APPLICATION NUMBER:

761044Orig1s000

SUMMARY REVIEW
## Summary Review for Regulatory Action

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<tr>
<th>Date</th>
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<tr>
<td>From</td>
<td>Joyce Korvick, MD, MPH&lt;br&gt;Deputy Director for Safety&lt;br&gt;Division of Gastroenterology and Inborn Errors Products&lt;br&gt;Office of New Drugs III&lt;br&gt;Center for Drug Evaluation and Research</td>
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<td>Subject</td>
<td>Signatory Summary Review</td>
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<tr>
<td>BLA #</td>
<td>761044</td>
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<tr>
<td>Applicant Name</td>
<td>Janssen Biotech, Inc.</td>
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<tr>
<td>Date of Submission</td>
<td>November 25, 2015</td>
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<td>PDUFA Goal Date</td>
<td>September 25, 2016</td>
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<tr>
<td>Proprietary Name / Established (USAN) Name</td>
<td>Stelara&lt;br&gt;Ustekinumab</td>
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<tr>
<td>Dosage Forms / Strength</td>
<td>Ustekinumab/injection&lt;br&gt;130 mg/26 ml (5 mg/ml)</td>
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<td>Proposed Indication(s)</td>
<td>STELARA® is indicated for the treatment of adult patients with moderately to severely active Crohn’s disease who have&lt;br&gt;• failed or were intolerant to immunomodulators or corticosteroids, but never failed treatment with a tumor necrosis factor (TNF) blocker OR&lt;br&gt;• failed or were intolerant to treatment with one or more TNF blocker.</td>
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<td>Action:</td>
<td>Approval</td>
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<td>Material Reviewed/Consulted</td>
<td>Names of discipline reviewers</td>
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<tr>
<td>CDTL Review</td>
<td>Julie Tomaino, MD, dated 9/23/2016</td>
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<td>Medical Officer Review</td>
<td>K.J. Lee, MD, dated 9/7/2016</td>
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<td>Statistical Review (DBIII)</td>
<td>M. Min, PhD, Y. Chen, PhD, dated 8/31/2016</td>
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<td>Pharmacology Toxicology Review</td>
<td>J. Peretz, PhD, S. Chakder, PhD, dated 7/19/2016</td>
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<tr>
<td>OPQ/Division of Biotechnology Review and Research III, Drug Product Review</td>
<td>Z. Liu, PhD, dated 8/18/2016</td>
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<td>OPQ/Application Technical Lead (DBRR III)</td>
<td>M. Gutierrez-Lugo, PhD, S. Kirshner, PhD, integrated review dated 8/31/2016</td>
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<td>Division of Microbiology Assessment (OPQ/OPF/Branch IV)</td>
<td>C. Gomez-Broughton, PhD, C. Thomas, PhD, P. Hughes, PhD, dated 8/31/2016</td>
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<td>OPQ/Division of Inspectional Assessment</td>
<td>M. Michaelis, Z. Qiu dated 8/31/2016</td>
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<td>Genomics and Targeted Therapy Review (OCP/DCP3)</td>
<td>A. Ramamoorthy, PhD, C. Grimstein, PhD, dated 8/9/2016 (included in amended clinical pharmacology review, 9/7/2016)</td>
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<td>Clinical Pharmacology Review (OCP/DCP3)</td>
<td>C. Hon, PhD, A. Balakrishnan, PhD, Y. Wang, PhD, H. Ahn, PhD, dated 8/9/2016, amended 9/7/2016</td>
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<td>Pharmacometrics Review (DPM/DCP3)</td>
<td>JE. Lee, PhD, N. Mehrotra, PhD, dated 8/4/2016</td>
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<td>Labeling review (OPDP, DMPP)</td>
<td>N. Booker, PharmD, MPH, M. Patel, PharmD, M. Williams, PhD, L. Griffiths, MHSPh, BSn, RN, dated 8/9/2016</td>
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<td>Labeling review (OSE/DMEPA)</td>
<td>S. Abraham, RPh, M. Mistry, PharmD, MPH, L. Merchant, PharmD, MS, dated 7/18/2016</td>
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<td>REMS Review (DRISK)</td>
<td>J. Sheppard, PharmD, J. Wilkins Parker, PharmD, C. LaCivita, PharmD, dated 8/1/2016</td>
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<td>Other: Consultation review (DPMH)</td>
<td>Maternal health review: L. Sahin, MD, M. Dinatale, MD, dated 8/16/2016</td>
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<td>OBP J Abdus-Samad dated 9/22/2016</td>
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<td>Division of Epidemiology (OSE)</td>
<td>J Weissfeld, S. Sandhu 8/17/2016</td>
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<td>Clinical site inspections (OSI)</td>
<td>S. Leibenhaut, MD, S. Thompson, K. Ayalew, dated 7/29/2016</td>
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DGIEP: Division of Gastroenterology and Inborn Errors Products,
OPQ: Office of Pharmaceutical Quality,
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,
OSE: Office of Surveillance and Epidemiology
DMEPA: Division of Medical Error Prevention and Analysis,
DRISK: Division of Risk Management,
DPMH: Division of Pediatric and Maternal Health
OSI: Office of Scientific Investigation
1. Introduction

Janssen Biotech, Inc. submitted BLA 761044 for Stelara (ustekinumab) on November 25, 2015 to support the following indication:

STELARA® is indicated for the treatment of adult patients with moderately to severely active Crohn’s disease who have
• failed or were intolerant to 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.

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.

This application proposed a new intravenous injection product to be used as the initial “induction” dose followed by subsequent subcutaneous treatment as “maintenance” dosing. Stelara is currently approved for the treatment of psoriasis and psoriatic arthritis. The Crohn’s disease dosing will utilize the currently approved subcutaneous prefilled syringe for the “maintenance” dosing.

The applicant and the Division discussed and originally agreed on the major endpoints of the pivotal clinical trials at a time when the Crohn’s Disease Activity Index (CDAI) score was being used as the major outcome variable. Approaches to studying Crohn’s disease have been evolving since then. During this time the Division recommended that Janssen collect additional data, including endoscopy and histology information that may inform further drug development for Crohn’s disease. The applicant also collected additional information from these patients that may be considered supportive of the indication and was understood to be exploratory in nature. This information may be useful in the future to inform designs of clinical trials for Crohn’s. The CDAI score was used in the evaluation of efficacy for this BLA. (for detailed regulatory history see clinical review).

This review summarizes the review team’s recommendations regarding the new product, the proposed indication, the dosing recommendations, and the safety of ustekinumab in the adult Crohn’s disease population, the currently approved risk evaluation and mitigation strategy (REMS), and the PLLR labeling conversion. The data submitted by Janssen supported approval.
2. 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. 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.

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.

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), 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 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. Product Quality

Stelara (ustekinumab) is currently approved for psoriasis and psoriatic arthritis under BLA 125261 from the same applicant. The currently approved presentations include prefilled syringe (PFS) and vial, both available in two strengths (90 mg/ml and 45 mg/0.5 ml). This
BLA cross references the drug substance section from BLA 125261. The Product Quality review relied on that BLA for the review of the drug substance.

Stelara’s new presentation consists of a final vial product for intravenous use at a 130 mg/26 ml (5 mg/ml) strength in a single-dose glass vial. This drug product is intended for the initial dose in the treatment of Crohn’s disease. This dose is administered by intravenous (IV) infusion after dilution with saline. Subsequent doses will be administered using the currently approved PFS presentation, 90 mg administered subcutaneously.

The new ustekinumab presentation contains the following excipients per vial: EDTA disodium salt dihydrate (8 mg), L-histidine (8 mg), L-histidine hydrochloride monohydrate (20 mg), methionine (4 mg), Polysorbate 80 (4 mg) and sucrose (4 mg). 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 1 glass tubing vial, capped with a 20 mm stopper with a 20 mm aluminum seal a light green flip-off button.

Primary Drug Product Review concludes:
“The data submitted in this application support the conclusion that the manufacture of ustekinumab final vial product for intravenous injection [FVP (IV)] is well controlled, and leads to a product that is pure and potent. The product is free from endogenous or adventitious infectious agents, sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product is produced from the multiple production runs presented. It is recommended that this product be approved for human use under conditions specified in the package insert.” No Post-Marketing Commitments/Requirements are recommended.

The Drug Products Microbiology review recommended approval from a microbiology quality perspective. “No additional inspectional follow-up items were identified.”

The facilities review concluded the following:

“There were no pre-approval inspections needed for this application since there are no changes to the drug substance manufacturing and only minor changes to the drug product manufacturing from the initial approval of BLA 125261. All facilities associated with the application were in a favorable compliance status. This submission is recommended for approval from a facility assessment perspective.”

The final integrated quality review of Stelara stated:
“The Office of Pharmaceutical Quality, CDER, recommends approval of STN 761044 for Stelara (ustekinumab), manufactured by Janssen Biotech, Inc. 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. We recommend that Stelara be approved for human use under the conditions specified in the package insert”

“Stelara is an anti-IL-12 and anti-IL-23 monoclonal antibody intended for the treatment of Crohn’s disease. The DS manufacturing process was previously reviewed and found to be well
controlled and should consistently deliver DS of desired quality. The DP manufacturing process is well controlled and should consistently deliver DP of desired quality. No CMC PMCs are issued with this BLA. Overall the facilities have favorable compliance status.”

“The dating period for the Drug Product is 24 months; 2-8°C.”

*I concur with the conclusions reached by the Product Quality reviewers regarding the acceptability of the manufacturing of the drug product and drug substance, including the dating period of the Drug Product. Manufacturing site inspections were acceptable. There are no outstanding issues.*

**4. Nonclinical Pharmacology/Toxicology**

The Applicant did not conduct any new nonclinical studies to support the current biologics licensing application. The Applicant is cross-referencing all nonclinical information previously submitted under BLA 125261 that is supportive of the proposed indication and new intravenous formulation of Stelara®. These studies were previously reviewed for BLA 125261 dated November 28, 2008 (J. Yao, Ph.D.; Dermatology and Dental Products).

“No approvability issues were identified for BLA 761044 from a nonclinical perspective.”

The nonclinical reviewers contributed to edits in section 8.1 and 8.2 of the professional product labeling.

*I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.*

**5. Clinical Pharmacology/Biopharmaceutics**

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. Data from these studies are used to support the clinical pharmacology section of this BLA submission.

**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.

**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.

Reference ID: 3990231
Absorption
In patients with Crohn’s disease, following the recommended intravenous induction dose, mean peak serum ustekinumab concentration was 125.2 ± 33.6 mcg/mL. Starting at Week 8, subcutaneous maintenance dosing of 90 mg ustekinumab was administered every 8 weeks. Steady state ustekinumab concentration was achieved by the start of the second maintenance dose. There was no apparent accumulation in ustekinumab concentration over time when given subcutaneously every 8 weeks. Mean steady-state trough concentration was 2.51 ± 2.06 mcg/mL for 90 mg ustekinumab administered every 8 weeks.

Distribution:
The total volume of distribution at steady-state was 4.62 L in patients with Crohn’s disease.

Elimination:
In a population pharmacokinetic analysis of ustekinumab, the clearance was 0.19 L/day (95% CI: 0.185, 0.197) with an estimated median terminal half-life of approximately 19 days in patients with Crohn’s disease.

Selection of Dosing Regimen:
The applicant conducted the major studies with two doses (additional detail in section 7 below) a fixed dose or weight-based dose. Exploration of the Dose-Response/Exposure Response, overall efficacy and safety of the doses used in CD patients in these studies, and immunogenicity are all considered in the reviews as they relate to the recommended dosing. These analyses and reviews of the data by the FDA reviewers supported the recommended labeled dosing (see final approved professional label).

Dose Response/Exposure Response Relationship:
Dr. C. Hon notes the following observations for the dose-response relationship in the clinical pharmacology review. For the induction dose, higher proportions of subjects 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 tumor necrosis factor-α (TNFα) 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 subjects 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 TNFα antagonist non-failure population, but not for the TNFα 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 study population (i.e., TNFα antagonist failure plus non-failure subjects); it would have been underpowered to detect the differences in clinical remission rate among different dose groups in either the TNFα 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 TNFα antagonist therapy. There was an
E-R relationship in the maintenance phase only in subjects who have not failed TNFα antagonist.

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 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.

In addition, the clinical pharmacology reviewers recommend against approval of the Applicant’s proposal to dose adjustment proposal was based on the response in a small subset of patients who met loss of response (LOR) criteria and had a dose adjustment. The finding is considered exploratory, and it is not acceptable for the final dose recommendation.

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

Drug-Drug Interactions:
Formal Drug-Drug interaction studies were not performed with ustekinumab in CD. A population PK analysis including the effect of concomitant use of immunomodulators including 6-mercaptopurine (6-MP), azathioprine (AZA) and methotrexate (MTX) was conducted by the applicant. The pharmacometrics reviewers found that this was not adequate to support specific language in the label under section 7. On the other hand, since a significant number of patients enrolled in these studies were receiving concomitant immunomodulators, and from a clinical point of view, this did not appear to affect the overall efficacy outcomes in this study; a more general statement was accepted in section 7 of the label.

“In Crohn’s disease studies, immunomodulators (6-mercaptopurine, azathioprine, methotrexate) were used concomitantly in approximately 30% of patients and corticosteroids were used concomitantly in approximately 40% of patients. Use of these concomitant therapies did not appear to influence the overall safety or efficacy of STELARA®”
Immunogenicity
Twenty-seven of 1154 (2.3%) subjects 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%) subjects were positive for neutralizing antibodies (NAb).

The concomitant use 6-MP, AZA, and MTX had an impact on immunogenicity. The proportion of ADA+ subjects was lower among those who received immunomodulators (7/375 subjects, 1.9%) compared with those who did not receive immunomodulators (20/779 subjects, 2.6%).

Immunogenicity had a negative impact on PK. While the PopPK model predicted a 13% higher clearance (CL) in ADA+ subjects, the median observed serum ustekinumab concentrations were approximately two to three-fold lower in subjects who were ADA+ than in subjects who were ADA-. At the individual subject 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.

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 studies 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 study. The clinical pharmacology review team identified several limitations in these exploratory analyses and concluded that the study results do not support drawing definitive conclusions. Complete details can be found in the Genomics and Targeted Therapy Review by Dr. A. Ramamoorthy, dated 9/7/2016.

Recommended PMC:
The formation of CYP450 enzymes can be altered by increased levels of certain cytokines (e.g., IL-1, IL-6, IL-10, TNFα, IFN) during chronic inflammation. Thus, an antagonist of IL-12 and IL-23, could normalize the formation of CYP450 enzymes. Upon initiation of ustekinumab in patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index, monitoring for therapeutic effect (e.g., for warfarin) or drug concentration (e.g., for cyclosporine) should be considered and the individual dose of the drug adjusted as needed. In order to more clearly define this relationship in patients with CD the clinical pharmacology reviewers recommended a PMC to study this effect in CD patients (section 13 lists the PMR/PMCs).

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics and pharmacometrics reviewers that there are no outstanding clinical pharmacology issues that preclude approval.
6. Clinical Microbiology

Not Applicable to this BLA.

7. Clinical/Statistical-Efficacy

Both the clinical and statistical reviewers are in agreement that Stelara demonstrated efficacy in the adult Crohn’s disease population. They agreed that the data supported the final labeled indication. The clinical trials that formed the basis of the efficacy analysis include two “induction” studies (3001 and 3002) and one “maintenance” study (3003). These studies were deemed to be adequate to support the indication.

As noted above, since this development program began DGIEP has determined that the CDAI score, while it has been used in the past, may not reflect the clinical status of the patients optimally. Currently under consideration as the primary outcome variable is “clinical remission”. The new definition being considered is a combination of key signs and symptoms of Crohn’s and results from endoscopy. The definitions of the primary and secondary outcomes in this application are based upon CDAI scoring. FDA performed additional exploratory analyses to further confirm the results. These were supportive only. In addition, the applicant also included exploratory evaluations of endoscopy and histology, as well as potential biomarkers which are yet to be validated. Complete details can be found in the Clinical Review as well as the Statistical Review.

Initial Intravenous Dosing: Study 3001 and 3002

During the conduct of these studies, the sponsor temporarily suspended dosing of subjects in November 2011 because a stability issue was identified with the batch of the IV drug used in the induction studies (130 mg ustekinumab in 26 mL [5 mg/mL]; (b) (4) ). To maintain the originally planned sample size in each of the induction studies, an additional 40 subjects were to be enrolled in the induction studies. Because knowledge of the stability issue could potentially bias the assessments, data from subjects who were enrolled before this study was temporarily suspended (28 from study 3001 and 12 from study 3002; among the 40 patients, 9 of them were included in the study 3003) were not used in the planned efficacy analyses accordingly.

Study 3001 and 3002 were of similar design, however, the patient population was slightly different based upon prior treatments received by the patients. Study 3001 enrolled patients with moderately to severely active Crohn’s disease who have failed or were intolerant to one or more TNF antagonist therapies, while study 3002 enrolled patients with moderately to severely active Crohn’s disease who failed or were intolerant to conventional therapy (corticosteroids and/or immunomodulators) but never failed TNF antagonist therapy. The baseline characteristics of the patients in both of these studies is similar; however, 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
contribute to the differences observed in treatment effect over placebo between studies (see results below).

Patients were randomized in a 1:1:1 ratio to receive a single IV administration of either placebo or 1 of 2 induction doses of ustekinumab at Week 0:

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

The applicant performed the analysis of pre-specified primary and major secondary outcomes based on a sequential testing procedure in order to control for Type I error. The following list details the order of the testing that was performed within each study. Testing continued to the next endpoint in the list, provided the preceding endpoint was significant.

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

The following definitions were used for the major outcomes:

**Clinical response at Week 6:** 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.

**Clinical remission at Week 8:** a CDAI score of <150 points.

**Clinical response at Week 8:** 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.

The results are displayed below.
Table 1. Study 3001 – Results for Primary and Secondary Efficacy Endpoints#

<table>
<thead>
<tr>
<th>Primary efficacy endpoint (clinical response at Week 6)</th>
<th>Placebo (N=247)</th>
<th>Ustekinumab 130 mg (N=245)</th>
<th>Ustekinumab 6 mg/kg* (N=249)</th>
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<tr>
<td>Number (%)</td>
<td>53 (21.5)</td>
<td>84 (34.3)</td>
<td>84 (33.7)</td>
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<td>p-value by CMH test**</td>
<td>0.002</td>
<td>0.003</td>
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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 2: Study 3002- Results for Primary and Secondary efficacy Endpoints#

<table>
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<tr>
<th>Primary efficacy endpoint (clinical response at Week 6)</th>
<th>Placebo (N=209)</th>
<th>Ustekinumab 130 mg (N=209)</th>
<th>Ustekinumab 6 mg/kg* (N=209)</th>
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<tbody>
<tr>
<td>Number (%)</td>
<td>60 (28.7)</td>
<td>108 (51.7)</td>
<td>116 (55.5)</td>
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<tr>
<td>p-value by CMH test**</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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</tbody>
</table>

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 (38.6) 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)

All outcomes were statistically significant and supported approval of Stelara for the initial dosing in Crohn’s disease. As discussed in the clinical pharmacology section of this review, the dose recommended was the tiered weight-based dosing approximating 6 mg/kg. This is also upon the numerically greater response in that treatment group for the most clinically meaningful endpoint compared to the 130 mg dose group.

The Applicant also evaluated C-reactive protein (CRP), fecal calprotectin, and fecal lactoferrin as markers of inflammation. At this time the Division considers these exploratory as these assays have not been cleared for use to monitor disease activity or measure the degree of severity.
Subcutaneous “maintenance” Dosing: Study 3003
Subjects in response to ustekinumab induction at Week 8 in Studies 3001 or 3002 were eligible to be enrolled into Study 3001. Patients were randomized to receive placebo, ustekinumab 90 mg SC q 12w, or ustekinumab 90 mg SC q8w. Patients in the every 12 week group who lost response could have their dose adjusted to every 8 weeks. These results among these randomized patients provided the database upon which the primary and secondary efficacy analyses were based. The primary endpoint was clinical remission at Week 44, defined by CDAI < 150 points. Secondary endpoints included the following in rank 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).

In order 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.

Compared to placebo, a greater proportion of patients in the ustekinumab 90 mg q8w treatment group had statistically significant results regarding 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.
Table 3: Study 3003- Results for Primary and Secondary Efficacy Endpoints

<table>
<thead>
<tr>
<th></th>
<th>Placebo SC (N=131)</th>
<th>Ustekinumab 90 mg SC q12w (N=129)</th>
<th>Ustekinumab 90 mg SC q8w (N=128)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary efficacy endpoint (clinical remission at Week 44)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number (%)</td>
<td>47 (35.9)</td>
<td>63 (48.8)</td>
<td>68 (53.1)</td>
</tr>
<tr>
<td>p-value by CMH test**</td>
<td>0.040</td>
<td>0.005</td>
<td></td>
</tr>
</tbody>
</table>

**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)    |                     |                                   |                                  |
   - 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)     |                     |                                   |                                  |
   - 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)
*B 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)

Regarding additional exploratory analyses, the Clinical Team leader commented as follows: "As discussed in the Clinical Pharmacology section of this review, and in the clinical review, by Dr. K.J. Lee, 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 90 mg q8w dose regimen, and I agree with their recommendation.” I am in agreement with this recommendation and this dose is reflected in the labeling.
Study 3003 enrolled patients from study 2001 and 3003 who may represent somewhat different patient populations. Among patients randomized to the 90 mg q 8 week treatment group, an analysis of clinical benefit (patients in clinical remission at Week 0 and Week 44) for was conducted for each of these patient populations. 61% (34/56) of patients randomized from Study 3001 into the maintenance trial were found to be in remission at Week 0 compared to 41% (23/56) at Week 44 in the ustekinumab treatment group. In the placebo arm, 44% (27/61) patients were in clinical remission at Weeks 0 as compared to 26% (16/61) at Week 44. The same comparison was made among patients randomized from study 3002. At Week 0 of study 3003, 64% (46/72) ustekinumab were in clinical remission and the rate was similar at Week 44 63% (45/72). In the placebo arm, 71% (50/70) patients were in clinical remission at Week 0 as compared to 44% (31/70) at Week 44. The data suggest that clinical remission decreased over time in the patients enrolled from study 3001 (i.e., patients who had failed/were intolerant to prior TNF blocker treatment). This information will be included in the labeling.

Another exploratory analysis included fistula response. In 34/388 (9%) patients with draining fistulas at induction baseline, a numerically greater proportion of ustekinumab treated patients achieved a fistula response (defined as greater than or equal to 50% reduction from baseline of the induction trial in the number of draining fistulas) compared with placebo over 44 weeks. The proportion of patients in fistula response at Week 44 was 5/11 (45%) for the placebo group and 7/8 (88%) for the ustekinumab 90 mg every 8 week dosing group. While this information is provocative, it is difficult to interpret due to the small sample size.

Of interest is an exploratory analysis of “maintainance” of clinical remission. The medical team leader outlines the results in her review as follows as an 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 4: Clinical Remission at Week 44 and in at least 10 out of 12 visits

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

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.”
As mentioned above the endoscopic substudy while useful as an exploratory study to further inform future endpoint development, the reviewers questioned the clinical meaningfulness of the small changes seen on the SES-CD scoring system.

**Appropriateness of the primary endpoint**

The clinical team leader’s memo summarizes this issue in Crohn’s research as follows: “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. 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 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 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 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).”

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 2) failed or were intolerant to treatment with one or more TNF blocker.
8. Safety

The safety of ustekinumab was assessed in 1407 patients with moderately to severely active Crohn’s disease (Crohn’s Disease Activity Index ([CDAI]) greater than or equal to 220 and less than or equal to 450) in three randomized, double-blind, placebo-controlled, parallel-group, multicenter studies. These 1407 patients included 40 subjects patients who received a prior investigational intravenous ustekinumab formulation but were not included in the efficacy analyses. In Studies 3001 and 3002 there were 470 patients who received ustekinumab 6 mg/kg as a weight-based single intravenous induction dose. Patients who were responders in either Study were randomized to receive a subcutaneous maintenance regimen of either 90 mg STELARA® every 8 weeks, or placebo for 44 weeks in Study 3003. Patients in these 3 studies trials may have received other concomitant therapies including aminosalicylates, immunomodulatory agents [azathioprine (AZA), 6 mercaptopurine (6 MP), methotrexate (MTX)], oral corticosteroids (prednisone or budesonide), and/or antibiotics for their Crohn’s Disease.

The overall safety profile of ustekinumab was consistent with the safety profile seen in the psoriasis and psoriatic arthritis clinical trials.

The most common adverse reactions are:
- Crohn’s Disease, induction (≥3%): vomiting.
- Crohn’s Disease, maintenance (≥3%): nasopharyngitis, injection site erythema, vulvovaginal candidiasis/mycotic infection, bronchitis, pruritus, urinary tract infection, and sinusitis.

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. Dr. K.J. Lee also reviewed this BLA submission for major cardiovascular events (MACE), which were observed in the trials for psoriasis. MACE events are defined as cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. The reviewer did not find conclusive evidence to establish causality of MACE to ustekinumab in this submission.

Infections
In patients with Crohn’s disease, serious or other clinically significant infections included anal abscess, gastroenteritis, and pneumonia. In addition, listeria meningitis and ophthalmic herpes were reported in one patient each.

Malignancies
With up to one year of treatment in the Crohn’s disease clinical studies, 0.2% of ustekinumab treated patients (0.36 events per hundred patient-years) and 0.2% of placebo treated patients (0.58 events per hundred patient-years) developed non-melanoma skin cancer. Malignancies other than non-melanoma skin cancers occurred in 0.2% of ustekinumab treated patients (0.27 events per hundred patient-years) and in none of the placebo treated patients.
Hypersensitivity Reactions Including Anaphylaxis
In CD studies, two patients reported hypersensitivity reactions following ustekinumab administration. One patient experienced signs and symptoms consistent with anaphylaxis (tightness of the throat, shortness of breath, and flushing) after a single subcutaneous administration (0.1% of patients receiving subcutaneous ustekinumab). In addition, one patient experienced signs and symptoms consistent with or related to a hypersensitivity reaction (chest discomfort, flushing, urticaria, and increased body temperature) after the initial intravenous ustekinumab dose (0.08% of patients receiving intravenous ustekinumab). These patients were treated with oral antihistamines or corticosteroids and in both cases symptoms resolved within an hour.

Reversible Posterior Leukoencephalopathy Syndrome
Although Reversible Posterior Leukoencephalopathy Syndrome (RPLS) was reported in psoriasis and psoriatic arthritis patients, it was not observed in any Crohn’s patients receiving ustekinumab in the clinical studies.

No new serious adverse reactions were reported among patients with Crohn’s disease treated with ustekinumab.

Although there was no clear increase in risk for malignancies based on the clinical data in adult Crohn’s disease patients, long term data are necessary to assess this risk. Crohn’s patients may present a different potential risk profile compared to psoriasis or psoriatic arthritis patients based on underlying disease state. In addition, this is the first in class product to treat CD patients, the patients are receiving an intravenous dose of ustekinumab, not approved previously, and the chronic dosing is higher than that recommended previously. For these reasons, the clinical team along with the Division of Epidemiology is requiring a PMR be conducted to assess the risk of malignancies as well as opportunistic infections among Crohn’s disease patients. Additionally, and for similar reasons, opportunistic infections will be studied in the PMR. (see section 13).

Risk Evaluation and Mitigation Strategy (REMS)
Ustekinumab was initially approved for the treatment of moderate to severe plaque psoriasis in September 2009 and for the treatment of psoriatic arthritis in September 2013 with a communication plan only REMS. The goal of the approved REMS is to mitigate the potential risks of serious infections, malignancy, and RPLS by informing prescribers of these risks. The safety profile of ustekinumab for Crohn’s disease was found to be similar to the approved indications of psoriasis and psoriatic arthritis.

There were no observed cases of RPLS observed in the clinical trials for ustekinumab in the Crohn’s disease trials and the warning for immunosuppression and RPLS will continue to be communicated through professional labeling.

In addition, gastroenterologists were part of the targeted outreach during the communication plan REMS for the psoriasis and psoriatic arthritis indication of ustekinumab. Usetekinumab was approved in 2009, and while the risks inherent to the drug have not changed, the strategies
required to mitigate the risks are different due to the differences stated above. A REMS modification is not necessary to ensure the benefits outweigh the risks for the proposed indication for moderate to severe Crohn’s disease.

Therefore, at this time, DRISK is not recommending a modification to the Stelara REMS. The DGIEP clinical reviewers agreed with this recommendation.

*I am in agreement with this recommendation. I am also in agreement with the clinical review team regarding the safety findings of ustekinumab for the treatment of adult Crohn’s disease.*

### 9. Advisory Committee Meeting

This application was not taken to an Advisory Committee as it is currently approved for Psoriasis and Psoriatic Arthritis, and there were no safety or efficacy matters which needed to be referred to the committee for further discussion.

### 10. Pediatrics

The Agency is in agreement with the initial Pediatric Study Plan (iPSP) dated November 19, 2015. Orphan designation was granted on May 18, 2016; therefore, Pediatric Research and Equity Act (PREA) will not apply.

Upon review of the overall pediatric development of Stelara for pediatric Crohn’s disease it was determined that pediatric studies should be waived in patients 0 to 2 years of age because studies are impossible or highly impracticable due to the low incidence of disease in this age group. However the Pediatric Review Committee (PeRC) agrees with the Division’s recommendation to defer pediatric trials in patients 2 to 17 year of age because the product is ready for approval in adults. Therefore, pediatric studies were listed as post-marketing commitments in the approval letter and are listed below.

### 11. Other Relevant Regulatory Issues

- **Office of Scientific Investigation** inspected six clinical investigator sites and two contract research organizations, those responsible for the collection of data from the endoscopy sub-study and histology study.
  - 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.

- Inspection of [b][4], the CRO responsible for the readings of the histology samples, confirmed that the histology study was designed as an exploratory study. The results of the study were not used in calculation of the primary efficacy outcome. The procedures agreed upon by the CRO and the sponsor was adhered to; however security controls do not appear adequate to meet standards to ensure data reliability. Although there is no evidence of tampering with data or misconduct by the CRO, without adequate controls for data integrity, OSI cannot assure data integrity of the data generated by this CRO. The sponsor acknowledged these issues and is working to implement controls in future trials. [b][4]

The reviewers concluded that “No violations were cited at inspection of any sties and all final classifications were ‘No Action Indicated’.” Therefore, the clinical data in the clinical trials is acceptable for use in regulatory determinations.

- Financial Disclosures were provided by the applicant, it was concluded that these disclosures had no effect on the outcome of the trials, or the integrity of the data.

- DMEPA worked with the review team during labeling negotiations and is agreeable with the final approved version. It was important that the new 130 mg/26 mL (5 mg/mL) IV infusion product carton be clearly labeled to avoid any confusion with the 45 mg/0.5 mL vial which is to be used for subcutaneous injection. The carton and containers for this new product are clearly marked “For Intravenous Infusion Only”. Office of Biotechnology Products reviewed the final product labeling and found it acceptable (Jibril Abdus-Samad, 9/22/2016).

There are no other unresolved relevant regulatory issues

12. Labeling
- Proprietary name DMEPA reviewed the name and it was found acceptable.
- Carton and immediate container labels cleared by OBP 9/22/2016.
- Physician labeling

Section 1: Indications and Usage

As noted above we are approving a more generalized statement, “the treatment of Crohn’s disease”.

Reference ID: 3990231
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” A general indication statement (e.g., “treatment”) may not be applicable to all future applications.”

I agree with the approach and rationale outlined above.

Section 2: Dosage and Administration
Updated data for dosing in adult Crohn’s disease

Section 5: Warnings and Precautions
Updated to include information on infections, that were observed during the phase 3 clinical trials in Crohn’s disease

Section 6: Adverse Reactions
Updated to include Crohn’s specific data
Section 8: Use in Specific Populations
The Pregnancy and Lactation subsections of labeling were structured to be consistent with the PLLR, as follows:

- 8.1 Pregnancy
  - The “Pregnancy” subsection of Stelara labeling was formatted in the PLLR format to include “Pregnancy Exposure Registry,” “Risk Summary,” and “Data” sections.

- 8.2 Lactation
  - The “Lactation” subsection of Stelara labeling was formatted in the PLLR format to include the “Risk Summary” section.

Therefore, DPMH recommended that the following risk/benefit statement is included in subsection 8.2 of labeling:

“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.”

- 8.3, Females and Males of Reproductive Potential, will not be included in Stelara labeling. Since there are no human data available on the effect of ustekinumab on fertility,

Section 12.3: Pharmacokinetics
In this BLA were the assessment of therapeutic proteins was performed using the BSD-ECLIA assay which is different from the BV-ECLIA assay which was used in BLA 125261. The two assays are not comparable. The information included in the label referring to the CD patients uses the current method [0][4].
The BV-ECLIA method is no longer in use.

Section 14: Clinical Studies
Updated to add data from the Crohn’s clinical trials.

Section 17: PATIENT COUNSELING INFORMATION
Pregnancy Registry
Inform patients that there is a pregnancy registry to monitor fetal outcomes of pregnant women exposed to STELARA [see Use in Specific Populations (8.1)].

Recommendations from the OPQ regarding the following points were incorporated into the labeling: Protect from light, Do not freeze, Do not shake, Product does not contain preservative, Discard any unused portion

Medication Guide
The Medication Guide was updated to include the current approval and reflect the commonly observed adverse reactions in adult Crohn’s disease patients.
13. Decision/Action/Risk Benefit Assessment

- Regulatory Action
  Approval

- Risk Benefit Assessment

Based upon the data reviewed above there is a favorable Benefit Risk balance for the approval of ustekinumab to be used to treat adult patients with moderately to severely active Crohn’s disease. The assessment is based on the following factors which were considered.

**Disease:** 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.

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 with residual, ongoing inflammation, patients may suffer from significant morbidity and/or mortality.

**Current treatment options:** 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. 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.

**Benefit:** 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 (a treatment difference of 13.6% and 20.6% for ustekinumab compared to placebo in studies 3001 and 3002, respectively.). Clinical remission at Week 44 also demonstrated statistical significance in the overall patient population who were in remission at Week 0 of maintenance (a treatment difference of 17.2%), 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.
Risks: 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. No new serious safety signal was identified in the review of this BLA.

Risk Management: Given that a REMS already exists that describes the serious safety risk of RPLS, no additional REMS is needed. In addition, the REMS includes gastroenterologists as a group of practitioners that is to be informed about this risk, no modifications of the REMS are necessary. The risks are also clearly outlined in the professional labeling and the Medication Guide.

- **Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies (REMS)**

Currently there is a communication plan only REMS for Stelara which was issued under BLA12526 for plaque psoriasis and psoriatic arthritis indications. No new serious safety signals were detected in the review of this BLA for Crohn’s disease. DRISK reviewed the current REMS for Stelara. The currently approved labeling for Stelara 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.

*The clinical reviewers and I agree with the DRISK conclusion that the currently approved REMS is adequate, and that the Medication Guide will be updated to include Crohn’s disease information where appropriate.*

- **Recommendation for other Postmarketing Requirements and Commitments**

Post-marketing requirements:
We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a known serious risk of malignancy and a known serious risk of opportunistic infections (such as tuberculosis [TB])

Furthermore, FDA has determined that the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess the known serious risks of malignancy and specific opportunistic infections (such as tuberculosis [TB]).

Therefore, based on appropriate scientific data, FDA has determined that Janssen is required to conduct the following PMR:
• Conduct a long-term, postmarketing, observational study to assess the long-term safety of Stelara (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]). 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.

Post-marketing commitments:
Stelara was granted orphan designation for Pediatric Crohn’s disease on May 18, 2016. As such PREA does not apply. However, the applicant and the DGIEP have agreed that this drug should be developed for Pediatric Crohn’s disease in patients aged 2 to 17 years. As such, these studies are listed as PMCs below.

• Conduct a clinical trial to assess whether Stelara (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).

• 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 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.
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/s/

JOYCE A KORVICK
09/23/2016