect on the outcome of the trial. (See Table 37 below for detailed disclosures).

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Table 37: Investigators with Financial Disclosure Forms 3454/3455 for Study 3002

<i>Investigator</i>	<i>Site #</i>	<i>Number of Patients Enrolled</i>	<i>Category of Disclosure (e.g. equity, significant payments of other sorts, etc.)</i>	<i>Description of Disclosure (e.g. "speaker fees", "research grant", "stocks owned", etc.)</i>	<i>Rationale or Steps taken to Minimize Bias</i>
(b) (6)			reported a significant equity interest in Janssen Research & Development, LLC and/or Johnson & Johnson, parent company of the sponsor of the trial	He is an advisor to Janssen	Stelara Crohn's (CNT01275CRD3002) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b) (6) site enrolled (b) (6) out of the total 640 patients in the trial.
			reported a payment from Janssen Research & Development and/or Johnson & Johnson in excess of \$25,000	for speaking and consultation over two year period	Stelara Crohn's (CNT01275CRD3002) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b) (6) site enrolled (b) (6) out of the total 640 patients in the trial.
			reported a payment from Janssen Research, LLC. & Development and/or Johnson & Johnson in excess of \$25,000	for speaking bureau.	Stelara Crohn's (CNT01275CRD3002) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b) (6) site enrolled (b) (6) out of the total 640 patients in the trial.
			reported a payment from Janssen Research, LLC. & Development and/or Johnson & Johnson in excess of \$25,000	for speaking and advisory board.	Stelara Crohn's (CNT01275CRD3002) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b) (6) site enrolled (b) (6) out of the total 640 patients in the trial.
			reported a significant equity interest in Janssen Research & Development, LLC and/or Johnson & Johnson, parent company of the sponsor of the trial	Spouse's trust owns approximately (b) (6) shares of Johnson & Johnson.	Stelara Crohn's (CNT01275CRD3002) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b) (6) site enrolled (b) (6) out of the total 640 patients in the trial.
			reported a payment from Janssen Research & Development and/or Johnson & Johnson in excess of \$25,000	for honoraria for speakers bureau.	Stelara Crohn's (CNT01275CRD3002) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b) (6) site enrolled (b) (6) out of the total 640 patients in the trial.

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(b) (6)	reported a payment from Janssen Research & Development and/or Johnson & Johnson in excess of \$25,000	for advisory board, honoraria	Stelara Crohn's (CNT01275CRD3002) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b) (6) site enrolled (b) (6) out of the total 640 patients in the trial.
	reported a proprietary or financial interest in the test product such as a patent, trademark, copyright, or licensing agreement		Stelara Crohn's (CNT01275CRD3002) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b) (6) site enrolled (b) (6) out of the total 640 patients in the trial.
	reported a payment from Janssen Research & Development and/or Johnson & Johnson in excess of \$25,000	for consultancy services	Stelara Crohn's (CNT01275CRD3002) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b) (6) site enrolled (b) (6) out of the total 640 patients in the trial.
	reported a payment from Centocor and/or Johnson & Johnson in excess of \$25,000	for consultancy services	Stelara Crohn's (CNT01275CRD3002) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b) (6) site enrolled (b) (6) out of the total 640 patients in the trial.
	reported a payment from Centocor and/or Johnson & Johnson in excess of \$25,000	for consultancy services.	Stelara Crohn's (CNT01275CRD3002) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b) (6) site enrolled (b) (6) out of the total 640 patients in the trial.
	reported a payment from Centocor and/or Johnson & Johnson in excess of \$25,000	for consultancy services.	Stelara Crohn's (CNT01275CRD3002) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b) (6) site enrolled (b) (6) out of the total 640 patients in the trial.
	reported a payment from Janssen Research & Development and/or Johnson & Johnson in excess of \$25,000	for consultancy services.	Stelara Crohn's (CNT01275CRD3002) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b) (6) site enrolled (b) (6) out of the total 640 patients in the trial.
	reported a payment from Janssen Research & Development and/or Johnson & Johnson in excess of \$25,000	for consultancy services	Stelara Crohn's (CNT01275CRD3002) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b) (6) site enrolled (b) (6) out of the total 640 patients in the trial.

Source: Applicant's response to IR dated 8/17/2016 for Study 3002.

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Table 38: Financial Interest Form for Covered Clinical Study 3003

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>2028</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>20</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>19</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator: <u>1</u> Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>17</u>		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

In Table 38 above, 20 investigators disclosed financial arrangements with the Applicant. Twelve of these arrangements were either payments attributed to research and educational support (4) or speaking/consulting fees (14). The highest enrolling of these sites was Dr. (b) (6) (b) (6) who enrolled (b) (6) patients, however, only (b) (6) of the patients enrolled at this site were in the randomized population of study 3003 used for the main efficacy analysis. Additionally, this investigator received a research grant and did not directly receive payment from the Applicant for consulting or speaking fees and investigation of this site by OSI did not reveal any protocol

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violations and determined study appeared to have been conducted adequately, and the data generated by this site may be used in support of the respective indication. An additional investigator, Dr. (b)(4) disclosed significant equity interest, as his spouse owned 1200 shares of stock in the Applicant’s company that is held in a trust. This investigator was not determined to have a high enrolling site. This reviewer believes that given the randomized, double-blind, placebo-controlled, parallel-dosing regimen, design of this trial which enrolled patients from multiple sites data was pooled, this reviewer does not conclude that the financial disclosures had an effect on the outcome of the trial. (See Table 39 below for detailed disclosures).

Table 39: Investigators with Financial Disclosure Forms 3454/3455 for Study 3003

<i>Investigator</i>	<i>Site #</i>	<i>Number of Patients Enrolled</i>	<i>Category of Disclosure (e.g. equity, significant payments of other sorts, etc.)</i>	<i>Description of Disclosure (e.g. “speaker fees”, “research grant”, “stocks owned”, etc.)</i>	<i>Rationale or Steps taken to Minimize Bias</i>
(b)(6)			reported a payment from Janssen Research & Development and/or Johnson & Johnson in excess of \$25,000	For research grant	Stelara Crohn’s (CNT01275CRD3003) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b)(6) site enrolled (b)(6) out of the total 1281 patients in the trial.
(b)(6)			reported a payment from Janssen Research & Development, LLC and/or Johnson & Johnson in excess of \$25,000	for speaking and consulting over two year period	Stelara Crohn’s (CNT01275CRD3003) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b)(6) site enrolled (b)(6) out of the total 1281 patients in the trial.
(b)(6)			reported a payment from Janssen Research & Development and/or Johnson & Johnson in excess of \$25,000	For support from (b)(6) and consultant fees.	Stelara Crohn’s (CNT01275CRD3003) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b)(6) site enrolled (b)(6) out of the total 1281 patients in the trial.

(b) (6)	reported a payment from Janssen Research & Development and/or Johnson & Johnson in excess of \$25,000	For speaker fees	Stelara Crohn's (CNT01275CRD3003) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b) (6) site enrolled (b) (6) out of the total 1281 patients in the trial.
	reported a payment from Janssen Research & Development and/or Johnson & Johnson in excess of \$25,000	For educational grants	Stelara Crohn's (CNT01275CRD3003) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b) (6) site enrolled (b) (6) out of the total 1281 patients in the trial.
	reported a payment from Janssen Research & Development, and/or Johnson & Johnson in excess of \$25,000	For speaker's fees	Stelara Crohn's (CNT01275CRD3003) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b) (6) site enrolled (b) (6) out of the total 1281 patients in the trial.
	reported a payment from Janssen Research & Development, LLC and/or Johnson & Johnson in excess of \$25,000	for speaker bureau.	Stelara Crohn's (CNT01275CRD3003) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b) (6) site enrolled (b) (6) out of the total 1281 patients in the trial.
	reported a payment from Janssen Research & Development, LLC and/or Johnson & Johnson in excess of \$25,000	for speaking fee	Stelara Crohn's (CNT01275CRD3003) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b) (6) site enrolled (b) (6) out of the total 1281 patients in the trial.
	reported a significant equity interest in Janssen Research & Development, LLC and/or Johnson & Johnson, parent company of the sponsor of the trial	Spouse's trust owns approximately (b) (6) shares of Johnson & Johnson	Stelara Crohn's (CNT01275CRD3003) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b) (6) site enrolled (b) (6) out of the total 1281 patients in the trial.

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(b) (6)	reported a payment from Janssen Research & Development and/or Johnson & Johnson in excess of \$25,000	for honoraria for speaking bureau.	Stelara Crohn's (CNTO1275CRD3003) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b) (6) site enrolled (b) (6) out of the 1281 patients in the trial
	reported a payment from Janssen Research & Development and/or Johnson & Johnson in excess of \$25,000	for advisory board honoraria	Stelara Crohn's (CNTO1275CRD3003) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b) (6) site enrolled (b) (6) out of the total 1281 patients in the trial
	reported a payment from Janssen Research & Development and/or Johnson & Johnson in excess of \$25,000	Research grant provided by Janssen Canada (\$175,000)	Stelara Crohn's (CNTO1275CRD3003) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b) (6) site enrolled (b) (6) out of the total 1281 patients in the trial
	reported a payment from Janssen Research & Development and/or Johnson & Johnson in excess of \$25,000	Speaker's bureau/honorarium	Stelara Crohn's (CNTO1275CRD3003) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b) (6) site enrolled (b) (6) out of the total 1281 patients in the trial
	reported a payment from Janssen Research & Development and/or Johnson & Johnson in excess of \$25,000	Honoraria for speaking	Stelara Crohn's (CNTO1275CRD3003) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b) (6) site enrolled (b) (6) out of the total 1281 patients in the trial
	reported a payment from Janssen Research & Development and/or Johnson & Johnson in excess of \$25,000	Honoraria for speaking and consulting	Stelara Crohn's (CNTO1275CRD3003) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b) (6) site enrolled (b) (6) out of the total 1281 patients in the trial

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(b) (6)	reported a payment from Janssen Research & Development and/or Johnson & Johnson in excess of \$25,000	For financial support to institution for an IBD research clinical and clinical teaching	Stelara Crohn's (CNT01275CRD3003) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b) (6) site enrolled (b) (6) out of the total 1281 patients in the trial
	reported a payment from Janssen Research & Development and/or Johnson & Johnson in excess of \$25,000	For consultancy services	Stelara Crohn's (CNT01275CRD3003) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b) (6) site enrolled (b) (6) out of the total 1281 patients in the trial
	reported a payment from Centocor and/or Johnson & Johnson in excess of \$25,000	for consultancy services	Stelara Crohn's (CNT01275CRD3003) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b) (6) site enrolled (b) (6) out of the total 1281 patients in the trial.
	reported a payment from Centocor and/or Johnson & Johnson in excess of \$25,000	for consultancy services.	Stelara Crohn's (CNT01275CRD3003) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b) (6) site enrolled (b) (6) out of the total 1281 patients in the trial.
	reported a payment from Centocor and/or Johnson & Johnson in excess of \$25,000	for consultancy services.	Stelara Crohn's (CNT01275CRD3003) study was a randomized, double-blind, placebo-controlled, parallel-group, consisting of multiple sites from which the data was pooled. Dr. (b) (6) site enrolled (b) (6) out of the total 1281 patients in the trial.

Source: Applicant's response to IR dated 8/17/2016 for Study 3003.

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12.3. Figures

Figure 38: SES-CD Scoring Components

	Ileum	Right colon	Transverse colon	Left colon	Rectum	Total
Presence and size of ulcers (0-3)	--	2	1	1	1	5
Extent of ulcerated surface (0-3)	--	1	1	1	1	4
Extent of affected surface (0-3)	--	2	1	1	1	5
Presence and type of narrowings (0-3)	--	3	0	0	0	3
SES-CD =						17

Source: Daperno et al. 2004. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. *Gastrointestinal Endoscopy*: 60 (4): 505-512.

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Figure 39: Global Histology Activity Score for Crohn's Disease

Table 1. Microscopic Crohn's disease activity according to the Scoring System for Crohn's disease adapted from D'Haens *et al.*¹⁸

Histological variable	Grading
Epithelial damage	0 = normal; 1 = focal; 2 = extensive
Architectural changes	0 = normal; 1 = moderate; 2 = severe
Mononuclear cells in lamina propria	0 = normal; 1 = moderate increase; 2 = severe increase
Polymorphonuclear cells in lamina propria	0 = normal; 1 = moderate increase; 2 = severe increase
Neutrophils in epithelium	1 = surface epithelium; 1 = cryptitis; 2 = crypt abscess
Erosion or ulceration	0 = no; 1 = yes
Granuloma	0 = no; 1 = yes

Source: Laharie et al. 2011. Mucosal healing with methotrexate in Crohn's disease: a prospective comparative study with azathioprine and infliximab. Alimentary Pharmacology and Therapeutics 33(6): 714-721.

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KERRY J LEE
09/07/2016

JULI A TOMAINO
09/07/2016