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APPLICATION NUMBER:

761044Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	September 22, 2016
From	Juli Tomaino, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	BLA 761044
Supplement#	
Applicant	Janssen Biotech, Inc.
Date of Submission	November 25, 2015
PDUFA Goal Date	September 25, 2016 (action date September 23, 2016)
Proprietary Name / Non-Proprietary Name	STELARA/ustekinumab
Dosage form(s) / Strength(s)	Initial dose is a single weight-based dose of approximately 6 mg/kg intravenous, then 90 mg subcutaneous injection every 8 weeks thereafter.
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Recommendation on Regulatory Action	<i>Approval</i>
Recommended Indication(s)/Population(s) (if applicable)	STELARA [®] is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have: failed or were intolerant to treatment with immunomodulators or corticosteroids, but never failed treatment with a tumor necrosis factor (TNF) blocker, or failed or were intolerant to treatment with one or more TNF blockers.

Benefit-Risk Summary and Assessment

The reviewers have recommended approval of ustekinumab for the treatment of adult patients with Crohn's disease, as specified in the indication statement of the label. I agree with the reviewers that the data submitted in this BLA establish a clinical benefit in adult patients with moderately to severely active Crohn's disease, and the use of ustekinumab is supported by evidence from adequate and well-controlled trials. This product offers a new mechanism of action for the treatment of Crohn's disease. In support of this BLA, the Applicant conducted three adequate and well-controlled phase 3 trials (two 8-week "induction" trials and one 44-week "maintenance" trial; total duration of 52 weeks). I recommend approval of BLA 761044 for the treatment of adult patients with moderately to severely active Crohn's disease who have failed or were intolerant to treatment with immunomodulators or corticosteroids, but never failed treatment with a TNF blocker, or patients who failed or were intolerant to treatment with one or more TNF blockers.

The data from two 8-week, multicenter, randomized, double-blind, placebo-controlled, parallel group trials in adult patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] score ≥ 220 and ≤ 450) evaluating a single weight-based intravenous (IV) infusion of approximately 6 mg/kg, 130 mg, or placebo demonstrated statistical significance on primary and ranked secondary endpoints, including clinical remission at Week 8. Although clinical remission at Week 8 was the first ranked secondary endpoint, it is considered to be the more clinically meaningful endpoint compared to the primary efficacy endpoint of clinical response at Week 6. One of the 8-week trials evaluated 741 patients who failed or were intolerant to prior TNF blocker treatment (study 3001); 52/249 (20.9%) patients were in clinical remission at Week 8 after a single weight-based IV dose of 6 mg/kg ustekinumab, as compared to 18/247 (7.3%) in the placebo arm ($p=0.003$), a treatment difference of 13.6%. The second 8-week trial evaluated 628 patients who failed or were intolerant to corticosteroids or immunomodulator treatment but never failed treatment with a TNF blocker (study 3002); 84/209 (40.2%) patients were in clinical remission at Week 8 after a single weight-based IV dose of 6 mg/kg ustekinumab, as compared to 41/209 (19.6%) on placebo ($p<0.001$), a treatment difference of 20.6%. Both trials also demonstrated statistical significance on multiple other pre-specified endpoints.

Patients who achieved at least clinical response at Week 8 of the "induction trials" were eligible to be re-randomized into the 44-week "maintenance" trial (study 3003). Patients were randomized to ustekinumab subcutaneous injection of 90 mg every 8 weeks (q8w), 90 mg every 12 weeks (q12w), or placebo. Statistical significance was demonstrated for the primary endpoint of clinical remission, defined by CDAI < 150 points, at Week 44, and also for the first and second ranked secondary endpoints: clinical response at Week 44 and clinical remission at Week 44 among patients in clinical remission at Week 0 of maintenance/Week 8 of induction. Based on the pre-specified testing order, statistical testing was stopped because the 90 mg q12w dosing regimen failed to meet statistical significance on the secondary endpoint of clinical remission at Week 44 among patients in remission at Week 0 of maintenance. Therefore, the third and fourth ranked secondary endpoints of corticosteroid-free remission at Week 44 and clinical remission at Week 44 among patients who had failed or were intolerant to treatment with TNF blockers could not be formally tested. At week 44, 68/128 (53.1%) patients in the 90 mg q8w dose regimen achieved clinical remission as compared to 47/131 (35.9%) in the placebo arm ($p=0.005$), a treatment difference of 17.2%. Clinical remission at week 44 among patients in remission at week 0 of maintenance/week 8 of induction was observed in 52/78 (66.7%) patients in the 90 mg q8w dose regimen, as compared to 36/79 (45.6%) in placebo ($p=0.007$), and 44/78 (56.4%) in the 90 mg q12w dose regimen (NS). In general, the trial demonstrated statistical

significance on multiple endpoints and the clinical benefit was observed in the overall patient population. Furthermore, the exploratory analysis performed by the statistical reviewer demonstrates that patients treated with 90 mg q8w continued to be in remission at the majority (10 out of 12) of visits during the 44 weeks. However, the proportion of patients in clinical remission declined between Week 0 and Week 44 of the maintenance trial in the subset of patients who failed or were intolerant to treatment with TNF blockers, suggesting that this subset of patients may not “maintain” remission to the same degree as patients who had not failed prior treatment with TNF blockers. In addition, (b) (4) the 90 mg q8w dosing regimen appeared to be the more favorable dosing regimen to “maintain” remission.

The safety profile was generally comparable to the known safety profile already described in the product label for the psoriasis and psoriatic arthritis indications, and overall similar to the safety profile of other immunosuppressant therapies used for the treatment of inflammatory bowel disease. There were no cases of reversible posterior leukoencephalopathy syndrome (RPLS) identified during the phase 3 clinical trials in Crohn’s disease. While clinical trials included in the BLA provided adequate efficacy and safety data to support approval of ustekinumab for the treatment of adult patients with moderately to severely active Crohn’s disease, there was some uncertainty about the risk of malignancy in this patient population, given that 1) ustekinumab is a first in class therapy for Crohn’s disease, 2) patients with Crohn’s disease are at increased risk for certain malignancies, 3) concomitant medication use may contribute to the risk, and 4) the dosage regimen for the treatment of Crohn’s disease includes introduction of an intravenous dose, following by higher dosage regimen for chronic administration as compared to the doses previously approved for other indications. Therefore, longer term exposure in a larger patient population is necessary to evaluate the risk of malignancy. Since efficacy and safety data included in the BLA are sufficient to support approval, additional long-term clinical outcome data will be collected in the post-marketing setting.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p>Analysis of Condition</p>	<p>Crohn's disease (CD) is a chronic, relapsing and remitting disease that may affect areas of the entire gastrointestinal tract. In North America, the prevalence of Crohn’s disease ranges from 30 to 200 per 100,000 adults and incidence ranges from 3 to 15 cases per 100,000 persons per year. In the United States and Canada, it is estimated that 10,000-47,000 people are diagnosed with Crohn’s disease each year, and up to 630,000 people have Crohn’s disease.</p> <p>Common signs and symptoms of Crohn’s disease include diarrhea, abdominal pain, weight loss, fever, and rectal bleeding, although rectal bleeding in Crohn’s disease is more commonly associated with colonic disease.</p> <p>Complications of Crohn’s disease include strictures, fistulae, abscess, and</p>	<p>Crohn's disease (CD) is a chronic, relapsing disease that may affect areas of the entire gastrointestinal tract. In North America, the prevalence of Crohn’s disease ranges from 30 to 200 per 100,000 adults and incidence ranges from 3 to 15 cases per 100,000 persons per year.</p> <p>Common signs and symptoms of CD include diarrhea, abdominal pain, weight loss, fever, and rectal bleeding, and extraintestinal complications. If left untreated or poorly treated</p>

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	<p>extraintestinal complications of the skin, eyes, and joints (e.g., erythema nodosum, pyoderma gangrenosum, uveitis, ankylosing spondylitis, arthritis). In addition, the inflammation in the bowel may lead to malabsorption that results in anemia, vitamin deficiency, nephrolithiasis or metabolic bone disease. Furthermore, long-term disease duration may be associated with GI tract adenocarcinoma.</p>	<p>with residual, ongoing inflammation, patients may suffer from significant morbidity and/or mortality.</p>
<p><u>Current Treatment Options</u></p>	<p>The overall goal in the treatment and management of Crohn’s disease is to “induce” and “maintain” remission. The choice of therapy is guided by the disease severity, location, and presence of other manifestations (i.e., extraintestinal complications, malabsorption, etc). Therapeutic options for treatment include 5-aminosalicylic acid (5-ASA) products (e.g., mesalamine), corticosteroids, antibiotics, immunomodulators (e.g., azathioprine [AZA], 6-mercaptopurine [6-MP], and methotrexate [MTX]), and biologic therapies (e.g., tumor necrosis factor [TNFα] blockers, anti-integrin therapies). Corticosteroids are not recommended for long-term use given the toxicities associated with chronic steroid use. While these medications are widely used in clinical practice, not all are FDA approved for the treatment of Crohn’s disease. There remains a need for novel therapies as not all patients will respond or have continued response to any given treatment. For example, approximately 10–30% of patients do not respond initially to TNF blockers and 20-50% lose response over time.</p>	<p>Ustekinumab offers a new mechanism of action for the treatment of Crohn’s disease in patients who have failed prior therapies. Additional therapies are needed since many patients lose response over time to currently available therapies, such as TNF blockers.</p>
<p><u>Benefit</u></p>	<p>The efficacy of ustekinumab was demonstrated in three adequate and well-controlled phase 3 trials (two 8-week “induction” trials and one 44-week “maintenance” trial; total duration of 52 weeks).</p> <p>Data were submitted from two 8-week, multicenter, randomized, double-blind, placebo-controlled, parallel group trials in adult patients with active moderate to severe Crohn’s disease (Crohn’s Disease Activity Index [CDAI] score ≥ 220 and ≤ 450); one trial enrolled patients who have failed or were intolerant to treatment with one or more TNF blockers (study 3001), and the other trial enrolled in patients who have failed or were intolerant to immunomodulators or corticosteroids, but never failed treatment with TNF blockers (study 3002). Patients were randomized to a single weight-based IV infusion of</p>	<p>The three adequate and well-controlled phase 3 trials (two 8-week “induction” trials and one 44-week “maintenance” trial; total duration of 52 weeks) demonstrated clinical benefit of ustekinumab for the treatment of patients who failed or were intolerant to one or more TNF blockers, and patients who have failed or were intolerant to immunomodulators or corticosteroids, but never failed TNF blocker treatment. Clinical remission at Week 8 after a single weight-based IV infusion of 6 mg/kg demonstrated statistical significance. Clinical remission at Week 44 also demonstrated</p>

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	<p>approximately 6 mg/kg, 130 mg, or placebo.</p> <p>Both trials demonstrated statistical significance on the primary and ranked secondary endpoints, including clinical remission at week 8. In study 3001, patients who failed/were intolerant to prior TNF blocker treatment, 52/249 (20.9%) patients were in clinical remission at Week 8 after a single IV dose of 6 mg/kg ustekinumab, as compared to 18/247 (7.3%), a treatment difference of 13.6%. In study 3002, patients who failed/were intolerant to corticosteroids or immunomodulators, 84/209 (40.2%) patients were in clinical remission at week 8 after a single IV dose of 6 mg/kg ustekinumab, as compared to 41/209 (19.6%) on placebo (p<0.001), a treatment difference of 20.6%. Both trials also demonstrated statistical significance on multiple other pre-specified endpoints.</p> <p>Patients who achieved at least clinical response at Week 8 of the “induction trials” were eligible to be re-randomized into the 44-week “maintenance” trial (study 3003). Study 3003 demonstrated statistical significance for the primary endpoint of clinical remission, defined by CDAI < 150 points, at Week 44, and also for the first and second ranked secondary endpoints: clinical response at Week 44, clinical remission at Week 44 among patients in clinical remission at Week 0 of maintenance/Week 8 of induction. Based on the pre-specified testing order, statistical testing was stopped because the 90 mg q12w dose regimen failed to meet statistical significance on the secondary endpoint of clinical remission at Week 44 among patients in remission at Week 0 of maintenance. At Week 44, 68/128 (53.1%) patients in the 90 mg q8w dose regimen achieved clinical remission as compared to 47/131 (35.9%) in the placebo arm (p=0.005), a treatment difference of 17.2%. Clinical remission at week 44 among patients in remission at Week 0 of maintenance/Week 8 of induction was observed in 52/78 (66.7%) patients in the 90 mg q8w dose regimen, as compared to 36/79 (45.6%) in placebo (p=0.007), and 44/78 (56.4%) in the 90 mg q12w dose regimen (NS vs placebo). Additionally, an exploratory analysis performed by the statistical reviewer demonstrated that patients treated with 90 mg q8w continued to be in remission at the majority</p>	<p>statistical significance in the overall patient population who were in remission at Week 0 of maintenance, and was supported by an exploratory analysis performed by the statistical reviewer to assure that patients were able to maintain remission during the majority of visits during the 44-week treatment period. However, clinical remission trended downward between Week 0 and Week 44 in the subset of patients who failed or were intolerant to TNF blockers, suggesting that this subset of patients may not maintain remission to the same degree as patients who had not failed prior treatment with TNF blockers.</p> <p>In addition, (b) (4)</p> <p>the evidence support 90 mg q8w as the favorable dosing regimen to “maintain” remission. (b) (4)</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>(10 out of 12) of visits during the 44 weeks. However, clinical remission trended downward between Week 0 to Week 44 of study 3003 in the subset of patients who failed or were intolerant to treatment with TNF blockers, suggesting that this subset of patients may not “maintain” remission to the same degree as patients who had not failed prior treatment with TNF blockers.</p> <p>In addition, [REDACTED] (b) (4) the evidence supports 90 mg q8w as the more favorable dosing regimen to “maintain” remission. Based on the small subset of patients who underwent dose escalation, it is not possible to determine whether patients who dose-escalated regained response due to the dose escalation or to the longer duration of therapy, since patients who remained on the q8w regimen also resulted in substantial proportion becoming responders or remitters.</p> <p>Furthermore, the dose-response relationship supports the following recommended dosing regimen: a single weight-based dose of ustekinumab 6 mg/kg IV followed by ustekinumab 90 mg SC every 8 weeks thereafter. The exposure-response (E-R) relationship also provides supportive evidence of clinical efficacy for the above recommended dosing.</p>	
<p><u>Risk</u></p>	<p>The safety population includes 1367 patients who participated in three phase 3 clinical trials, with an overall duration of exposure up to 52 weeks in the phase 3 trials. Common adverse reactions observed during studies 3001 and 3002 through Week 8 in at least 3% of patients treated with a single weight-based dose of approximately 6 mg/kg ustekinumab and greater than placebo included abdominal pain and vomiting. Adverse reactions observed through Week 44 in study 3003 in at least 3% of patients treated with ustekinumab 90 mg q8w and greater than placebo included nasopharyngitis, injection site erythema, bronchitis, vulvovaginal candidiasis/mycotic infection, pruritus, sinusitis, and urinary tract infection.</p> <p>In addition, two patients reported serious hypersensitivity reactions following a single dose of ustekinumab. One patient developed anaphylaxis reported as</p>	<p>The safety profile was generally comparable to the known safety profile already described in the product label for the psoriasis and psoriatic arthritis indications, and overall similar to the safety profile of other immunosuppressant therapies used for the treatment of inflammatory bowel disease. There were no cases of reversible posterior leukoencephalopathy syndrome (RPLS) identified during the phase 3 clinical trials in Crohn’s disease.</p> <p>The safety concerns identified will be described</p>

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	<p>tightness of the throat, shortness of breath, and flushing following a subcutaneous dose, and the other patient exhibited symptoms of chest discomfort, flushing, urticaria, and increased body temperature following an intravenous dose.</p> <p>Malignancies included multiple myeloma, basal cell carcinoma, nonmelanoma skin cancers, metastatic small bowel adenocarcinoma and a carcinoid tumor, chronic myeloid leukemia and seminoma.</p> <p>Serious or other clinically significant infections included active primary tuberculosis, listeria meningitis, and ophthalmic herpes in one patient each.</p> <p>One patient who received a single IV dose of ustekinumab followed by SC dosing for 2 months experienced symptoms of visual impairment, dizziness and numbness/tingling of her mouth. MRI of this patient exhibited multiple areas of abnormality in the white matter tracts of both hemispheres; however, the MRI findings appeared to be non-specific and were not clearly consistent with acute demyelination.</p>	<p>in the product label.</p>
<p><u>Risk Management</u></p>	<p>Labeling: Product labeling will address safety concerns identified, including serious infection, malignancy, and hypersensitivity reactions.</p> <p>Risk Mitigation: A REMS modification is not required for ustekinumab.</p> <p>Post-approval Studies and Trials: Post-approval, the Applicant will conduct an observational study to assess the long-term safety of ustekinumab versus other therapies used in the treatment of adults with moderate to severe Crohn’s disease. The study’s primary outcome is malignancy. Secondary outcomes include, but are not limited to, opportunistic infections (e.g., tuberculosis [TB]).</p> <p>The Applicant will also conduct pediatric trials as PMCs.</p> <p>In addition, the Applicant will conduct a post-marketing commitment trial to</p>	<p>The product labeling adequately addresses the safety concerns identified with the use of ustekinumab in patients with Crohn’s disease.</p> <p>A REMS modification is not required.</p> <p>Post-marketing study will be conducted to assess the long-term safety of ustekinumab versus other therapies used in the treatment of adults with moderate to severe Crohn’s disease. The Applicant will also address the pediatric indications as post-marketing commitments, and conduct a trial to evaluate whether ustekinumab alters the metabolism or PK of CYP substrates.</p>

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	assess whether ustekinumab alters the metabolism or pharmacokinetics (PK) of cytochrome P450 (CYP) substrates in Crohn’s disease (CD) patients treated with ustekinumab (e.g., using a cocktail of relevant CYP probe drugs).	

1. Background

On November 25, 2015, Janssen Biotech (the Applicant) submitted a biologics license application (BLA) to support marketing approval of Stelara[®] (ustekinumab) for the treatment of adult patients with moderately to severely active Crohn's disease. The results of three adequate and well-controlled trials in adult patients with Crohn's disease were submitted to BLA 761044 to support the following indication:

- “Stelara[®] is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have:
 - o failed or were intolerant to treatment with immunomodulators or corticosteroids, but never failed treatment a TNF blocker or
 - o failed or were intolerant to treatment with one or more TNF blockers.”

All the review disciplines recommend in favor of approval; however, they have recommended several post-marketing requirements and commitments to address long-term safety, drug interactions, and the pediatric population. I agree with their recommendations.

Clinical Background

Crohn's disease (CD) is a chronic, relapsing disease, characterized by transmural inflammation and by skip lesions that may affect areas of the entire gastrointestinal tract. In North America, the prevalence of Crohn's disease ranges from 30 to 200 per 100,000 adults and incidence ranges from 3 to 15 cases per 100,000 persons per year.¹ In the United States and Canada, it is estimated that 10,000-47,000 people are diagnosed with Crohn's disease each year, and up to 630,000 people have Crohn's disease.¹

Common signs and symptoms of CD include diarrhea, abdominal pain, weight loss, fever, and rectal bleeding, although rectal bleeding in Crohn's disease is more commonly associated with colonic disease. Complications of Crohn's disease include strictures, fistulae, abscess, and extraintestinal complications of the skin, eyes, and joints (e.g., erythema nodosum, pyoderma gangrenosum, uveitis, ankylosing spondylitis, arthritis). In addition, the inflammation in the bowel may lead to malabsorption that results in anemia, vitamin deficiency, nephrolithiasis or metabolic bone disease. Furthermore, long-term disease duration may be associated with gastrointestinal tract adenocarcinoma.²

The overall goal in the treatment of Crohn's disease is to “induce” and “maintain” remission. The choice of therapy is guided by the disease severity, location, and presence of other manifestations (i.e., extraintestinal complications, malabsorption, etc). Therapeutic options for the treatment of CD include 5-aminosalicylic acid (5-ASA) products (e.g., mesalamine),

¹ Loftus EV, Jr. Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. *Gastroenterology* 2004; 126:1504-17.

² Lichtenstein, G., Hanauer, S., Sandborn, W., The Practice Parameters Committee of the American College of Gastroenterology. Management of Crohn's Disease in Adults. *Am J Gastroenterol* 2009;104(2):465-83.

corticosteroids, antibiotics, immunomodulators (e.g., azathioprine [AZA], 6-mercaptopurine [6-MP], and methotrexate [MTX]), and biologic therapies (e.g., tumor necrosis factor [TNF α] blockers, anti-integrin therapies). Corticosteroids are not recommended for long-term use given the toxicities associated with chronic steroid use.² While these medications are widely used in clinical practice, not all are FDA approved for the treatment of Crohn's disease. There remains a need for novel therapies for the treatment of Crohn's disease as not all patients will respond or have continued response to any given treatment. For example, approximately 10–30% of patients do not respond initially to TNF blockers and 20-50% lose response over time.³

Regulatory Background

Stelara (ustekinumab) is a humanized IgG1, kappa anti-interleukin (IL) 12/23 monoclonal antibody and will be the first in this pharmacologic class indicated for the treatment of Crohn's disease. Stelara was originally approved in 2009 (BLA 125261) for moderate to severe plaque psoriasis, and subsequently for the treatment of active psoriatic arthritis in 2013. 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 by alerting and warning healthcare providers about the risks. The elements of the REMS include a communication plan to disseminate information on the risks of serious infection, malignancy, and RPLS to providers, including gastroenterologists.

The current submission, BLA 761044, was submitted as an original BLA based on advice provided by the Agency, and supported by the PDUFA User-Fee staff, during the pre- BLA meeting. The Division, PDUFA User-Fee staff, Office of Regulatory Policy (ORP), and the Office of Biotechnology Products (OBP) held an internal teleconference on May 19, 2016, to discuss whether this BLA should remain a separate BLA or be consolidated as a supplement under BLA 125261. OBP concluded that BLA 761044 should have been submitted as a supplemental BLA given the evolving interpretation of the term “alike” in the Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees (2004). However, the User-Fee staff interprets the Guidance differently, and stated that this application was submitted consistent with current CDER policy as an original BLA, as discussed during the Type B pre-BLA meeting, on May 12, 2015. The outcome of the internal meeting was that OBP, ORP, and the user-fee staff will continue to discuss internally, and BLA 761044 will remain as a standalone BLA until the Division receives further guidance. See memorandum of internal teleconference, dated May 25, 2016, for details.

The major meetings and regulatory history are summarized. For more details, refer to the medical officer review, by Dr. K.J. Lee, dated September 7, 2016.

- January 15, 2004: A pre-IND meeting (IND 11632) was held to discuss clinical development of ustekinumab for the treatment of patients with moderately to severely active Crohn's disease. The Division recommended a dose-ranging study be conducted.

³ Roda, G., et al. Loss of Response to Anti-TNFs: Definition, Epidemiology, and Management. *Clin Transl Gastroenterol*; 2016 Jan; 7(1): e135.

- July 18, 2007: An End-of-Phase 2 (EOP2) meeting was held to discuss the phase 3 development plan. The key recommendations included:
 - Study a broader population, including those who failed conventional therapy in addition to patients who had an inadequate response to TNF antagonist therapies.
 - Perform an additional phase 2 trial to estimate the optimal IV induction dose and the dose and regimen for use in a phase 3 maintenance trial.
- February 17, 2011: A Type C meeting to discuss key elements of the phase 3 trial design. The clinical development program consisted of two induction trials and a single, large maintenance trial. The Division recommended that the Applicant select a more narrow population, and the Applicant proposed a patient population similar to the populations enrolled in studies submitted in this BLA to support marketing approval. In addition, the proposed phase 3 program incorporated a new IV formulation (5 mg/mL).
- August 23, 2011: FDA was notified of a stability issue [REDACTED] (b) (4) with the proposed 5 mg/mL IV formulation, and informed the Applicant of this issue.
- December 21 and 23, 2011: The Applicant reported that their own investigation indicated that the IV formulation was likely to [REDACTED] (b) (4). The Applicant quarantined clinical supplies and suspended IV dosing in the ongoing phase 3 studies. In February 2012, the Applicant replaced the 5 mg/mL IV formulation with a 90 mg/mL vial formulation, which was marketed at that time, and clinical trials resumed. The root cause of the instability with the 5 mg/mL formulation was identified and resolved. Patients who had received the 5 mg/mL formulation would be excluded from the phase 3 efficacy analyses because knowledge of the stability issue could potentially introduce bias. A new formulation was ultimately developed, which is the to-be-marketed 130 mg/26 mL (5 mg/mL) formulation.
- December 18, 2013: A Type C meeting in the form of written responses addressed the proposed design and strategy for the CMC and pharmacokinetic (PK) comparability data package between the to-be-marketed 5 mg/mL IV and the 90 mg/mL IV formulation. The general approach appeared reasonable; however, the Division requested that additional information be submitted for review to further support the comparability package. In addition, the efficacy endpoints were discussed. The Division stated that clinical remission is the preferred primary endpoint for Crohn's disease trials; however, considering that the ongoing induction trial was estimated to complete enrollment in the second quarter of 2014, the Division recommended that the Applicant not amend the protocol or SAP.
- May 12, 2015: A Type B pre-BLA meeting was held. The following are key discussion items from the meeting:
 - The Division stated that the wording of the indication statement will ultimately be a review issue and that the FDA currently favors general indication statements that describe the indication of the drug and the necessary information to describe appropriate use (e.g., patient population). A description of the studies and key endpoints would be included in Section 14.

- The Division did not agree to the Applicant's proposed endpoint of mucosal healing (defined by patients achieving lack of ulcerations on endoscopy), as stated in the endoscopic substudy SAP. Whether this definition, in conjunction with available histologic data, supports a [REDACTED] (b) (6) [REDACTED] remained a review issue.
 - The Division recommended that endoscopic substudy data from the two induction trials be analyzed separately first, before any statistical inference is made for the pooled data from both studies. Whether or not pooling the endoscopic substudy data to assess endoscopic endpoints, as proposed by the Applicant, results in valid and interpretable results remained a review issue.
 - The Division recommended additional supportive analyses of the proportion of patients that discontinue corticosteroids during the trial and can remain off steroids through week 44 (for a period of at least 30, 90, etc. days).
 - The Division did not object to the Applicant's proposal to submit an original BLA for the treatment of Crohn's disease, along with the payment of the appropriate user fee, as long as the application follows the requirements in the Guidance for Industry - Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees.
- July 2, 2015: The Division issued an Advice Letter in response to the Applicant's proposal to perform an integrated analysis of the endoscopic data from the two induction trials [REDACTED] (b) (4) [REDACTED]. While the trials have similar study designs, there could be important differences between the two trials that result from actual conduct of the trials that could impact validity of conclusions from a pooled analysis (e.g., distinct dropout rates) and could result in differences in treatment effects observed in this subgroup between trials. The proposed pooled analysis would at best only be counted as single trial evidence, [REDACTED] (b) (4) [REDACTED].
- November 19, 2015: The Agency issued an agreement on the initial Pediatric Study Plan (iPSP). The key issues that lead to an agreement were:
 - Lowering the partial waiver age from 6 years to 2 years of age.
 - Considering adding a placebo arm based on their exposure response data between adults and pediatrics. Of note, the Applicant's European proposal contains a placebo arm.
 - November 25, 2015: BLA 761044 was submitted to support an indication for the treatment of adults with moderately to severely active Crohn's disease.

Submission and Review

The BLA was received electronically on November 25, 2015, and granted a Standard Review status with a goal date of September 25, 2016 (action date of September 23, 2016). The

submission was presented to the Pediatric Review Committee (PeRC) on August 24, 2016. The Applicant applied for Orphan Designation on February 10, 2016, and orphan designation was granted on May 18, 2016; therefore, PREA will not apply. The review disciplines have written review documents. The primary review documents relied upon in my CDTL memo are listed below:

Review Team - Disciplines	Name(s) of discipline reviewers
Medical Officer Review	K.J. Lee, MD, dated 9/7/2016
Statistical Review (DBIII)	M. Min, PhD, Y. Chen, PhD, dated 8/31/2016
Nonclinical (DGIEP)	J. Peretz, PhD, S. Chakder, PhD, dated 7/19/2016
OPQ/Division of Biotechnology Review and Research III, Drug Product Review	Z. Liu, PhD, dated 8/18/2016
OPQ/Application Technical Lead (DBRR III)	M. Gutierrez-Lugo, PhD, S. Kirshner, PhD, integrated review dated 8/31/2016
Division of Microbiology Assessment (OPQ/OPF/Branch IV)	C. Gomez-Broughton, PhD, C. Thomas, PhD, P. Hughes, PhD, dated 8/31/2016
OPQ/Division of Inspectional Assessment	M. Michaelis, Z. Qiu dated 8/31/2016
Clinical Pharmacology Review (OCP/DCP3)	C. Hon, PhD, A. Balakrishnan, PhD, Y. Wang, PhD, H. Ahn, PhD, dated 9/7/2016
Pharmacometrics Review (DPM/DCP3)	JE. Lee, PhD, N. Mehrotra, PhD, dated 8/24/2016
Genomics and Targeted Therapy Review (OCP/GTT)	A. Ramamoorthy, PhD, C. Grimstein, PhD, dated 9/7/2016
Labeling review (OPDP, DMPP)	N. Booker, PharmD, MPH, M. Patel, PharmD, M. Williams, PhD, L. Griffiths, MSHS-Ph, BSn, RN, dated 8/9/2016
Labeling review (OSE/DMEPA)	S. Abraham, RPh, M. Mistry, PharmD, MPH, L. Merchant, PharmD, MS, dated 7/18/2016
REMS Review (DRISK)	J. Sheppard, PharmD, J. Wilkins Parker, PharmD, C. LaCivita, PharmD, dated 8/1/2016
Other: Consultation review (DPMH)	Maternal health review: L. Sahin, MD, M. Dinatale, MD, dated 8/16/2016
Clinical site inspections (OSI)	S. Leibenhaut, MD, S. Thompson, K. Ayalew, dated 7/29/2016

DGIEP: Division of Gastroenterology and Inborn Errors Products, OPQ: Office of Pharmaceutical Quality, DBRR: Division of Biotechnology Review and Research, OPF: Office of Process and Facilities, OBP: Office of Biotechnology Products, OCP: Office of Clinical Pharmacology, DCP3: Division of Clinical Pharmacology 3, OPDP: Office of Prescription Drug Promotion, DMPP: Division of Medical Policy Programs, DMEPA: Division of Medical Error Prevention and Analysis, DRISK: Division of Risk Management, DPMH: Division of Pediatric and Maternal Health

The reader is referred to the primary review documents for more specific details of the application and review conclusions. This memo summarizes the information contained in BLA 761044 and selected information from the primary review documents.

2. Product Quality

For complete information, refer to the integrated Office of Pharmaceutical Quality (OPQ) review by Dr. M. Gutierrez-Lugo, dated August 31, 2016. The review team from the Office of Pharmaceutical Quality (OPQ) recommends approval of BLA 761044, based on their determination that the data submitted in this application are adequate to support the conclusion that the manufacture of Stelara 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. The OPQ reviewers recommended that this product be approved for human use under conditions specified in the package insert. They do not recommend PMRs or PMCs. I agree with their recommendations and have summarized the key review findings below.

Stelara (ustekinumab) is a humanized IgG1 kappa monoclonal antibody, produced in a (b) (4) cell line, that recognizes the p40 subunit common to both human IL-12 and IL-23, and inhibits the binding of IL-12 and IL-23 to the IL-12 β 1 receptor chain and subsequent intracellular signaling by both cytokines. IL-12 induces immune cells toward a T helper 1 (Th1) phenotype (stimulates interferon-gamma [IFN- γ] production), while IL-23 induces a T helper 17 (Th17) pathway (promotes secretion of IL-17A, IL-21, and IL-22). Both cytokines stimulate TNF production, resulting in the intestinal inflammation and epithelial cell injury typical of Crohn's disease.

The currently approved presentations include a pre-filled syringe (PFS) and vial, both available in two strengths (90 mg/ml and 45 mg/0.5 ml). The new presentation is a 130 mg/26 ml (5 mg/ml) strength. Stelara is presented in a single-dose glass vial containing 130 mg/26 ml of ustekinumab, which will be used as an initial intravenous (IV) dose, based on body weight as defined in the labeling, after dilution with saline. After the initial IV dose, the patient will switch to a maintenance dose using the currently approved PFS presentation (approved under BLA 125261), which is administered as 90 mg subcutaneous injection every 8 weeks.

Proposed dosage forms/presentations

Solution for IV infusion: 130 mg/26 mL in a single-dose vial

For subcutaneous (SC) injection: 90 mg/mL and 45 mg/0.5 mL in a single-use prefilled syringe, approved under BLA 125261.

CMC/Drug Substance Quality Review

This BLA cross-references the drug substance (DS) section from BLA 125261 from the same Applicant. The ustekinumab 130 mg/26 mL (5 mg/mL) final vial drug product for intravenous administration (FVP [IV]) is made with the same drug substance used to manufacture the ustekinumab FVP for subcutaneous administration covered under BLA 125261. The drug substance information provided in BLA 125261 was found to be acceptable.

CMC/Drug Product Quality Review

The drug substance (DS) manufacturing process was previously reviewed and found to be well controlled and should consistently deliver DS of desired quality. The drug product (DP) manufacturing process is well controlled and should consistently deliver DP of desired quality.

As described in the OPQ review by Dr. Z. Liu, dated 8/24/2016, potency is defined as the percent activity relative to a qualified ustekinumab reference standard; the potency assay is the same as described in BLA 125261. The new ustekinumab presentation contains the following excipients per vial: EDTA disodium salt dihydrate ((b) (4) mg), L-histidine ((b) (4) mg), L-histidine hydrochloride monohydrate ((b) (4) mg), methionine ((b) (4) mg), Polysorbate 80 ((b) (4) mg) and sucrose ((b) (4) mg). The raw materials are tested according to pharmacopoeial monographs, pH and osmolality are tested ensure appropriate concentrations of excipients in the (b) (4)

(b) (4) and the concentrations of EDTA, methionine, and PS80 are included in the DP release and stability specifications.

As summarized in Dr. Liu's review (b) (4) The original 5 mg/mL FVP (IV) formulation was used for IV induction dosing in phase 3 clinical trial (CRD3001 and CRD3002); however, due to stability issues with the original 5 mg/mL FVP (IV) formulation, the Applicant replaced the original 5 mg/mL FVP (IV) formulation with the approved 90 mg/mL FVP formulation for the IV induction administrations in the phase 3 clinical trials, while the to-be-marketed 5 mg/mL FVP (IV) formulation was being developed. The to-be-marketed 5 mg/mL FVP (IV) formulation has the same excipient components as the approved 90 mg/mL FVP formulation, with the addition of EDTA (0.02 mg/mL) and L-methionine (0.4 mg/mL) (b) (4). Dr. Liu notes that the rationale for the formulation change from the 90 mg/mL FVP and PFS presentation to the 5 mg/mL FVP (IV) presentation (b) (4) was reasonable.

The Applicant also conducted analytical and PK (phase 1 study NAP1002) comparability studies between the to-be-marketed 5 mg/mL FVP (IV) formulation and the approved 90 mg/mL FVP formulation to establish a bridge between these formulations. Dr. Liu determined that the 5 mg/mL FVP (IV) presentation is comparable to the 90 mg/mL FVP and PFS presentations in terms of their biophysical, biochemical and biological properties. In response to an Information Request, dated August 8, 2016, the Applicant provided release data for all 90 mg/mL FVP and PFS batches (n=9) used in the phase 3 Crohn's disease clinical trials and the phase 1 PK comparability trial. The batch release data were reviewed and the reviewers concluded that the data support comparability between the batches used in the clinical trials and the to-be-marketed 5 mg/mL FVP (IV) batches. The review of the PK data is summarized below in the Clinical Pharmacology section of this document.

Stelara is supplied as 30 ml vial containing 26 ml of ustekinumab at the concentration of 5 mg/ml (130 mg). The container closure system consist of a 30 ml Type I (b) (4) glass tubing vial, capped with a 20 mm stopper with (b) (4) (b) (4) (b) (4) a 20 mm aluminum seal a light green flip-off button. The dating period for drug product is 24 months at $5 \pm 3^{\circ}\text{C}$.

The following are labeling recommendations by the product quality reviewers:

- Protect from light
- Do not freeze
- Do not shake
- Product does not contain preservative
- Discard any unused portion

Facilities review/inspection

The integrated quality review by Dr. Gutierrez-Lugo states that under inspectional observations, no 483 observations were issued for the drug product manufacturing facilities in the last 2-3 years, and overall the drug product facilities have a favorable compliance status.

CMC/Manufacturing Process Review

(b) (4)

CMC/Microbiology Review

The Product Quality Microbiology reviewers recommend approval of BLA 761044. The microbiology reviewer, Dr. Gomez-Broughton, determined that sterile filtration of ustekinumab was validated [REDACTED] (b) (4) for the sterile filtration of ustekinumab FVP (IV). In addition, the results from the process validation, hold time, and media fill studies suggest that FVP (IV) manufacturing process is under control. She also concluded that the [REDACTED] (b) (4) procedures and environmental conditions were appropriate, and the Applicant's commitment to limit endotoxin samples storage time [REDACTED] (b) (4) is adequate. No additional inspectional follow-up items were identified.

3. Nonclinical Pharmacology/Toxicology

The nonclinical team has recommended approval, and I agree with the recommendation. The reviewers have not recommended PMCs or PMRs. For complete information, the reader is referred to the Pharmacology/Toxicology review by Dr. J. Peretz (primary review), dated 7/19/2016. I have summarized the key review findings below.

The Applicant did not conduct any new nonclinical studies to support the current application. Previously submitted nonclinical information under BLA 125261 was cross-referenced, and is supportive of the proposed indication and new intravenous formulation of Stelara. These studies were previously reviewed by Dr. J. Yao, Division of Dermatology and Dental Products, under BLA 125261, dated November 28, 2008.

The nonclinical review summarizes the excipients used in the ustekinumab IV drug product. There are no novel excipients in the proposed drug product. The nonclinical reviewer did not find any impurities or degradants of concern. There were no changes in the IV drug product specifications from the previously approved product under BLA 125261. All analyses for the intended batches of the commercial drug product for the single IV induction dosing for Crohn's disease were within the acceptance criteria or below the specified acceptance limit. Therefore, the nonclinical reviewer concluded they are acceptable.

In the originally proposed product label, the Applicant (b) (4). The nonclinical reviewer recommends that the following language describing the animal data remain in section 8.1: “In a combined embryo-fetal development and pre- and post-natal development toxicity study, pregnant cynomolgus monkeys were administered subcutaneous doses of ustekinumab twice weekly (b) (4) from the beginning of organogenesis to Day 33 after delivery. Neonatal deaths occurred in the offspring of one monkey administered ustekinumab at 22.5 mg/kg and one monkey dosed at 45 mg/kg. No ustekinumab related effects on functional, morphological, or immunological development were observed in the neonates from birth through six months of age.”

The serum concentrations of ustekinumab in pregnant monkeys is >100 times the serum concentration in patients who were treated subcutaneously with 90 mg of ustekinumab. The serum concentration of ustekinumab in pregnant monkeys is 24 times higher than the serum concentration in patients treated via IV infusion.

The final labeling includes recommended changes by the nonclinical reviewer and DPMH consultants.

4. Clinical Pharmacology

The reader is referred to the integrated Clinical Pharmacology review by Dr. C. Hon, dated September 7, 2016, which includes the Genomics and Targeted Therapy review by Dr. A. Ramamoorthy, and the Pharmacometrics review by Dr. J.E. Lee, dated August 24, 2016, for complete information. The clinical pharmacology review team considers the clinical pharmacology information submitted to support this BLA acceptable, provided that the Applicant and the Agency come to a mutually satisfactory agreement regarding the language in the package insert.

The clinical pharmacology and pharmacometrics reviewers concluded that for induction dosing, the proposal of a single IV dose of ustekinumab at approximately 6 mg/kg using weight-based tiers is acceptable. For the maintenance dosing, the proposed dosing regimen of ustekinumab 90 mg SC q8w is acceptable. (b) (4)

I agree with their recommendations.

The clinical pharmacology reviewers recommend the following post-marketing commitment (PMC): 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).

The above PMC recommendation is based on the current understanding that CD patients have elevated levels of pro-inflammatory 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.

The ustekinumab clinical development program for the treatment of moderately to severely active CD included one phase 1 (NAP1002) study in healthy subjects, and two phase 2 studies (C0379T07 and C0743T26) and three phase 3 studies (CRD3001, CRD3002 and CRD3003) in subjects with moderate to severe active CD (Figure 1). Data from these studies are used to support the clinical pharmacology section of this BLA submission. I have summarized the key review findings below.

Pharmacokinetics (PK) of ustekinumab

The clinical pharmacology reviewer determined that after a single IV administration of ustekinumab at doses of 1, 3, or 6 mg/kg, median serum ustekinumab concentrations in all treated subjects were approximately dose proportional at all sampling time points through Week 8. After the first maintenance dose at Week 0, the steady-state appeared to have been reached at Week 12 or Week 8 prior to the administration of the second maintenance dose for ustekinumab 90 mg SC q12w and 90 mg SC q8w, respectively.

Absorption: The bioavailability following SC ustekinumab administration in patients with CD was estimated to be 78.3%.

Distribution: The population pharmacokinetic estimates for the central (V2) and peripheral (V3) volumes of distribution (and 95% CI) in CD patients with an approximate body weight of 70 kg were 2.74 (2.69, 2.78) L and 1.88 (1.66, 2.13) L, respectively. These results indicate that ustekinumab primarily distributed in the intravascular space, with limited distribution to the extravascular space.

Elimination: The typical value of the terminal elimination half-life of ustekinumab in patients with CD was approximately 19 days.

Dose-Response (D-R)/Exposure-Response (E-R) Relationships

The clinical pharmacology review team determined that there were dose-dependent and concentration-dependent increases in clinical efficacy of ustekinumab for both the induction dose and the maintenance dosing regimen.

Dr. C. Hon note the following observations for the dose-response relationship in the clinical pharmacology review. For the induction dose, higher proportions of patients achieved clinical remission at Week 8 in the ~6 mg/kg IV dose group than the 130 mg IV dose group in both patient populations who have and who have not failed/were intolerant to prior TNF antagonist therapy. Both the clinical remission rates of the ~6 mg/kg and the 130 mg dose group achieved statistical significance vs placebo for both patient populations. For the maintenance dosing regimen, the proportion of patients who achieved clinical remission at Week 44 was slightly higher in the 90 mg/kg SC q8w group than the 90 mg SC q12w group for both patient populations. The clinical remission rate at Week 44 in the 90 mg SC q8w group achieved statistical significance vs placebo for the TNF antagonist non-failure population, but not for the TNF antagonist failure population. The reviewers point out that the study was designed to detect the differences in clinical remission rate among the different dose groups for the entire trial population (i.e., TNF α antagonist failure plus non-failure patients); the trial would have been

underpowered to detect the differences in clinical remission rate among different dose groups in either the TNF α failure or non-failure population.

An E-R relationship was established in the induction phase in both patient populations who have and who have not failed/were intolerant to prior TNF α antagonist therapy. There was an E-R relationship in the maintenance phase only in patients who have not failed TNF α antagonist.

Dose adjustment in the maintenance phase

In study 3003, randomized patients who met loss of response (LOR) criteria at any time between Week 8 and Week 32 were eligible to have a single dose adjustment to 90 mg SC q8w. Fifty-one of the 133 patients randomized to the placebo group underwent a dose adjustment to ustekinumab 90 mg SC q8w after meeting LOR criteria, 29/132 patients randomized to the ustekinumab 90 mg SC q12w group had a dose adjustment to q8w after meeting LOR criteria, and 28/131 patients randomized to the ustekinumab 90 mg SC q8w group met LOR criteria for dose adjustment but continued to receive q8w per protocol. It is important to note that the patients who lost response were not re-randomized to receive the same dosing regimen or to escalate the dose; therefore, there was no concurrent control arm to differentiate the effect of dose escalation versus longer duration on the same dosing regimen. The response of these patients 16 weeks after the dose adjustment is summarized below in Table 1.

Table 1: Summary of Remission/Response Rates at 16 Weeks after Dose Adjustment in Patients who Experienced Loss of Response

	Dose Adjustment		
	Placebo SC → 90 mg SC q8w	90 mg SC q12w → 90 mg SC q8w	90 mg SC q8w → 90 mg SC q8w
No. randomized subjects	133	132	131
No. subjects who met LOR and had a dose adjustment	51	29	28
Response 16 weeks after dose adjustment			
Clinical remission	39.2%	41.1%	32.1%
Clinical response	70.6%	55.2%	46.4%

(source: reproduced from the clinical pharmacology review, by Dr. C. Hon, dated 9/7/2016)

The clinical pharmacology reviewers concluded that the approximately 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 was more effective in achieving clinical remission than the 90 mg SC q12w. It is not possible to determine whether this difference is due to the escalated dosing regimen since the improvement could have occurred from the longer duration of therapy. Furthermore, data from the patients who remained on the q8w regimen suggest that additional time on the same dosing regimen also results in substantial proportion of patients becoming responders or remitters. (b) (4)

Safety

Overall, the incidence of adverse events (AEs), serious adverse events (SAEs), infections, and serious infections appeared similar between the 130 mg and ~6 mg/kg dose groups in the

induction phase. The incidence of these safety events appeared similar across the serum ustekinumab concentration quartiles during induction.

The clinical pharmacology reviewer observed a slightly higher incidence of serious infections in the ustekinumab 90 mg SC q12w group than the ustekinumab 90 mg SC q8w during the maintenance phase up to the point of dose adjustment. While the number of serious infections was small and the duration of follow up was short, the clinical pharmacology reviewers concluded that this finding should be taken into consideration when comparing the two dosing regimens.

Recommended Dosing Regimen

The clinical pharmacology reviewers concluded that the dose-response relationship supports the following recommended dosing regimen: a single dose of ustekinumab ~6 mg/kg IV followed by ustekinumab 90 mg SC q8w. The exposure-response (E-R) relationship also provides supportive evidence of clinical efficacy for the above recommended dosing regimens.

Body Weight

A key consideration during the review was whether body weight impacted clinical remission results at Week 8 and Week 44; this concern was communicated to the Applicant in a Discipline Review Letter and Information Request, dated July 21, 2016. The clinical pharmacology review team performed subgroup analyses evaluating the ustekinumab concentrations in patients treated with either the 130 mg or the ~6 mg/kg dose by three body weight tiers (i.e., ≤55 kg, >55kg and ≤85 kg, and >85 kg), and compared the clinical remission rates across body weight groups to assess the impact of the body weight on clinical remission at Week 8 in the induction phase and clinical remission at Week 44 in the maintenance phase. The results indicated that the differences in ustekinumab concentrations caused by weight tier-based dosing did not translate into differences in the clinical remission rates at Week 8, although higher concentrations with ~6 mg/kg dose seemed to lead to higher remission rates at Week 8 compared to 130 mg dose; the same conclusion holds for comparison of remission rates at Week 44 across the three body weight tiers. When the combined data from all three body weight tiers were compared across the two dose regimens, the ~6 mg/kg dose showed a greater remission rate than the 130 mg dose. The review team concluded that body weight tier-based dosing did not have a significant impact on clinical remission at Week 8 or Week 44; therefore, the proposed three body weight tier-based dosing is acceptable. Please refer to the integrated Clinical Pharmacology review by Dr. C. Hon, dated September 7, 2016, and the Pharmacometrics review by Dr. J.E. Lee, dated August 24, 2016, for more information.

Drug-Drug Interactions

No formal drug-drug interaction studies or disease-drug-drug interaction studies were conducted for ustekinumab in CD. The effect of concomitant use of immunomodulators including 6-mercaptopurine (6-MP), azathioprine (AZA) and methotrexate (MTX) was not adequately evaluated in the population PK analysis. Thus, the proposed language for Section 12 of the label was not accepted by the clinical pharmacology and pharmacometrics reviewers. Refer to the Pharmacometrics review by Dr. J.E. Lee, dated August 24, 2016, for more information.

Immunogenicity

Twenty-seven of 1154 (2.3%) patients who received at least one dose of ustekinumab during induction or maintenance were positive for antidrug antibodies (ADA) in the phase 3 trials, and of these 17 (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 [1.9%]) compared with those who did not receive immunomodulators (20/779 [2.6%]).

Immunogenicity had a negative impact on PK. While the PopPK model predicted a 13% higher clearance (CL) in ADA+ patients, the median observed serum ustekinumab concentrations were approximately two to three-fold lower in patients who were ADA+ than in patients who were ADA-. At the individual patient level, the mean ustekinumab concentration in ADA+ samples was reduced by 42.8% to 89.1% when compared to the mean ustekinumab concentration in ADA- samples.

The clinical pharmacology reviewers concluded that the assessment of the impact of immunogenicity on clinical efficacy is inconclusive because the number of subjects who became ADA+ was small in the phase 3 trials.

PK Comparability of 90 mg/mL Liquid-in-Vial (LIV) formulation (currently marketed) and 5 mg/mL LIV formulation (to-be-marketed)

The PK comparability was established between the proposed to-be-marketed 5 mg/mL LIV formulation and the currently marketed 90 mg/mL LIV formulation when administered intravenously (IV) at 6 mg/kg dose.

Serum Biomarker and Tissue mRNA Expression

The Applicant assessed a series of serum proteins in subsets of patients in the phase 2b and phase 3 trials to assess the effects of ustekinumab on biomarkers related to CD and the mechanism of action of ustekinumab. The Applicant also explored the pharmacodynamic effect of ustekinumab on the expression of mRNA in the phase 2b trial. The clinical pharmacology review team identified several limitations in these exploratory analyses and concluded that the results do not support drawing definitive conclusions. (b) (4)

Please see the Genomics and Targeted Therapy Review by Dr. A. Ramamoorthy, dated 9/7/2016, for more information.

5. Clinical Microbiology

Clinical microbiology considerations do not apply to this application because ustekinumab is not intended as an antimicrobial product.

6. Clinical/Statistical- Efficacy

The reader is referred to the Clinical review by Dr. K.J. Lee, dated September 7, 2016, and the Statistical review by Dr. M. Min, August 31, 2016, for complete information. The Statistical reviewer stated that the data and quality of the BLA submission were acceptable from a

statistical perspective. The clinical reviewer, Dr. K.J. Lee, recommends approval of BLA 761044 with the requirement for a postmarketing study to evaluate the long-term safety related to malignancies and serious opportunistic infections. I agree with her recommendations. Below, I will summarize the key findings from the clinical and statistical reviews.

The Applicant submitted three adequate and well-controlled phase 3 trials to support the effectiveness of ustekinumab for the treatment of adult patients with moderate to severe Crohn's disease who 1) failed or were intolerant to treatment with immunomodulators or corticosteroids, but never failed treatment with a TNF blocker, or 2) failed or were intolerant to treatment with one or more TNF blockers. The Applicant also conducted an endoscopic substudy to evaluate endoscopic and histologic improvement with ustekinumab treatment. The three main trials will be discussed first, followed by a discussion of the endoscopic substudy.

Trial Design

Study CNT01275CRD3001 (referred to as study 3001 in this document)

Study 3001 was an 8-week, multicenter (178 centers), randomized, double-blind, placebo-controlled, parallel group trial in 769 adult patients with active⁴ moderate to severe Crohn's disease (Crohn's Disease Activity Index [CDAI] score ≥ 220 and ≤ 450) who have failed or were intolerant⁵ to one or more TNF blockers. The trial evaluated three dosing regimens of ustekinumab single intravenous (IV) dose of 130 mg, approximately 6 mg/kg weight-based dosing (260 mg for patients ≤ 55 kg, 390 mg for patients > 55 and ≤ 85 kg, and 520 mg for patients > 85 kg), and placebo. The randomization was stratified by region (Asia, Eastern Europe, or rest of world), CDAI score (≤ 300 or > 300), and initial response to TNF antagonist therapy (yes or no).

Study CNT01275CRD3002 (referred to as study 3002 in this document)

The study design of study 3002 was identical to study 3001, except for the patient population that included 640 adult patients with moderate to severe Crohn's disease who had failed or were intolerant to conventional therapy (i.e., immunomodulators or corticosteroids), but never failed treatment with a TNF blocker enrolled from 175 centers.

Patients who were treated with ustekinumab, and achieved at least clinical response (defined as a reduction from baseline in the CDAI score of ≥ 100 points) or clinical remission (CDAI < 150) at Week 8 of either study 3001 or 3002 were eligible to be randomized into study 3003 (see below). 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 efficacy analyses for 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 trial. Of note, the primary endpoint assessment for studies 3001 and 3002 was performed at Week 6; however, patients were randomized into study 3003 at Week 8 based on FDA advice provided in meeting minutes,

⁴ Active disease defined by meeting CDAI criteria and one of the following: c-reactive protein (CRP) > 3 mg/L, fecal calprotectin > 250 mg/kg, or endoscopy within 3 months prior to baseline visit with evidence of active disease.

⁵ Intolerant defined as documented adverse reaction based on one of the following: acute infusion/administration reaction, delayed infusion/administration reaction (e.g., delayed hypersensitivity, serum sickness), or injection site reaction, which precluded continued use of the therapy, in the opinion of the treating physician.

dated February 17, 2011. The FDA recommended that in order to demonstrate maintenance of response or remission, subjects would need to meet the definitions of clinical response or remission, respectively, at the time of enrollment into study 3003 at Week 8, which explains why the primary efficacy endpoint for induction studies was assessed at Week 6 but only ustekinumab responders/remitters at Week 8 were re-randomized into study 3003.

Study CNT01275CRD3003 (referred to as study 3003 in this document)

Study 3003 was a 44-week (52 weeks from the initial dose), multicenter (260 centers), randomized, double-blind, placebo-controlled, parallel group study in 397 adult patients who met the criteria for at least clinical response after completing either study 3001 or 3002. The trial evaluated two dosing regimens of ustekinumab, 90 mg every 8 weeks (90 mg q8w) and 90 mg every 12 weeks (90 mg q12w), compared to placebo.

The Applicant temporarily suspended dosing of patients in November 2011 because a stability issue was identified with the IV formulation (130 mg/26 mL [5 mg/mL; (b) (4)]). Data from 40 patients (28 patients from study 3001, 12 from study 3002; among the 40 subjects, 9 were randomized in study 3003) who were enrolled prior to study suspension were not used in the planned efficacy analyses because knowledge of the stability issue could potentially introduce bias. 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. Therefore, the sample size of the efficacy analyses for each trial was 741 patients for study 3001, 628 patients for study 3002, and 388 patients for study 3003.

Primary Endpoint: Study 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 was attained. In addition, patients with a missing CDAI score at Week 6 were considered as treatment failures.

Secondary Endpoints: Study 3001 and 3002 (listed in the order of testing)

- 1) Clinical remission at Week 8, defined as a CDAI score of < 150 points.
- 2) 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.
- 3) 70-point response at Week 6, defined as a reduction from baseline in the CDAI score of ≥ 70 points.
- 4) 70-point response at Week 3, defined as a reduction from baseline in the CDAI score of ≥ 70 points.

Primary Endpoint: Study 3003

Clinical remission at Week 44, defined by CDAI < 150 points.

Secondary Endpoints: Study 3003 (listed in the order of testing)

- 1) Clinical response at Week 44, defined as a reduction from Week 0 of induction study 3001 or 3002 in the CDAI score of ≥ 100 points. 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.

- 2) Clinical remission at Week 44 among patients in clinical remission at Week 0 of study 3003.
- 3) Corticosteroid-free remission at Week 44, defined as a CDAI score of < 150 points and not 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.
- 4) Clinical remission at Week 44 in the subset of patients who were refractory or intolerant to TNF-antagonist therapy (i.e., patients randomized from study 3001).

As described in the statistical review, to control the overall Type 1 error rate, the primary endpoint was tested in a fixed sequence. Specifically, the ustekinumab 90 mg SC q8w group was first compared with the placebo group at the 2-sided 0.05 level of significance. If the ustekinumab 90 mg SC q8w group was significantly different from the placebo group, then the ustekinumab 90 mg SC q12w group was compared with the placebo group at the 2-sided 0.05 level of significance.

In addition, the Applicant conducted exploratory analyses utilizing alternative definitions to the CDAI, including clinical remission defined by daily mean abdominal pain scores ≤ 1 and stool frequency ≤ 3 . It is important to note that an abdominal pain score of 1 represents mild pain and may not reflect a state of remission for patients. Also, while the stool frequency count of ≤ 3 stools per day is often considered normal stool frequency, the consistency of the stools should also return to normal or to a consistency that is considered by patients to be a state of remission. The results of these analyses are described in the clinical review by Dr. K.J. Lee, dated 9/7/2016, and statistical review by Dr. Min, 8/31/2016.

Appropriateness of the primary endpoint

The primary endpoint utilizing the CDAI was agreed upon and pre-specified prior to the shift in current thinking by the Division on what constitutes a clinically meaningful treatment benefit in Crohn's disease, given that disease activity indices have been shown to correlate poorly with intestinal inflammation.^{6,7} Since the time that these trials were designed, the Division has moved away from utilizing the CDAI to define the primary efficacy endpoint in clinical trials intended to support approval and product labeling for Crohn's disease. Instead, the clinical trials should provide evidence of the drug's impact on both key signs and symptoms (i.e., a clinical benefit) and on the disease process itself (via endoscopic improvement), as co-primary efficacy endpoints. In addition, it is recommended that clinical remission be the primary endpoint of induction and maintenance trials. In fact, this recommendation was discussed with the Applicant at the Type C meeting, held on December 18, 2013. The Division stated that clinical remission is the preferred primary endpoint for Crohn's disease trials; however, considering that the ongoing induction trial was estimated to complete enrollment in the second quarter of 2014, the Division recommended that the Applicant not amend the protocol or SAP. Therefore, the

⁶ Colombel, JF., et al. Converging Goals of Treatment of Inflammatory Bowel Disease From Clinical Trials and Practice. *Gastroenterology* 2015; 48:37-51.

⁷ Peyrin-Biroulet L, Reinisch W, Colombel JF, et al. Clinical Disease Activity, C-reactive protein Normalisation and Mucosal Healing in Crohn's Disease in the SONIC Trial. *Gut* 2014;63:88-95.

primary endpoint of clinical response for study 3001 and 3002 is acceptable in this specific situation and given that the first ranked secondary endpoint is clinical remission, which is the more clinically meaningful endpoint.

Additionally, a “maintenance” of remission [REDACTED] (b) (4) should be based on patients who were 1) re-randomized into the maintenance trial after the induction trial, 2) in remission at the start of the maintenance trial, and 3) able to maintain remission throughout the majority of the trial duration. The efficacy endpoints selected for study 3003 do not support this [REDACTED] (b) (4) since the endpoints do not account for other time points in between Week 0 and Week 44. The concern is that patients may experience flares of disease during the 44 week treatment period despite being in remission at the start and end of the trial. The potential for interim disease flares does not support that patients were able to “maintain” remission. Endpoints designed to demonstrate efficacy for “maintenance” of remission should account for additional time points during the maintenance trial(s) to show that patients in remission were able to continue in remission for the majority of the “maintenance” phase. Based on this concern, the statistical reviewer performed exploratory analyses to determine whether patients were able to maintain remission at multiple time points during study 3003 (i.e., at 10 out of 12 visits, including week 44). The results are summarized below in this document.

Efficacy Results

Study 3001 and 3002

The outcome of clinical remission (and response) was replicated in the two induction trials. The primary endpoint and key secondary endpoints achieved statistical significance for both studies 3001 and 3002, thereby supporting that ustekinumab is able to induce clinical response and remission after a single IV dose, in both patient populations: patients who have failed/were intolerant to TNF blocker therapy and patients who failed/were intolerant to corticosteroids and/or immunomodulators. Clinical remission is the more clinically meaningful endpoint as remission is the ultimate goal of the treatment. As shown below, the proportion of patients in clinical remission at Week 8 in the ustekinumab weight-based 6 mg/kg dosing regimen appears to be numerically greater than the 130 mg dosing regimen, and statistically significant vs placebo for both studies 3001 and 3002, supporting the selection of the 6 mg/kg single IV dose. The Applicant also evaluated multiple other endpoints; the primary and ranked secondary endpoints are shown below for both trials.

Table 2: Study 3001- Results for Primary and Secondary Efficacy Endpoints[#]

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

[#]Randomized Subjects Excluding Those Enrolled Prior to Study Restart (n= 741)

(source: reproduced from Table 4 of statistical review by Dr. M. Min, dated 8/31/2016)

Table 3: Study 3002- Results for Primary and Secondary Efficacy Endpoints[#]

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

[#]Randomized Subjects Excluding Those Enrolled Prior to Study Restart (n= 627)

(source: reproduced from Table 8 of statistical review by Dr. M. Min, dated 8/31/2016)

The two tables above demonstrate statistical significance on primary and secondary endpoints in both trials. While clinical remission at Week 8 is most clinically meaningful endpoint, the other endpoints provide additional support for the clinical benefit for a single IV dose of ustekinumab as the initial dose. The treatment effect over placebo for clinical remission at Week 8 in the ustekinumab 6 mg/kg dosing regimen is numerically greater for study 3002 compared to study 3001, but it should be noted that median baseline CDAI score was slightly lower for study 3002

(median 293) compared to study 3001 (median 317). Differences in disease severity, even if small, may have contributed to the observed differences in treatment effect over placebo.

Additional Endpoints

The Applicant also evaluated multiple other endpoints, many of which provide additional supportive evidence of the clinical benefit of ustekinumab. One of the endpoints assessed the proportion of patients in clinical remission over time at Weeks 3, 6 and 8. As noted by the clinical reviewer, the proportion of patients in clinical remission at each time point was numerically greater in the 6 mg/kg dose as compared to the 130 mg dose (refer to Figures 24 and 25 in the clinical review by Dr. Lee, dated 9/7/2016).

The Applicant also evaluated C-reactive protein (CRP), fecal calprotectin, and fecal lactoferrin as markers of inflammation. As stated in the clinical review, the CRP level that reflects active inflammation is not standardized, and data are lacking at this time to support that CRP can reliably predict intestinal inflammation. Certain fecal calprotectin assays are FDA cleared for use as an in vitro diagnostic aid to differentiate inflammatory bowel disease from irritable bowel syndrome, when used with other testing as part of the total clinical picture. Fecal lactoferrin assays have also been cleared for use as an in vitro diagnostic to detect fecal leukocytes. Additionally, while literature suggests that these inflammatory markers reflect the presence of intestinal inflammation, the assays have not been cleared for use to monitor disease activity or measure the degree of severity. Therefore, until additional information are available on the ability of these inflammatory markers to monitor disease activity, the results of the CRP and fecal calprotectin and lactoferrin analyses may be informative but are considered as exploratory.

Refer to the statistical review by Dr. M. Min and clinical review by Dr. K.J. Lee for a complete discussion of the other endpoints evaluated in studies 3001 and 3002 that are not covered in this memo.

Study 3003

The proportion of patients in the ustekinumab 90 mg q8w dose regimen was statistically significant as compared to placebo for the primary endpoint of clinical remission at Week 44, and first and second ranked secondary endpoints of clinical response at week 44 and clinical remission at Week 44 among patients in remission at Week 0 (the start of study 3003). Based on the pre-specified testing order, since the 90 mg q12w dosing regimen failed to meet statistical significance on the second ranked secondary endpoint, clinical remission at Week 44 among patients in remission at week 0 of maintenance (Week 8 remitters from studies 3001 or 3002), statistical testing was stopped. The results are shown below in Table 4.

Table 4: Study 3003- Results for Primary and Secondary Efficacy Endpoints[#]

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

[#]Randomized Subjects Excluding Those Enrolled Prior to Study Restart (n= 388)

*Based on the pre-specified testing sequence, it failed at this endpoint for low dose (90 mg q12w), 3rd and 4th secondary efficacy endpoints should not be tested.

(source: reproduced from Table 12 of statistical review by Dr. M. Min, 8/31/2016)

The statistical reviewer points out that the sensitivity analyses, using the observed case, last observation carried forward, multiple imputation, and the worst case missing data methods, were robust for the q8w dosing regimen (i.e., all but the worst-case analysis were significant); however, while treatment effects were in the same direction and of generally similar magnitude to those in the primary analysis, the sensitivity analyses for the q12w regimen were generally not significant.

As discussed in the Clinical Pharmacology section of this review, and in the clinical review, by Dr. K.J. Lee, (b) (4)

(b) (4) the 90 mg q12w regimen failed to achieve statistical significance over placebo on the clinically important endpoint of clinical remission at Week 44 among patients in remission at Week 0 of study 3003. Furthermore, Dr. Lee notes in her review that the proportion of patients discontinuing for adverse events, many of which were related to underlying Crohn's disease, in the q12w regimen was double the proportion in the q8w regimen, further supporting concerns of inferior clinical benefit of the q12w regimen. Importantly, when the statistical reviewer performed an exploratory analysis (shown below) of clinical remission at Week 44 and at 10/12 visits during study 3003, only the q8w regimen achieved statistical

significance over placebo. For these reasons, the review team has recommended approval of (b) (4) the 90 mg q8w dose regimen, and I agree with their recommendation.

While the efficacy analyses for the overall population suggests a favorable effect of ustekinumab, an additional analysis was conducted to determine the proportion of patients in clinical remission at each visit by induction trial for the 90 mg q8w dose regimen. At Week 0 of the maintenance trial, 34/56 (61%) ustekinumab-treated patients who failed or were intolerant to TNF blocker therapies were in clinical remission but the proportion in remission decreased to 23/56 (41%) at Week 44. In the placebo arm, 27/61 (44%) patients were in clinical remission at Week 0 as compared to 16/61 (26%) at Week 44. The same downward trend was not observed for patients randomized from study 3002. At Week 0 of study 3003, 46/72 (64%) ustekinumab-treated patients who failed immunomodulator therapy or corticosteroids were in clinical remission and was similar at Week 44 (45/72 [63%]). In the placebo arm, 50/70 (71%) patients were in clinical remission at Week 0 as compared to 31/70 (44%) at Week 44. The data suggest that clinical remission decreased over time in the patients randomized from study 3001 (i.e., patients who had failed/were intolerant to treatment with a prior TNF blocker).

Exploratory analyses to support the indication

The statistical reviewer also conducted analyses to evaluate the proportion of patients who achieved clinical remission at Week 44 and in at least 10 out of 12 visits in study 3003 to determine whether remission was “maintained” throughout the 44-week trial. As shown in the table below, the 90 mg q8w dosing regimen demonstrated statistical significance compared to placebo.

Table 5: Clinical Remission at Week 44 and in at least 10 out of 12 visits

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

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

(source: reproduced from Table 36 of statistical review, analysis performed by statistical reviewer, dated 8/31/2016)

While these analyses are exploratory and post-hoc, the results provide reassurance that patients treated with ustekinumab 90 mg q8 generally continued to be in clinical remission during the majority of the 44-week maintenance trial. The results also provide additional supportive information in favor of the 90 mg q8w dosing regimen (b) (4). However, when this exploratory endpoint is analyzed by induction trial (study 3001 vs 3002), the difference from placebo in the patient population of study 3001 (patients failed/were intolerant to prior TNF blockers) was numerically smaller than observed in the patient population from study 3002, which is not unexpected given that the proportion of patients who failed/were intolerant to prior treatment with a TNF blocker trended downward between Week 0 to Week 44 of study 3003. Of note, the statistical reviewer also performed this exploratory analysis using the patient population in remission at the start of study 3003, simulating the situation where remitters are re-randomized into the maintenance study; the q8w dosing regimen achieved statistical significance over placebo (not shown).

Additional Endpoints

The Applicant also evaluated multiple other endpoints, many of which provide additional supportive evidence of the clinical benefit of ustekinumab. One of the additional endpoints assessed “sustained clinical remission” (defined by the Applicant as clinical remission, CDAI < 150 points, at weeks 36, 40, and 44). The ustekinumab 90 mg q12w (52/129 [40.3%], p=0.023) and q8w (59/128 [46.1%], p<0.001) dosing regimens were statistically significant when compared with placebo (34/131 [26.0%]).

Another endpoint assessed was fistula response, defined as a $\geq 50\%$ reduction in the number of open and draining fistulas. At entry into study 3003, there were 34/388 (8.8%) patients with a fistula. Of the 34 patients, 5/7 (71.4%) patients in the ustekinumab q12 week group and 7/8 (87.5%) in the q8 week dose regimen met the criteria for fistula response at Week 44, as compared with 5/11 (45.5%) in placebo. These results were not statistically significant. I agree with Dr. K.J. Lee’s conclusion that 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 draining fistulas until additional data are available in a larger cohort of patients.

Refer to the clinical review by Dr. K.J. Lee, dated September 7, 2016, for a complete discussion of the other endpoints evaluated in study 3003 that are not covered in this memo.

Endoscopic Substudy

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

The primary endpoint was the change from baseline in SES-CD score. Secondary endpoints evaluated the proportion of subjects without mucosal ulcerations and endoscopic remission, as measured by the SES-CD score 0-2. The results of the endoscopic substudy are described in greater detail in the clinical review by Dr. K.J. Lee and statistical review by Dr. M. Min; however, I will summarize the key considerations during the review. 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). Given that the mean baseline SES-CD score was 13.5 points, a decrease of 2.8 points is unlikely to represent a clinically meaningful change since the resulting endoscopic score represents a continued state of active disease. The mean change from baseline in SES-CD score did not achieve statistical significance at Week 44, and the numerical difference from placebo was small. Furthermore, at Week 8 and Week 44, the endpoint of endoscopic remission (SES-CD score of 0-2) was not statistically significant.

The primary analysis population for endoscopy endpoints at Week 8 was performed using the integrated population from studies 3001 and 3002, and data were pooled across the induction

dose groups. The primary analysis population for endoscopy endpoints at Week 44 was performed using the randomized population from study 3003, and the data were pooled across maintenance dose groups. In the pre-BLA meeting minutes, from the meeting held on May 12 2015, the FDA recommended that endoscopic substudy data from the two induction trials be analyzed separately first, before any statistical inference is made for the pooled data from both studies, and communicated that whether or not pooling the endoscopic substudy data to assess endoscopic endpoints, as proposed, results in valid and interpretable results will be a review issue.

The statistical reviewer notes in her review that in the endoscopy substudy SAP (November 7, 2015) submitted by the Applicant, no multiplicity procedure was proposed to control overall type I error, and the Applicant did not incorporate FDA's recommendations into the SAP. The pooled analyses were not agreed upon by the FDA, and it is difficult to interpret the pooled analyses since the patient populations and dosing regimens were combined. Furthermore, as described above, the mean change from baseline does not clearly represent a clinically meaningful change since the resulting endoscopic score represents a continued state of active disease. Additionally, the reviewers noted a high amount of missing data for this substudy. (b) (4)

Of note, the Applicant also evaluated histology as an exploratory endpoint, using the Global Histology Activity Score (GHAS). The scoring system appears reasonable to evaluate histology in Crohn's disease but additional studies are needed before the GHAS can be used as a reliable endpoint to define histologic remission in clinical trials (b) (4) Refer to the clinical review, dated 9/7/2016, for details.

Conclusions on the Substantial Evidence of Effectiveness

The Applicant has provided the substantial evidence of effectiveness required under 21 CFR 314.126(a)(b) to support approval based on three adequate and well-controlled trials. Two adequate and well-controlled 8-week trials demonstrated a statistically significant proportion of patients in clinical response at week 6 and clinical remission at week 8 (i.e., primary and first ranked secondary endpoints) as compared to placebo. Although clinical remission was the first ranked secondary endpoint, it is considered to be the more clinically meaningful endpoint. Of the patients who failed/were intolerant to prior TNF blocker treatment, 52/249 (20.9%) patients were in clinical remission at week 8 after a single IV dose of 6 mg/kg ustekinumab, as compared to 18/247 (7.3%), a treatment difference of 13.6%. Of the patients who failed/were intolerant to corticosteroids or immunomodulators, 84/209 (40.2%) were in clinical remission after a single IV dose of 6 mg/kg ustekinumab, as compared to 41/209 (19.6%) on placebo (p<0.001), a treatment difference of 20.6%. The review team has concluded that the results of these two trials represent a clinically meaningful benefit, and I agree with their conclusions.

The Applicant also conducted a third adequate and well-controlled 44-week maintenance trial to evaluate chronic administration of subcutaneous dosing after a single IV induction dose. The total duration was 52 weeks from the start of the induction trials. Patients in clinical response/remission from the two induction trials were re-randomized into the maintenance trial. This trial demonstrated statistical significance on the proportion of patients in clinical remission

at Week 44, clinical response at Week 44, and clinical remission at Week 44 among patients in remission at Week 0 (at the start of the maintenance trial, 8 weeks after the initial IV induction dose). It is important to note that the second ranked secondary endpoint (i.e., clinical remission at Week 44 among patients in remission at Week 0) does not account for other time points between the first and last visit of the maintenance trial. The exploratory analysis performed by the statistical reviewer demonstrates that patients treated with 90 mg q8w continued to be in remission at the majority (10 out of 12) of visits during the 44 weeks. I agree with the review team that the results of the phase 3 trial, supported by the statistical reviewer's exploratory analysis, represent a clinically meaningful benefit. However, it is important to note that while still numerically greater than placebo, the subgroup of patients who failed/were intolerant to prior treatment with TNF blockers did not appear to "maintain" remission to the same degree as patients who had failed/were intolerant to immunomodulators or corticosteroids. (b) (4)

[Redacted]

[Redacted] (b) (4)

The patients who lost response and underwent dose escalation were not re-randomized to receive the same dose or to dose-escalate; therefore, there was no concurrent control arm to determine whether any observed difference was due to the escalated dose. The improvement could have occurred from the longer duration of therapy, since a substantial proportion of patients who remained on the q8w regimen also regained response or achieved remission. Patients in all three groups achieved remission or regained clinical response, which further supports the benefit of the q8w dose regimen.

[Redacted] (b) (4)

The review team's concerns over the q12w dose regimen were communicated to the Applicant in a Discipline Review Letter/Information Request, dated July 21, 2016. In response, the Applicant concluded, based on subgroup analyses using CRP > 3 mg/L or < 3 mg/L at maintenance baseline, that patients with greater "burden of inflammation" (higher CRP values) are more likely to require the q8w dosing, and no differences in efficacy were observed between the q8w and q12w regimens in patients with lower CRP values. The Applicant reports a similar trend with fecal calprotectin, and results of post-hoc analyses using CRP > or < 10 mg/L. As stated previously in this review, the CRP and fecal calprotectin level that reflects active inflammation or the degree of inflammation present is not standardized. The assays have not been cleared for use to monitor disease activity. Therefore, these analyses are considered exploratory. At this time, in the absence of data to support a value(s) that is correlated with the severity of intestinal inflammation, it is premature to make conclusions about efficacy in subgroups of patients where the level of intestinal inflammation is based on CRP or fecal calprotectin values.

Based on the totality of the data, I agree with the review team that ustekinumab should be approved for the treatment of adult patients with moderate to severe Crohn's disease who have 1)

failed or were intolerant to treatment with immunomodulators or corticosteroids, but never failed treatment with a TNF blocker, or failed or were intolerant to treatment with one or more TNF blockers.

7. Safety

The reader is referred to the Clinical review by Dr. K.J. Lee, dated September 7, 2016, for complete information. Below, I will summarize the key safety findings from the clinical review.

The safety population includes 1367 patients who participated in three phase 3 clinical trials, with an overall duration of exposure up to 52 weeks in the phase 3 trials. As described in the clinical review by Dr. K.J. Lee, the safety data from the three studies (study 3001, 3002, and 3003) were reviewed separately by trial, and an integrated review of studies 3001 and 3002 was performed given that the studies utilized the same dose regimens and formulation (single IV dose). The safety data from study 3003 were analyzed separately given that study 3003 evaluated chronic dosing of a different formulation and dose regimen. In addition, the clinical reviewer considered the safety data from the non-randomized patient population.

In study 3001 (N=740), the proportion of patients with at least 1 treatment-emergent adverse event (TEAE) were similar across the treatment groups: 159/245 (64.9%) patients in the placebo group, 159/246 (64.6%) in the 130 mg, and 164/249 (65.9%) in the 6 mg/kg ustekinumab dose groups. In study 3002 (N=647), the proportions of patients who reported at least 1 TEAE were also similar across the treatment groups: 113/208 (54.3%) patients in the placebo group, 106/212 (50.0%) in the 130 mg, and 115/207 (55.6%) 6 mg/kg ustekinumab dose regimens.

Table 6: 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.

(source: reproduced from Table 26 of the clinical review by Dr. K.J. Lee, dated 9/7/2016, page 217/277)

Table 7: 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.

(source: reproduced from Table 27 of the clinical review by Dr. K.J. Lee, dated 9/7/2016, page 218/277)

As described in the clinical review and previously in this document, data from 40 patients who were enrolled prior to study suspension were not used in the efficacy analyses (28 patients from study 3001, 12 from study 3002; among the 40 patients, 9 were randomized in study 3003). However, these patients were included in the pooled safety analysis across induction studies 3001 and 3002. Based on the pooled analyses of studies 3001 and 3002, vomiting and abdominal pain occurred in at least 3% of patients and greater than placebo. Abdominal pain occurred in generally similar proportions between the ustekinumab (7%) and placebo (6%) groups, and only one patient in study 3001 reported serious abdominal pain. Furthermore, in the maintenance study 3003, abdominal pain was observed in a higher proportion of patients in the placebo group and is not described in the label for the psoriasis or psoriatic arthritis indications, supporting the review team's conclusions that the abdominal pain reported through week 8 was probably related to the underlying disease.

In study 3003 (N=396), 42/133 (31.6%) patients in the placebo arm, 34/132 (25.8%) patients in the q12w dosing regimen, and 39/131 (29.8%) patients in the q8w dosing regimen experienced at least 1 TEAE. See Table 8 below.

Table 8: 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%)
Urinary tract infection	3(2.3%)	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)
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.

(source: reproduced from Table 28 of the clinical review by Dr. K.J. Lee, dated 9/7/2016, pages 219-220/277)

Serious Adverse Events

For studies 3001 and 3002, the proportion of patients who had 1 or more serious adverse events was highest in the placebo group and similar between the two ustekinumab dose arms: 27/453 (6.0%) patients in the placebo arm, 22/458 (4.8%) in the 130 mg group, and 24/456 (5.3%) in the 6 mg/kg group. In study 3003, the overall proportion of patients experiencing 1 or more SAEs was comparable across the dose groups: 28/133 (21%) patients in placebo, 25/132 (18.9%) in 90 mg q12w dosing regimen and 19/131 (14.5%) in the q8w dosing regimen. Dr. K.J. Lee notes that the majority of SAEs were Crohn's related illness: 10/133 (7.5%) patients in placebo, 8/132 (6.1%) in the q12 regimen, and 6/131 (4.6%) in the q8w dosing regimen. No SAE occurred in more than 1 patient, except for events of Crohn's disease.

Deaths

There were no deaths during the double-blind portion of the phase 3 trials; however, 6 deaths have been reported at the time of this review. Five deaths occurred during the long term

extension (LTE) (3 cardiovascular, 1 infectious, 1 renal failure, and 1 suicide) and one additional death was provided in the 120 day safety update (infectious). Dr. K.J. Lee reviewed all of the deaths and did not find conclusive evidence that any of the deaths reported were clearly attributed to the study drug due to co-morbid conditions or confounding factors.

Serious Infections

In studies 3001 and 3002, serious infections occurred in a small number of patients and in a slightly higher proportion of patients in the 6 mg/kg dose regimen (8/456 [1.8%]) as compared to the 130 mg dose regimen (6/458 [1.3%]) and placebo (6/453 [1.3%]). In study 3003, serious infections occurred in a greater proportion of patients in the q12w dosing regimen (7/132 [5.3%]) as compared to placebo (3/133 [2.3%]), while the proportion of serious infection in the q8w dosing regimen was similar to placebo (3/131 [2.3%]). Serious infections unrelated to Crohn's disease included pneumonia, gastroenteritis, appendicitis, post-operative wound infection, Klebsiella bacteremia, E.coli sepsis, listeria meningitis, ophthalmic herpes. The clinical reviewer concluded that the patient with E. coli sepsis had other confounding factors, making it difficult to establish causality to ustekinumab; sepsis is currently described in Section 5 Warnings and Precautions of the label. In addition, there was one case of active tuberculosis (TB) in a patient during the maintenance trial who had received an initial dose of 130mg IV followed by placebo in study 3003. The patient with TB received the BCG vaccine as an infant and had a negative chest X-ray and negative QuantiFERON test at screening; therefore, the TB appeared to be consistent with active primary TB (shown on chest X-ray and CT scan) and not suggestive of disseminated TB, which is described in the label. See clinical review by Dr. K.J. Lee for further details. Serious infections will be further studied in the post-marketing setting using FDA's Sentinel System to assess this risk. Refer to ARIA sufficiency memo, by Dr. J. Weissfeld and Dr. S. Sandhu, dated 8/19/2016, for details.

Malignancy

In studies 3001 and 3002, one patient was diagnosed with multiple myeloma during the safety follow-up period 199 days after the initial ustekinumab 6 mg/kg IV single dose. Another patient in the placebo group developed a basal cell carcinoma. In study 3003, basal cell carcinoma was reported in two randomized patients, 1 patient in the placebo arm and 1 patient in the ustekinumab 90 mg q8w dosing regimen. Additionally, in the non-randomized patient population, 6 nonmelanoma skin cancers were reported in 3 patients, and 2 other malignancies (metastatic small bowel adenocarcinoma and a carcinoid tumor) were reported in 1 patient. During the 120 day safety update, two additional malignancies were reported (chronic myeloid leukemia and seminoma) in one patient each. Dr. K.J. Lee concluded that there does not appear to be a clear increased risk of malignancy in patients treated with ustekinumab vs placebo based on the phase 3 clinical data; however, she recommends collecting additional post-marketing data to determine whether there is an increased risk of malignancy with longer-term ustekinumab treatment. Malignancies may not be detected during a 52-week clinical trial period. Given the experience with other immunosuppressive treatments for Crohn's disease, malignancies observed with previously approved indications for ustekinumab, and the introduction of an intravenous dose followed by a higher dosing regimen for the Crohn's indication as compared to the psoriasis and psoriatic arthritis indications, I agree with her recommendation for post-marketing studies. For further details on the malignancies, refer to Dr. K.J. Lee's clinical review, dated September 7, 2016.

Hypersensitivity Reactions

In studies 3001 and 3002, signs and symptoms suggestive of hypersensitivity reactions were experienced by 11/453 (2.4%) patients in the placebo group, 15/458 (3.3%) in the 130 mg dose group, and 12/247 (2.8%) in the 6 mg/kg dose group. One patient in study 3003 developed a hypersensitivity reaction following a subcutaneous dose of ustekinumab. Of these reactions, two patients experienced reactions that were considered to be serious hypersensitivity reactions following a single dose of ustekinumab. One patient developed chest discomfort, flushing, urticaria, and increased body temperature following an intravenous dose, and one patient developed anaphylaxis, reported as tightness of the throat, shortness of breath, and flushing following a subcutaneous dose. The impact of anti-drug antibodies (ADA) is described above in the Clinical Pharmacology section of this document.

Demyelinating Disease

One patient who received a single IV dose of ustekinumab following by subcutaneous dosing for 2 months experienced symptoms of visual impairment, dizziness and numbness/tingling of her mouth. MRI of this patient demonstrated multiple areas of abnormality in the white matter tracts of both hemispheres, possibly demyelinating disease. The Applicant conducted further review of the MRI findings and submitted additional information (b) (4)

Upon further review, the MRI findings appear to be non-specific and are not clearly consistent with acute demyelination as none of the lesions were enhancing, and there were confounding factors. The Applicant and FDA will continue to monitor for possible events of demyelinating disease.

Other Relevant Safety Issues

As described in the clinical review, Dr. K.J. Lee also reviewed this BLA submission for specific adverse reactions, including Reversible Posterior Leukoencephalopathy Syndrome (RPLS), which are described in the currently approved label for the psoriasis and psoriatic arthritis indications. No cases of RPLS have occurred in patients with Crohn's disease at the time of this review. Dr. K.J. Lee also reviewed this BLA submission for events of major cardiovascular events (MACE), which were observed in the trials for psoriasis, but did not find conclusive evidence to establish causality to ustekinumab in this submission. MACE events included cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. The potential MACE events were also reviewed by the Applicant by an independent blinded adjudicated process.

As stated in the clinical review, malignancy, serious infection, and hypersensitivity reactions are reflected in the currently approved label; however, I agree with Dr. K.J. Lee that post-marketing studies should be conducted to evaluate the long-term safety of ustekinumab treatment given that ustekinumab is the first in this class of therapies for Crohn's disease, patients with Crohn's disease have different and potentially higher risk for certain malignancies as compared to patients with psoriasis or psoriatic arthritis, and the dosing regimen is different than the dosing for the other indications (i.e., new IV dose and higher "maintenance" dosing regimen).

8. Advisory Committee Meeting

No advisory committee meeting was held for this submission.

9. Pediatrics

The Division consulted the Division of Pediatric and Maternal Health (DPMH) to aid in the review of the labeling. The DPMH recommendations have been incorporated into the final labeling.

The Agency issued an agreement on the initial Pediatric Study Plan (iPSP), dated November 19, 2015. Orphan designation was granted on May 18, 2016; therefore, PREA will not apply. The PMC language was being negotiated at the time of this document. Refer to the Approval Letter for final language, agreed pediatric requirements, and timelines for submission. The following pediatric PMCs are proposed by the review team under BLA 761044:

- Conduct a dose-ranging study to determine the pharmacokinetics/pharmacodynamics, safety, and tolerability of Stelara (ustekinumab) induction dosing in pediatric patients 2 to 17 years of age with moderately to severely active Crohn's disease despite conventional therapy.
- Conduct a randomized, controlled, blinded, multicenter study of the safety and efficacy of Stelara (ustekinumab) in pediatric patients 2 to 17 years of age with moderately to severely active Crohn's disease despite conventional therapy.

In addition, we are waiving pediatric study requirements in patients 0 to < 2 years of age with moderately to severely active Crohn's disease because studies are impossible or highly impractical. This is because there is a low incidence of the disease in this age group.

The proposed pediatric post-marketing trials were discussed with PeRC on August 24, 2016 and PeRC agreed with the Division's recommendations to defer pediatric trials in patients 2 to 17 years of age because the product is ready for approval in adults, and waive studies in patients < 2 years of age.

10. Other Relevant Regulatory Issues

Office of Scientific Investigations

The Clinical reviewer selected 6 clinical investigator (CI) sites and two contract research organizations (CRO), responsible for the collection of data from the endoscopy substudy and histology study, for inspection. No violations were cited at inspection of any sites and all final classifications were No Action Indicated. The inspector determined that the trials appear to have been conducted adequately, and the data generated by the 6 clinical sites and CRO for the endoscopy substudy [REDACTED] (b) (4). Refer to the review by Dr. S. Leibenhaut, dated 7/29/2016, for details; I have summarized the following findings:

- Upon inspection of [REDACTED] (b) (4), the CRO responsible for reading the histology samples, the investigator determined that while the CRO and the Applicant adhered to the agreed upon procedures, security controls did not appear adequate to meet standards to ensure data reliability. The study was designed to be exploratory and the results were not used in determination of the primary efficacy outcome. Although there is no evidence of tampering with data or misconduct by the CRO, without adequate controls for data integrity, OSI could not assure data integrity of the data generated by this CRO. The

Applicant acknowledged these issues and is working to implement controls in future trials.

- During inspection, it was noted that the line listings did not always match the calculated CDAI score documented in the source records. This was attributed to the Applicant calculating the CDAI score reported in the line listings using the hematocrit value obtained from the subject's blood sample drawn at the time of the visit, whereas the clinical site used the hematocrit value obtained from the subject's blood sample drawn at the time of the previous visit as per the protocol. This finding was communicated to the review team. The review team issued an IR to the Applicant to determine whether the differences in CDAI would have resulted in different efficacy results and/or eligibility for study 3003, which was based on achieving at least clinical response, defined by CDAI score. In order to assess the impact of any misclassification, the statistical reviewer performed sensitivity analyses, and the overall conclusions were unchanged. See statistical and clinical reviews for complete details.

Proprietary Name

The Office of Medication Error Prevention and Risk Management determined that the proprietary name, Stelara, was acceptable. Refer to the Proprietary Name Request Conditionally Acceptable letter, dated 3/11/2016, and name review by S. Abraham, M. Mistry, and L. Merchant from DMEPA, dated 3/10/2016.

Financial Disclosures

Dr. K.J. Lee states in her clinical review that the Applicant adequately disclosed financial arrangements, none of which raise concern over the integrity of the data. Refer to the clinical review, dated September 7, 2016, for details.

11. Labeling

Prescribing Information

Labeling negotiations between the Applicant and the review team were ongoing at the time of this document. Refer to the approved label for the final language. The key changes to the label are summarized below.

Section 1: Indications and Usage

- Revised the indication statement for clarity.

(b) (4)

(b) (4)



(b) (4) Therefore, because of the specific challenges with describing the results of the phase 3 trials submitted to support product labeling for this BLA, the language for the indication statement will include “treatment of” (b) (4)

Section 2: Dosage and Administration

- Revised to clarify and simplify the instructions, and include dosing and administration for Crohn’s disease.

Section 5: Warnings and Precautions

- Updated to include information on infections, including tuberculosis, malignancy, and hypersensitivity reactions that were observed during the phase 3 clinical trials in Crohn’s disease.

Section 6: Adverse Events

- Revised to include tables of adverse reactions that occurring during the phase 3 clinical trials in patients with Crohn’s disease to provide more detailed information to prescribers.

Section 8: Use in Specific Populations

- Revised as per DPMH recommendations to add the following risk/benefit statement to subsection 8.2 because the clinical relevance to breastfeeding is not clear, although available

limited data do not indicate a safety signal; there are no data on the presence of ustekinumab in human milk:

- The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for STELARA and any potential adverse effects on the breastfed child from STELARA or from the underlying maternal condition.
- As stated in the PLLR labeling review by the maternal health reviewers, animal reproductive studies of administration of ustekinumab did not show any adverse effects on fertility. Since there are no human data available on the effect of ustekinumab on fertility, Subsection 8.3, Females and Males of Reproductive Potential, will not be included in Stelara labeling.

Section 12.3: Pharmacokinetics

- Revised to include updated PK information from the bioanalytical method (i.e., MSD-ECLIA) used to determine ustekinumab concentrations in patients with Crohn's disease; this method is not comparable to the original method (i.e., BV-ECLIA) used to generate the PK data in the psoriasis patients in BLA 125261, and the BV-ECLIA method is no longer in use.

Section 14: Clinical Studies

- Revised to include details on use of concomitant therapy.
- Removed (b) (4)
- (b) (4)
- Removed corticosteroid-free remission and clinical remission in subgroups of patients from the table, and summarized these endpoints in the text below the table.
- Added text to describe the downward trend in clinical remission for the patients who had failed or were intolerant to prior treatment with TNF blockers.
- Removed (b) (4)
- Removed (b) (4)

In addition to the review team and consultants, the labeling was also reviewed by the Division of Medication Error Prevention and Analysis (DMEPA), and the Office of Prescription Drug Promotion (OPDP). Their comments and recommendations have been incorporated into final labeling. Labeling negotiations were ongoing at the time of this document. For final labeling agreements, the reader is referred to the approved product label for Stelara.

12. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

The Office of Surveillance and Epidemiology (OSE), Office of Medication Error Prevention and Risk Management (DRISK) reviewed whether a risk evaluation and mitigation strategy (REMS) was needed for BLA 761044. Ustekinumab is currently approved with a communication plan only REMS for the plaque psoriasis and psoriatic arthritis indications under BLA 125261, and the approved labeling includes a Medication Guide. The goal of the REMS is to evaluate and mitigate the potential risks of serious infections, malignancy, and RPLS associated with Stelara (ustekinumab) by alerting and warning healthcare providers about the risks. The currently approved REMS includes outreach to gastroenterologists, who are aware of the risks associated

with immunosuppressant medications used to treat inflammatory bowel disease. In addition, the risks will be appropriately communicated in the product label. DRISK determined that a REMS modification to the approved REMS is not necessary. See review by J. Sheppard and C. Lacivita, dated August 1, 2016, for complete details.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

Refer to the Approval Letter for the final PMR/PMC language. The language was being negotiated at the time of this document. The following PMR/PMCs are proposed by the review team.

Post-marketing requirements:

PMR 1: Conduct a long-term, postmarketing, observational study to assess the long-term safety of ustekinumab versus other therapies used in the treatment of adults with moderate to severe Crohn's disease. The study's primary outcome is malignancy. Secondary outcomes include, but are not limited to, opportunistic infections (i.e., tuberculosis [TB]). Specify concise case definitions, and provide outcome validation for both primary and secondary outcomes. Describe and 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 18 months of ustekinumab exposure at the end of the study. Follow for a period of at least 7 years.

- DEPI-I has determined that the new pharmacovigilance system (Sentinel) will be sufficient to assess the risk for serious infections; therefore, FDA will conduct a study in FDA's Sentinel System to assess this risk. However, the new pharmacovigilance system will not be sufficient to assess the risks of malignancy and specific opportunistic infections, which are described above in the post-marketing requirement.

The Division discussed the plan for issuing this PMR with OSE/Division of Epidemiology I. Refer to ARIA sufficiency memo, by Dr. J. Weissfeld and Dr. S. Sandhu, dated 8/19/2016, for details.

Post-marketing commitments:

PMC 1: Conduct a dose-ranging trial to determine the pharmacokinetics/pharmacodynamics, safety, and tolerability of STELARA (ustekinumab) induction dosing in pediatric patients 2 to 17 years of age with moderately to severely active Crohn's disease despite conventional therapy.

PMC 2: Conduct a randomized, controlled, blinded, multicenter trial to evaluate the safety and efficacy of STELARA (ustekinumab) in pediatric patients 2 to 17 years of age with moderately to severely active Crohn's disease despite conventional therapy.

PMC 3: Conduct a clinical trial to assess whether ustekinumab alters the metabolism or pharmacokinetics of cytochrome P450 (CYP) substrates in Crohn's disease (CD) patients treated with ustekinumab (e.g., using a cocktail of relevant CYP probe drugs).

13. Recommended Comments to the Applicant

No comments to the Applicant are recommended at this time.

APPEARS THIS WAY ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JULI A TOMAINO
09/23/2016