CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

761044Orig1s003

Trade Name:	**STELARA**
Generic or Proper Name:	ustekinumab
Sponsor:	Janssen Biotech
Approval Date:	October 18, 2019

Indication:

STELARA® is a human interleukin-12 and -23 antagonist indicated for the treatment of: Adult patients with:

- *moderate to severe plaque psoriasis (Ps)* who are candidates for phototherapy or systemic therapy.
- *active psoriatic arthritis (PsA),* alone or in combination with methotrexate.
- *moderately to severely active Crohn's disease (CD).*
- *moderately to severely active ulcerative colitis.*

Adolescent patients (12 years or older) with:

- *moderate to severe plaque psoriasis*, who are candidates for phototherapy or systemic therapy.

CENTER FOR DRUG EVALUATION AND RESEARCH

761044Orig1s003

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CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER

BLA 761044/S-003
BLA 125261/S-152

SUPPLEMENT APPROVAL

Janssen Biotech, Inc.
Attention: Yulia Pincus, PhD
Associate Director
Welsh and McKean Roads, P.O. Box 776
Spring House, PA 19477

Dear Dr. Pincus:

Please refer to your supplemental Biologics License Application (sBLA) dated December 20, 2018, received December 20, 2018, and your amendments, submitted under section 351(a) of the Public Health Service Act for STELARA (ustekinumab) Injection.

This Prior Approval supplemental biologics license application provides for the addition of the indication of treatment of adults with moderately to severely active ulcerative colitis.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF HIGHLIGHTS ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov,[1] that is identical to the enclosed labeling (text for the Prescribing Information, Instructions for Use, and Medication Guide) and include the labeling changes proposed in any pending “Changes Being Effected” (CBE) supplements.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

SENTINEL/ARIA NOTIFICATION

The Food and Drug Administration Amendments Act of 2007 (FDAAA) required FDA to establish a national electronic system to monitor the safety of FDA-regulated medical products. In fulfillment of this mandate, FDA established the Sentinel System, which enables FDA to proactively monitor drug safety using electronic health data from multiple data sources that contribute to the Sentinel Distributed Database.

FDA plans to evaluate STELARA (ustekinumab) in the Sentinel System as part of the implementation of section 505(o) of the FDCA. We have determined that the new pharmacovigilance system, Sentinel's Active Risk Identification and Analysis (ARIA) System, established under section 505(k)(3) of the FDCA, is sufficient to assess the known serious risk: serious infection.

The ARIA safety assessment will be posted to the Sentinel website at this location: https://www.sentinelinitiative.org. Once there is sufficient product uptake to support an analysis, an analysis plan will be posted online. After the analysis is complete, FDA will also post the results on the Sentinel website. FDA will notify you prior to posting the analysis plan and prior to posting the results.

REQUIRED PEDIATRIC ASSESSMENTS

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

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 the known serious risk of malignancy and the known serious risk of opportunistic infections. Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

3736-1 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 ulcerative colitis. 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.

The ongoing observational study in patients with Crohn's disease with the same objectives, may be amended to also enroll patients with ulcerative colitis.

The timetable you submitted on September 27, 2019 states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	02/2020
Final Protocol Submission:	09/2020
Interim Report:	12/2025
Study Completion:	08/2029
Final Report Submission:	08/2030

Submit the protocol(s) to your IND 124512, with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final report(s) to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Submission of the protocol(s) for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312 or FDA's regulations under 21 CFR parts 50 (Protection of Human Subjects) and 56 (Institutional Review Boards).

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials

required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3736-2 A one-year, randomized, controlled, blinded trial to evaluate the safety, efficacy, and pharmacokinetics of Stelara (ustekinumab) in pediatric patients 2 to 17 years of age with moderately to severely active ulcerative colitis.

The timetable you submitted on September 27, 2019 , states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	05/2020
Trial Completion:	03/2025
Final Report Submission:	09/2025

3736-3 A multi-center, open-label extension study to evaluate the long-term safety of Stelara (ustekinumab) in pediatric patients 2 to 17 years of age with moderately to severely active ulcerative colitis who participated in PMC 3736-2.

The timetable you submitted on October 17, 2019, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	09/2020
Trial Completion:	03/2026
Final Report Submission:	09/2026

3736-4 A clinical trial to assess whether ustekinumab alters the metabolism or pharmacokinetics of cytochrome P450 (CYP) substrates in UC patients treated with ustekinumab (e.g., using a cocktail of relevant CYP probe drugs).

The ongoing trial in patients with Crohn's disease with the same objectives, may be amended to also enroll patients with ulcerative colitis.

The timetable you submitted on October 10, 2019, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	03/2020
Trial Completion:	08/2024
Final Report Submission:	02/2025

Submit clinical protocols to your IND 124512 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the Prescribing Information to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5] For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.[6]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, contact Kelly Richards, Senior Regulatory Health Project Manager, at (240) 402-4276 or kelly.richards@fda.hhs.gov

Sincerely,

{See appended electronic signature page}

Jessica J. Lee, MD, MMSc
Associate Director
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

[3] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[6] http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm

ENCLOSURE(S):

- Content of Labeling
    - Prescribing Information
    - Medication Guide
    - Instructions for Use

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JESSICA J LEE
10/18/2019 02:53:34 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761044Orig1s003

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use STELARA® safely and effectively. See full prescribing information for STELARA®.

STELARA® (ustekinumab) injection, for subcutaneous or intravenous use
Initial U.S. Approval: 2009

----------RECENT MAJOR CHANGES----------

Indications and Usage, Ulcerative Colitis (1.4)	10/2019
Dosage and Administration (2.3)	10/2019
Warnings and Precautions (5.1)	10/2019

----------INDICATIONS AND USAGE----------

STELARA® is a human interleukin-12 and -23 antagonist indicated for the treatment of:

Adult patients with:

- *moderate to severe plaque psoriasis (Ps)* who are candidates for phototherapy or systemic therapy. (1.1)
- *active psoriatic arthritis (PsA),* alone or in combination with methotrexate. (1.2)
- *moderately to severely active Crohn's disease (CD).* (1.3)
- *moderately to severely active ulcerative colitis.* (1.4)

Adolescent patients (12 years or older) with:

- *moderate to severe plaque psoriasis*, who are candidates for phototherapy or systemic therapy. (1.1)

----------DOSAGE AND ADMINISTRATION----------

Psoriasis Adult Subcutaneous Recommended Dosage (2.1):

Weight Range (kilogram)	Dosage Regimen
less than or equal to 100 kg	45 mg administered subcutaneously initially and 4 weeks later, followed by 45 mg administered subcutaneously every 12 weeks
greater than 100 kg	90 mg administered subcutaneously initially and 4 weeks later, followed by 90 mg administered subcutaneously every 12 weeks

Psoriasis Adolescent (12 years and older) Subcutaneous Recommended Dosage (2.1): Weight based dosing is recommended at the initial dose, 4 weeks later, then every 12 weeks thereafter.

Weight Range (kilogram)	Dosage Regimen
less than 60 kg	0.75 mg/kg
60 kg to 100 kg	45 mg
greater than 100 kg	90 mg

Psoriatic Arthritis Adult Subcutaneous Recommended Dosage (2.2):

- The recommended dosage is 45 mg administered subcutaneously initially and 4 weeks later, followed by 45 mg administered subcutaneously every 12 weeks.
- For patients with co-existent moderate-to-severe plaque psoriasis weighing greater than 100 kg, the recommended dosage is 90 mg administered subcutaneously initially and 4 weeks later, followed by 90 mg administered subcutaneously every 12 weeks.

Crohn's Disease and Ulcerative Colitis Initial Adult Intravenous Recommended Dosage (2.3): A single intravenous infusion using weight-based dosing:

Weight Range (kilogram)	Recommended Dosage
up to 55 kg	260 mg (2 vials)
greater than 55 kg to 85 kg	390 mg (3 vials)
greater than 85 kg	520 mg (4 vials)

Crohn's Disease and Ulcerative Colitis Maintenance Adult Subcutaneous Recommended Dosage (2.3): A subcutaneous 90 mg dose 8 weeks after the initial intravenous dose, then every 8 weeks thereafter.

----------DOSAGE FORMS AND STRENGTHS----------

Subcutaneous Injection (3)

- Injection: 45 mg/0.5 mL or 90 mg/mL in a single-dose prefilled syringe
- Injection: 45 mg/0.5 mL in a single-dose vial

Intravenous Infusion (3)

- Injection: 130 mg/26 mL (5 mg/mL) solution in a single-dose vial (3)

----------CONTRAINDICATIONS----------

Clinically significant hypersensitivity to ustekinumab or to any of the excipients. (4)

----------WARNINGS AND PRECAUTIONS----------

- Infections: Serious infections have occurred. Do not start STELARA® during any clinically important active infection. If a serious infection or clinically significant infection develops, consider discontinuing STELARA® until the infection resolves. (5.1)
- Theoretical Risk for Particular Infections: Serious infections from mycobacteria, salmonella and Bacillus Calmette-Guerin (BCG) vaccinations have been reported in patients genetically deficient in IL-12/IL-23. Diagnostic tests for these infections should be considered as dictated by clinical circumstances. (5.2)
- Tuberculosis (TB): Evaluate patients for TB prior to initiating treatment with STELARA®. Initiate treatment of latent TB before administering STELARA®. (5.3)
- Malignancies: STELARA® may increase risk of malignancy. The safety of STELARA® in patients with a history of or a known malignancy has not been evaluated. (5.4)
- Hypersensitivity Reactions: Anaphylaxis or other clinically significant hypersensitivity reactions may occur. (5.5)
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS): One case was reported. If suspected, treat promptly and discontinue STELARA®. (5.6)
- Noninfectious Pneumonia: Cases of interstitial pneumonia, eosinophilic pneumonia and cryptogenic organizing pneumonia have been reported during post-approval use of STELARA®. If diagnosis is confirmed, discontinue STELARA® and institute appropriate treatment. (5.9)

----------ADVERSE REACTIONS----------

Most common adverse reactions are:

- Psoriasis (≥3%): nasopharyngitis, upper respiratory tract infection, headache, and fatigue. (6.1)
- Crohn's Disease, induction (≥3%): vomiting. (6.1)
- Crohn's Disease, maintenance (≥3%): nasopharyngitis, injection site erythema, vulvovaginal candidiasis/mycotic infection, bronchitis, pruritus, urinary tract infection, and sinusitis. (6.1)
- Ulcerative colitis, induction (≥3%): nasopharyngitis (6.1)
- Ulcerative colitis, maintenance (≥3%): nasopharyngitis, headache, abdominal pain, influenza, fever, diarrhea, sinusitis, fatigue, and nausea (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Biotech, Inc. at 1-800-JANSSEN (1-800-526-7736) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Psoriasis (Ps)

STELARA® is indicated for the treatment of patients 12 years or older with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

1.2 Psoriatic Arthritis (PsA)

STELARA® is indicated for the treatment of adult patients with active psoriatic arthritis. STELARA® can be used alone or in combination with methotrexate (MTX).

1.3 Crohn's Disease (CD)

STELARA® is indicated for the treatment of adult patients with moderately to severely active Crohn's disease.

1.4 Ulcerative Colitis

STELARA® is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis.

2 DOSAGE AND ADMINISTRATION

2.1 Psoriasis

Subcutaneous Adult Dosage Regimen

- For patients weighing 100 kg or less, the recommended dose is 45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks.
- For patients weighing more than 100 kg, the recommended dose is 90 mg initially and 4 weeks later, followed by 90 mg every 12 weeks.

In subjects weighing more than 100 kg, 45 mg was also shown to be efficacious. However, 90 mg resulted in greater efficacy in these subjects *[see Clinical Studies (14)]*.

Subcutaneous Adolescent Dosage Regimen

Administer STELARA® subcutaneously at Weeks 0 and 4, then every 12 weeks thereafter.

The recommended dose of STELARA® for adolescents (12-17 years old) based on body weight is shown below (Table 1).

Table 1: Recommended Dose of STELARA® for Subcutaneous Injection in Adolescent Patients with Psoriasis

Body Weight of Patient at the Time of Dosing	Recommended Dose
less than 60 kg	0.75 mg/kg
60 kg to 100 kg	45 mg
more than 100 kg	90 mg

For adolescent patients weighing less than 60 kg, the administration volume for the recommended dose (0.75 mg/kg) is shown in Table 2; withdraw the appropriate volume from the single-dose vial.

Table 2: Injection volumes of STELARA® 45 mg/0.5mL single-dose vials for adolescent psoriasis patients less than 60 kg

Body Weight (kg) at the time of dosing	Dose (mg)	Volume of injection (mL)
30	22.5	0.25
31	23.3	0.26
32	24	0.27
33	24.8	0.27
34	25.5	0.28
35	26.3	0.29
36	27	0.3
37	27.8	0.31
38	28.5	0.32
39	29.3	0.32
40	30	0.33
41	30.8	0.34
42	31.5	0.35
43	32.3	0.36
44	33	0.37
45	33.8	0.37
46	34.5	0.38
47	35.3	0.39
48	36	0.4
49	36.8	0.41
50	37.5	0.42
51	38.3	0.42
52	39	0.43
53	39.8	0.44
54	40.5	0.45
55	41.3	0.46
56	42	0.46
57	42.8	0.47
58	43.5	0.48
59	44.3	0.49

2.2 Psoriatic Arthritis

Subcutaneous Adult Dosage Regimen

- The recommended dose is 45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks.
- For patients with co-existent moderate-to-severe plaque psoriasis weighing more than 100 kg, the recommended dose is 90 mg initially and 4 weeks later, followed by 90 mg every 12 weeks.

2.3 Crohn's Disease and Ulcerative Colitis

Intravenous Induction Adult Dosage Regimen

A single intravenous infusion dose of STELARA® using the weight-based dosage regimen specified in Table 3 *[see Instructions for dilution of STELARA® 130 mg vial for intravenous infusion (2.6)]*.

Table 3: Initial Intravenous Dosage of STELARA®

Body Weight of Patient at the time of dosing	Dose	Number of 130 mg/26 mL (5 mg/mL) STELARA® vials
55 kg or less	260 mg	2
more than 55 kg to 85 kg	390 mg	3
more than 85 kg	520 mg	4

Subcutaneous Maintenance Adult Dosage Regimen

The recommended maintenance dosage is a subcutaneous 90 mg dose administered 8 weeks after the initial intravenous dose, then every 8 weeks thereafter.

2.4 General Considerations for Administration

- STELARA® is intended for use under the guidance and supervision of a physician. STELARA® should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician. The appropriate dose should be determined by a healthcare provider using the patient's current weight at the time of dosing. In adolescent patients, it is recommended that STELARA® be administered by a health care provider. If a physician determines that it is appropriate, a patient may self-inject or a caregiver may inject STELARA® after proper training in subcutaneous injection technique. Patients should be instructed to follow the directions provided in the Medication Guide *[see Medication Guide]*.
- The needle cover on the prefilled syringe contains dry natural rubber (a derivative of latex). The needle cover should not be handled by persons sensitive to latex.
- It is recommended that each injection be administered at a different anatomic location (such as upper arms, gluteal regions, thighs, or any quadrant of abdomen) than the previous injection, and not into areas where the skin is tender, bruised, erythematous, or indurated.

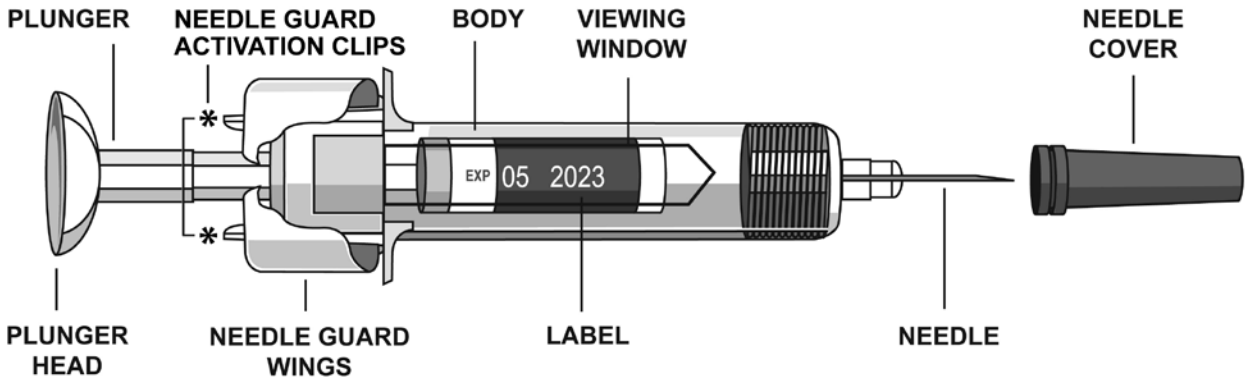
When using the single-dose vial, a 1 mL syringe with a 27 gauge, ½ inch needle is recommended.

- Prior to administration, visually inspect STELARA® for particulate matter and discoloration. STELARA® is a colorless to light yellow solution and may contain a few small translucent or white particles. Do not use STELARA® if it is discolored or cloudy, or if other particulate matter is present. STELARA® does not contain preservatives; therefore, discard any unused product remaining in the vial and/or syringe.

2.5 Instructions for Administration of STELARA® Prefilled Syringes Equipped with Needle Safety Guard

Refer to the diagram below for the provided instructions.

To prevent premature activation of the needle safety guard, do not touch the NEEDLE GUARD ACTIVATION CLIPS at any time during use.

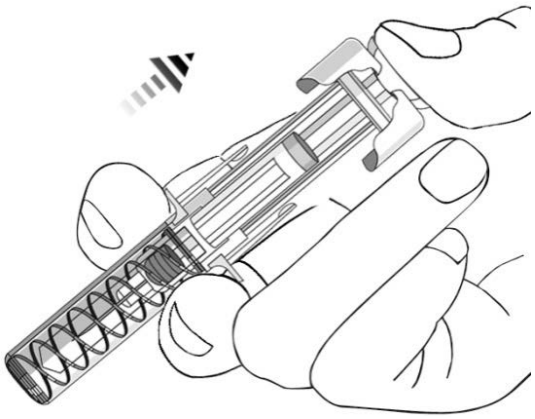


- Hold the BODY and remove the NEEDLE COVER. **Do not hold the PLUNGER or PLUNGER HEAD while removing the NEEDLE COVER or the PLUNGER may move. Do not use the prefilled syringe if it is dropped without the NEEDLE COVER in place**.

- Inject STELARA® subcutaneously as recommended *[see Dosage and Administration (2.1, 2.2, 2.3)]*.

- Inject all of the medication by pushing in the PLUNGER until the PLUNGER HEAD is completely between the needle guard wings. **Injection of the entire prefilled syringe contents is necessary to activate the needle guard**.

- After injection, maintain the pressure on the PLUNGER HEAD and remove the needle from the skin. Slowly take your thumb off the PLUNGER HEAD to allow the empty syringe to move up until the entire needle is covered by the needle guard, as shown by the illustration below:



- Used syringes should be placed in a puncture-resistant container.

2.6 Preparation and Administration of STELARA® 130 mg/26 mL (5 mg/mL) Vial for Intravenous Infusion (Crohn's Disease and Ulcerative Colitis)

STELARA® solution for intravenous infusion must be diluted, prepared and infused by a healthcare professional using aseptic technique.

1. Calculate the dose and the number of STELARA® vials needed based on patient weight (Table 3). Each 26 mL vial of STELARA® contains 130 mg of ustekinumab.

2. Withdraw, and then discard a volume of the 0.9% Sodium Chloride Injection, USP from the 250 mL infusion bag equal to the volume of STELARA® to be added (discard 26 mL sodium chloride for each vial of STELARA® needed, for 2 vials- discard 52 mL, for 3 vials- discard 78 mL, 4 vials- discard 104 mL).

3. Withdraw 26 mL of STELARA® from each vial needed and add it to the 250 mL infusion bag. The final volume in the infusion bag should be 250 mL. Gently mix.

4. Visually inspect the diluted solution before infusion. Do not use if visibly opaque particles, discoloration or foreign particles are observed.

5. Infuse the diluted solution over a period of at least one hour. Once diluted, the infusion solution may be stored for up to four hours prior to infusion.

6. Use only an infusion set with an in-line, sterile, non-pyrogenic, low protein-binding filter (pore size 0.2 micrometer).

7. Do not infuse STELARA® concomitantly in the same intravenous line with other agents.

8. STELARA® does not contain preservatives. Each vial is for single use only. Discard any remaining solution. Dispose any unused medicinal product in accordance with local requirements.

Storage

If necessary, the diluted infusion solution may be stored for up to 4 hours at room temperature up to 25°C (77°F). Do not freeze. Discard any unused portion of the infusion solution.

3 DOSAGE FORMS AND STRENGTHS

STELARA® (ustekinumab) is a colorless to light yellow solution and may contain a few small translucent or white particles.

Subcutaneous Injection

- Injection: 45 mg/0.5 mL or 90 mg/mL solution in a single-dose prefilled syringe
- Injection: 45 mg/0.5 mL solution in a single-dose vial

Intravenous Infusion

- Injection: 130 mg/26 mL (5 mg/mL) solution in a single-dose vial

4 CONTRAINDICATIONS

STELARA® is contraindicated in patients with clinically significant hypersensitivity to ustekinumab or to any of the excipients *[see Warnings and Precautions (5.5)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Infections

STELARA® may increase the risk of infections and reactivation of latent infections. Serious bacterial, fungal, and viral infections were observed in subjects receiving STELARA® *[see Adverse Reactions (6.1)]*.

Serious infections requiring hospitalization, or otherwise clinically significant infections, reported in clinical studies included the following:

- *Psoriasis*: diverticulitis, cellulitis, pneumonia, appendicitis, cholecystitis, sepsis, osteomyelitis, viral infections, gastroenteritis and urinary tract infections.
- *Psoriatic arthritis*: cholecystitis.
- *Crohn's disease*: anal abscess, gastroenteritis, ophthalmic herpes zoster, pneumonia, and listeria meningitis.
- *Ulcerative colitis*: gastroenteritis, ophthalmic herpes zoster, pneumonia, and listeriosis.

Treatment with STELARA® should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated. Consider the risks and benefits of treatment prior to initiating use of STELARA® in patients with a chronic infection or a history of recurrent infection.

Instruct patients to seek medical advice if signs or symptoms suggestive of an infection occur while on treatment with STELARA® and consider discontinuing STELARA® for serious or clinically significant infections until the infection resolves or is adequately treated.

5.2 Theoretical Risk for Vulnerability to Particular Infections

Individuals genetically deficient in IL-12/IL-23 are particularly vulnerable to disseminated infections from mycobacteria (including nontuberculous, environmental mycobacteria), salmonella (including nontyphi strains), and Bacillus Calmette-Guerin (BCG) vaccinations. Serious infections and fatal outcomes have been reported in such patients.

It is not known whether patients with pharmacologic blockade of IL-12/IL-23 from treatment with STELARA® may be susceptible to these types of infections. Appropriate diagnostic testing should be considered, e.g., tissue culture, stool culture, as dictated by clinical circumstances.

5.3 Pre-treatment Evaluation for Tuberculosis

Evaluate patients for tuberculosis infection prior to initiating treatment with STELARA®.

Do not administer STELARA® to patients with active tuberculosis infection. Initiate treatment of latent tuberculosis prior to administering STELARA®. Consider anti-tuberculosis therapy prior to initiation of STELARA® in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. Closely monitor patients receiving STELARA® for signs and symptoms of active tuberculosis during and after treatment.

5.4 Malignancies

STELARA® is an immunosuppressant and may increase the risk of malignancy. Malignancies were reported among subjects who received STELARA® in clinical studies *[see Adverse Reactions (6.1)]*. In rodent models, inhibition of IL-12/IL-23p40 increased the risk of malignancy *[see Nonclinical Toxicology (13)]*.

The safety of STELARA® has not been evaluated in patients who have a history of malignancy or who have a known malignancy.

There have been post-marketing reports of the rapid appearance of multiple cutaneous squamous cell carcinomas in patients receiving STELARA® who had pre-existing risk factors for developing non-melanoma skin cancer. All patients receiving STELARA® should be monitored for the appearance of non-melanoma skin cancer. Patients greater than 60 years of age, those with a medical history of prolonged immunosuppressant therapy and those with a history of PUVA treatment should be followed closely *[see Adverse Reactions (6.1)]*.

5.5 Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis and angioedema, have been reported with STELARA® *[see Adverse Reactions (6.1, 6.3)]*. If an anaphylactic or other clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue STELARA®.

5.6 Reversible Posterior Leukoencephalopathy Syndrome

One case of reversible posterior leukoencephalopathy syndrome (RPLS) was observed in clinical studies of psoriasis and psoriatic arthritis. The subject, who had received 12 doses of STELARA® over approximately two years, presented with headache, seizures and confusion. No additional STELARA® injections were administered and the subject fully recovered with appropriate treatment. No cases of RPLS were observed in clinical studies of Crohn's disease or ulcerative colitis.

RPLS is a neurological disorder, which is not caused by demyelination or a known infectious agent. RPLS can present with headache, seizures, confusion and visual disturbances. Conditions with which it has been associated include preeclampsia, eclampsia, acute hypertension, cytotoxic agents and immunosuppressive therapy. Fatal outcomes have been reported.

If RPLS is suspected, administer appropriate treatment and discontinue STELARA®.

5.7 Immunizations

Prior to initiating therapy with STELARA®, patients should receive all age-appropriate immunizations as recommended by current immunization guidelines. Patients being treated with STELARA® should not receive live vaccines. BCG vaccines should not be given during treatment with STELARA® or for one year prior to initiating treatment or one year following discontinuation of treatment. Caution is advised when administering live vaccines to household contacts of patients receiving STELARA® because of the potential risk for shedding from the household contact and transmission to patient.

Non-live vaccinations received during a course of STELARA® may not elicit an immune response sufficient to prevent disease.

5.8 Concomitant Therapies

In clinical studies of psoriasis the safety of STELARA® in combination with other immunosuppressive agents or phototherapy was not evaluated. Ultraviolet-induced skin cancers

developed earlier and more frequently in mice genetically manipulated to be deficient in both IL-12 and IL-23 or IL-12 alone *[see Nonclinical Toxicology (13.1)]*.

5.9 Noninfectious Pneumonia

Cases of interstitial pneumonia, eosinophilic pneumonia and cryptogenic organizing pneumonia have been reported during post-approval use of STELARA®. Clinical presentations included cough, dyspnea, and interstitial infiltrates following one to three doses. Serious outcomes have included respiratory failure and prolonged hospitalization. Patients improved with discontinuation of therapy and in certain cases administration of corticosteroids. If diagnosis is confirmed, discontinue STELARA® and institute appropriate treatment *[see Postmarketing Experience (6.3)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the label:

- Infections *[see Warnings and Precautions (5.1)]*
- Malignancies *[see Warnings and Precautions (5.4)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.5)]*
- Reversible Posterior Leukoencephalopathy Syndrome *[see Warnings and Precautions (5.6)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adult Subjects with Plaque Psoriasis

The safety data reflect exposure to STELARA® in 3117 adult psoriasis subjects, including 2414 exposed for at least 6 months, 1855 exposed for at least one year, 1653 exposed for at least two years, 1569 exposed for at least three years, 1482 exposed for at least four years and 838 exposed for at least five years.

Table 4 summarizes the adverse reactions that occurred at a rate of at least 1% and at a higher rate in the STELARA® groups than the placebo group during the placebo-controlled period of Ps STUDY 1 and Ps STUDY 2 *[see Clinical Studies (14)]*.

Table 4: Adverse Reactions Reported by ≥1% of Subjects through Week 12 in Ps STUDY 1 and Ps STUDY 2

		STELARA®	
	Placebo	**45 mg**	**90 mg**
Subjects treated	**665**	**664**	**666**
Nasopharyngitis	51 (8%)	56 (8%)	49 (7%)
Upper respiratory tract infection	30 (5%)	36 (5%)	28 (4%)
Headache	23 (3%)	33 (5%)	32 (5%)
Fatigue	14 (2%)	18 (3%)	17 (3%)

Diarrhea	12 (2%)	13 (2%)	13 (2%)
Back pain	8 (1%)	9 (1%)	14 (2%)
Dizziness	8 (1%)	8 (1%)	14 (2%)
Pharyngolaryngeal pain	7 (1%)	9 (1%)	12 (2%)
Pruritus	9 (1%)	10 (2%)	9 (1%)
Injection site erythema	3 (<1%)	6 (1%)	13 (2%)
Myalgia	4 (1%)	7 (1%)	8 (1%)
Depression	3 (<1%)	8 (1%)	4 (1%)

Adverse reactions that occurred at rates less than 1% in the controlled period of Ps STUDIES 1 and 2 through week 12 included: cellulitis, herpes zoster, diverticulitis and certain injection site reactions (pain, swelling, pruritus, induration, hemorrhage, bruising, and irritation).

One case of RPLS occurred during clinical studies *[see Warnings and Precautions (5.6)]*.

Infections

In the placebo-controlled period of clinical studies of psoriasis subjects (average follow-up of 12.6 weeks for placebo-treated subjects and 13.4 weeks for STELARA®-treated subjects), 27% of STELARA®-treated subjects reported infections (1.39 per subject-year of follow-up) compared with 24% of placebo-treated subjects (1.21 per subject-year of follow-up). Serious infections occurred in 0.3% of STELARA®-treated subjects (0.01 per subject-year of follow-up) and in 0.4% of placebo-treated subjects (0.02 per subject-year of follow-up) *[see Warnings and Precautions (5.1)]*.

In the controlled and non-controlled portions of psoriasis clinical studies (median follow-up of 3.2 years), representing 8998 subject-years of exposure, 72.3% of STELARA®-treated subjects reported infections (0.87 per subject-years of follow-up). Serious infections were reported in 2.8% of subjects (0.01 per subject-years of follow-up).

Malignancies

In the controlled and non-controlled portions of psoriasis clinical studies (median follow-up of 3.2 years, representing 8998 subject-years of exposure), 1.7% of STELARA®-treated subjects reported malignancies excluding non-melanoma skin cancers (0.60 per hundred subject-years of follow-up). Non-melanoma skin cancer was reported in 1.5% of STELARA®-treated subjects (0.52 per hundred subject-years of follow-up) *[see Warnings and Precautions (5.4)]*. The most frequently observed malignancies other than non-melanoma skin cancer during the clinical studies were: prostate, melanoma, colorectal and breast. Malignancies other than non-melanoma skin cancer in STELARA®-treated patients during the controlled and uncontrolled portions of studies were similar in type and number to what would be expected in the general U.S. population according to the SEER database (adjusted for age, gender and race).[1]

Adolescent Subjects with Plaque Psoriasis

The safety of STELARA® was assessed in a study of 110 subjects 12 to 17 years of age with moderate to severe plaque psoriasis. The safety profile in these subjects through Week 60 was similar to the safety profile from studies in adults with plaque psoriasis.

Psoriatic Arthritis

The safety of STELARA® was assessed in 927 patients in two randomized, double-blind, placebo-controlled studies in adult patients with active psoriatic arthritis (PsA). The overall safety profile of STELARA® in patients with PsA was consistent with the safety profile seen in adult psoriasis clinical studies. A higher incidence of arthralgia, nausea, and dental infections was observed in STELARA®-treated patients when compared with placebo-treated patients (3% vs. 1% for arthralgia and 3% vs. 1% for nausea; 1% vs. 0.6% for dental infections) in the placebo-controlled portions of the PsA clinical studies.

Crohn's Disease

The safety of STELARA® 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 patients who received a prior investigational intravenous ustekinumab formulation but were not included in the efficacy analyses. In Studies CD-1 and CD-2 there were 470 patients who received STELARA® 6 mg/kg as a weight-based single intravenous induction dose and 466 who received placebo *[see Dosage and Administration (2.3)]*. Patients who were responders in either Study CD-1 or CD-2 were randomized to receive a subcutaneous maintenance regimen of either 90 mg STELARA® every 8 weeks, or placebo for 44 weeks in Study CD-3. Patients in these 3 studies may have received other concomitant therapies including aminosalicylates, immunomodulatory agents [azathioprine (AZA), 6-mercaptopurine (6-MP), MTX], oral corticosteroids (prednisone or budesonide), and/or antibiotics for their Crohn's disease *[see Clinical Studies (14.4)]*.

The overall safety profile of STELARA® was consistent with the safety profile seen in the adult psoriasis and psoriatic arthritis clinical studies. Common adverse reactions in Studies CD-1 and CD-2 and in Study CD-3 are listed in Tables 5 and 6, respectively.

Table 5: Common adverse reactions through Week 8 in Studies CD-1 and CD-2 occurring in ≥3% of STELARA®-treated patients and higher than placebo

	Placebo N=466	**STELARA® 6 mg/kg single intravenous induction dose N=470**
Vomiting	3%	4%

Other less common adverse reactions reported in patients in Studies CD-1 and CD-2 included asthenia (1% vs 0.4%), acne (1% vs 0.4%), and pruritus (2% vs 0.4%).

Table 6: Common adverse reactions through Week 44 in Study CD-3 occurring in ≥3% of STELARA®-treated patients and higher than placebo

	Placebo N=133	**STELARA® 90 mg subcutaneous maintenance dose every 8 weeks N=131**
Nasopharyngitis	8%	11%
Injection site erythema	0	5%

Vulvovaginal candidiasis/mycotic infection	1%	5%
Bronchitis	3%	5%
Pruritus	2%	4%
Urinary tract infection	2%	4%
Sinusitis	2%	3%

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 zoster were reported in one patient each *[see Warnings and Precautions (5.1)]*.

Malignancies

With up to one year of treatment in the Crohn's disease clinical studies, 0.2% of STELARA®-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 STELARA®-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 STELARA® 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 STELARA®). 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 STELARA® dose (0.08% of patients receiving intravenous STELARA®). These patients were treated with oral antihistamines or corticosteroids and in both cases symptoms resolved within an hour.

Ulcerative Colitis

The safety of STELARA® was evaluated in two randomized, double-blind, placebo-controlled clinical studies (UC-1 [IV induction] and UC-2 [SC maintenance]) in 960 adult patients with moderately to severely active ulcerative colitis *[see Clinical Studies (14.5)]*. The overall safety profile of STELARA® in patients with ulcerative colitis was consistent with the safety profile seen across all approved indications. Adverse reactions reported in at least 3% of STELARA®-treated patients and at a higher rate than placebo were:

- Induction (UC-1): nasopharyngitis (7% vs 4%).
- Maintenance (UC-2): nasopharyngitis (24% vs 20%), headache (10% vs 4%), abdominal pain (7% vs 3%), influenza (6% vs 5%), fever (5% vs. 4%), diarrhea (4% vs 1%), sinusitis (4% vs 1%), fatigue (4% vs 2%), and nausea (3% vs 2%).

Infections

In patients with ulcerative colitis, serious or other clinically significant infections included gastroenteritis and pneumonia. In addition, listeriosis and ophthalmic herpes zoster were reported in one patient each *[see Warnings and Precautions (5.1)]*.

Malignancies

With up to one year of treatment in the ulcerative colitis clinical studies, 0.4% of STELARA®-treated patients (0.48 events per hundred patient-years) and 0.0% of placebo-treated patients (0.00 events per hundred patient-years) developed non-melanoma skin cancer. Malignancies other than non-melanoma skin cancers occurred in 0.5% of STELARA®-treated patients (0.64 events per hundred patient-years) and 0.2% of placebo-treated patients (0.40 events per hundred patient-years).

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of the incidence of antibodies to ustekinumab in the studies described below with the incidence of antibodies to other products may be misleading.

Approximately 6 to 12.4% of subjects treated with STELARA® in psoriasis and psoriatic arthritis clinical studies developed antibodies to ustekinumab, which were generally low-titer. In psoriasis clinical studies, antibodies to ustekinumab were associated with reduced or undetectable serum ustekinumab concentrations and reduced efficacy. In psoriasis studies, the majority of patients who were positive for antibodies to ustekinumab had neutralizing antibodies.

In Crohn's disease and ulcerative colitis clinical studies, 2.9% and 4.6% of patients, respectively, developed antibodies to ustekinumab when treated with STELARA® for approximately one year. No apparent association between the development of antibodies to ustekinumab and the development of injection site reactions was seen.

6.3 Postmarketing Experience

The following adverse reactions have been reported during post-approval of STELARA®. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to STELARA® exposure.

Immune system disorders: Serious hypersensitivity reactions (including anaphylaxis and angioedema), other hypersensitivity reactions (including rash and urticaria) *[see Warnings and Precautions (5.5)]*.

Respiratory, thoracic and mediastinal disorders: Interstitial pneumonia, eosinophilic pneumonia and cryptogenic organizing pneumonia *[see Warnings and Precautions (5.9)]*.

Skin reactions: Pustular psoriasis, erythrodermic psoriasis.

7 DRUG INTERACTIONS

7.1 Live Vaccines

Avoid use of live vaccines with STELARA® *[see Warnings and Precautions (5.7)]*.

7.2 Concomitant Therapies

In psoriasis studies the safety of STELARA® in combination with immunosuppressive agents or phototherapy has not been evaluated *[see Warnings and Precautions (5.8)]*. In psoriatic arthritis studies, concomitant MTX use did not appear to influence the safety or efficacy of STELARA®. In Crohn's disease and ulcerative colitis induction studies, immunomodulators (6-MP, AZA, MTX) were used concomitantly in approximately 30% of patients and corticosteroids were used concomitantly in approximately 40% and 50% of Crohn's disease and ulcerative colitis patients, respectively. Use of these concomitant therapies did not appear to influence the overall safety or efficacy of STELARA®.

7.3 CYP450 Substrates

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, STELARA®, an antagonist of IL-12 and IL-23, could normalize the formation of CYP450 enzymes. Upon initiation of STELARA® 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 *[see Clinical Pharmacology (12.3)]*.

7.4 Allergen Immunotherapy

STELARA® has not been evaluated in patients who have undergone allergy immunotherapy. STELARA® may decrease the protective effect of allergen immunotherapy (decrease tolerance) which may increase the risk of an allergic reaction to a dose of allergen immunotherapy. Therefore, caution should be exercised in patients receiving or who have received allergen immunotherapy, particularly for anaphylaxis.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy registry that monitors pregnancy outcomes in women exposed to STELARA® during pregnancy. Patients should be encouraged to enroll by calling 1-877-311-8972.

Risk Summary

Limited data on the use of STELARA® in pregnant women are insufficient to inform a drug associated risk *[see Data]*. In animal reproductive and developmental toxicity studies, no adverse developmental effects were observed after administration of ustekinumab to pregnant monkeys at

exposures greater than 100 times the human exposure at the maximum recommended human subcutaneous dose (MRHD).

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated population(s) are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage of clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Human Data

Limited data on use of STELARA® in pregnant women from observational studies, published case reports, and postmarketing surveillance are insufficient to inform a drug associated risk.

Animal Data

Ustekinumab was tested in two embryo-fetal development toxicity studies in cynomolgus monkeys. No teratogenic or other adverse developmental effects were observed in fetuses from pregnant monkeys that were administered ustekinumab subcutaneously twice weekly or intravenously weekly during the period of organogenesis. Serum concentrations of ustekinumab in pregnant monkeys were greater than 100 times the serum concentration in patients treated subcutaneously with 90 mg of ustekinumab weekly for 4 weeks.

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 at exposures greater than 100 times the human subcutaneous exposure 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.

8.2 Lactation

Risk Summary

There are no data on the presence of ustekinumab in human milk, the effects on the breastfed infant, or the effects on milk production. Ustekinumab was present in the milk of lactating monkeys administered ustekinumab. Due to species-specific differences in lactation physiology, animal data may not reliably predict drug levels in human milk. Maternal IgG is known to be present in human milk. Published data suggest that the systemic exposure to a breastfed infant is expected to be low because ustekinumab is a large molecule and is degraded in the gastrointestinal tract. However, if ustekinumab is transferred into human milk the effects of local exposure in the gastrointestinal tract are unknown.

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.

8.4 Pediatric Use

The safety and effectiveness of STELARA® have been established in pediatric patients 12 to 17 years old with moderate to severe plaque psoriasis. Use of STELARA® in this age group is supported by evidence from a multicenter, randomized, 60-week trial that included a 12-week, double-blind, placebo-controlled, parallel-group portion, in 110 pediatric subjects 12 years and older *[see Adverse Reactions (6.1), Clinical Studies (14.2)]*. The safety and effectiveness of STELARA® for pediatric patients less than 12 years of age with psoriasis have not been established.

The safety and effectiveness of STELARA® have not been established in pediatric patients with psoriatic arthritis, Crohn's disease or ulcerative colitis.

8.5 Geriatric Use

Of the 6709 patients exposed to STELARA®, a total of 340 were 65 years or older (183 patients with psoriasis, 65 patients with psoriatic arthritis, 58 patients with Crohn's disease and 34 patients with ulcerative colitis), and 40 patients were 75 years or older. Although no overall differences in safety or efficacy were observed between older and younger patients, the number of patients aged 65 and over is not sufficient to determine whether they respond differently from younger patients.

10 OVERDOSAGE

Single doses up to 6 mg/kg intravenously have been administered in clinical studies without dose-limiting toxicity. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment be instituted immediately.

11 DESCRIPTION

Ustekinumab is a human IgG1κ monoclonal antibody against the p40 subunit of the IL-12 and IL-23 cytokines. Using DNA recombinant technology, ustekinumab is produced in a well characterized recombinant cell line and is purified using standard bio-processing technology. The manufacturing process contains steps for the clearance of viruses. Ustekinumab is comprised of 1326 amino acids and has an estimated molecular mass that ranges from 148,079 to 149,690 Daltons.

STELARA® (ustekinumab) Injection is a sterile, preservative-free, colorless to light yellow solution and may contain a few small translucent or white particles with pH of 5.7- 6.3.

STELARA® for Subcutaneous Use

Available as 45 mg of ustekinumab in 0.5 mL and 90 mg of ustekinumab in 1 mL, supplied as a sterile solution in a single-dose prefilled syringe with a 27 gauge fixed ½ inch needle and as 45 mg of ustekinumab in 0.5 mL in a single-dose 2 mL Type I glass vial with a coated stopper. The syringe is fitted with a passive needle guard and a needle cover that contains dry natural rubber (a derivative of latex).

Each 0.5 mL prefilled syringe or vial delivers 45 mg ustekinumab, L-histidine and L-histidine monohydrochloride monohydrate (0.5 mg), Polysorbate 80 (0.02 mg), and sucrose (38 mg).

Each 1 mL prefilled syringe delivers 90 mg ustekinumab, L-histidine and L-histidine monohydrochloride monohydrate (1 mg), Polysorbate 80 (0.04 mg), and sucrose (76 mg).

STELARA® for Intravenous Infusion

Available as 130 mg of ustekinumab in 26 mL, supplied as a single-dose 30 mL Type I glass vial with a coated stopper.

Each 26 mL vial delivers 130 mg ustekinumab, EDTA disodium salt dihydrate (0.52 mg), L-histidine (20 mg), L-histidine hydrochloride monohydrate (27 mg), L-methionine (10.4 mg), Polysorbate 80 (10.4 mg) and sucrose (2210 mg).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ustekinumab is a human IgG1κ monoclonal antibody that binds with specificity to the p40 protein subunit used by both the IL-12 and IL-23 cytokines. IL-12 and IL-23 are naturally occurring cytokines that are involved in inflammatory and immune responses, such as natural killer cell activation and CD4+ T-cell differentiation and activation. In *in vitro* models, ustekinumab was shown to disrupt IL-12 and IL-23 mediated signaling and cytokine cascades by disrupting the interaction of these cytokines with a shared cell-surface receptor chain, IL-12Rβ1. The cytokines IL-12 and IL-23 have been implicated as important contributors to the chronic inflammation that is a hallmark of Crohn's disease and ulcerative colitis. In animal models of colitis, genetic absence or antibody blockade of the p40 subunit of IL-12 and IL-23, the target of ustekinumab, was shown to be protective.

12.2 Pharmacodynamics

Psoriasis

In a small exploratory study, a decrease was observed in the expression of mRNA of its molecular targets IL-12 and IL-23 in lesional skin biopsies measured at baseline and up to two weeks post-treatment in subjects with psoriasis.

Ulcerative Colitis

In both study UC-1 (induction) and study UC-2 (maintenance), a positive relationship was observed between exposure and rates of clinical remission, clinical response, and endoscopic improvement. The response rate approached a plateau at the ustekinumab exposures associated with the recommended dosing regimen for maintenance treatment *[see Clinical Studies (14.5)]*.

12.3 Pharmacokinetics

Absorption

In adult subjects with psoriasis, the median time to reach the maximum serum concentration (T_{max}) was 13.5 days and 7 days, respectively, after a single subcutaneous administration of 45 mg (N=22) and 90 mg (N=24) of ustekinumab. In healthy subjects (N=30), the median T_{max} value (8.5 days) following a single subcutaneous administration of 90 mg of ustekinumab was comparable to that observed in subjects with psoriasis.

Following multiple subcutaneous doses of STELARA® in adult subjects with psoriasis, steady-state serum concentrations of ustekinumab were achieved by Week 28. The mean (±SD) steady-state trough serum ustekinumab concentrations were 0.69 ± 0.69 mcg/mL for patients less than or equal to 100 kg receiving a 45 mg dose and 0.74 ± 0.78 mcg/mL for patients greater than 100 kg receiving a 90 mg dose. There was no apparent accumulation in serum ustekinumab concentration over time when given subcutaneously every 12 weeks.

Following the recommended intravenous induction dose, mean ±SD peak serum ustekinumab concentration was 125.2 ± 33.6 mcg/mL in patients with Crohn's disease, and 129.1 ± 27.6 mcg/mL in patients with ulcerative colitis. Starting at Week 8, the recommended 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 ±SD steady-state trough concentration was 2.5 ± 2.1 mcg/mL in patients with Crohn's disease, and 3.3 ± 2.3 mcg/mL in patients with ulcerative colitis for 90 mg ustekinumab administered every 8 weeks.

Distribution

Population pharmacokinetic analyses showed that the volume of distribution of ustekinumab in the central compartment was 2.7 L (95% CI: 2.69, 2.78) in patients with Crohn's disease and 3.0 L (95% CI: 2.96, 3.07) in patients with ulcerative colitis. The total volume of distribution at steady-state was 4.6 L in patients with Crohn's disease and 4.4 L in patients with ulcerative colitis.

Elimination

The mean (±SD) half-life ranged from 14.9 ± 4.6 to 45.6 ± 80.2 days across all psoriasis studies following subcutaneous administration. Population pharmacokinetic analyses showed that the clearance of ustekinumab was 0.19 L/day (95% CI: 0.185, 0.197) in patients with Crohn's disease and 0.19 L/day (95% CI: 0.179, 0.192) in patients with ulcerative colitis with an estimated median terminal half-life of approximately 19 days for both IBD (Crohn's disease and ulcerative colitis) populations.

These results indicate the pharmacokinetics of ustekinumab were similar between patients with Crohn's disease and ulcerative colitis.

Metabolism

The metabolic pathway of ustekinumab has not been characterized. As a human IgG1κ monoclonal antibody, ustekinumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

Specific Populations

Weight

When given the same dose, subjects with psoriasis or psoriatic arthritis weighing more than 100 kg had lower median serum ustekinumab concentrations compared with those subjects weighing 100 kg or less. The median trough serum concentrations of ustekinumab in subjects of higher

weight (greater than 100 kg) in the 90 mg group were comparable to those in subjects of lower weight (100 kg or less) in the 45 mg group.

Age: Geriatric Population

A population pharmacokinetic analysis (N=106/1937 patients with psoriasis greater than or equal to 65 years old) was performed to evaluate the effect of age on the pharmacokinetics of ustekinumab. There were no apparent changes in pharmacokinetic parameters (clearance and volume of distribution) in subjects older than 65 years old.

Age: Pediatric Population

Following multiple recommended doses of STELARA® in adolescent subjects 12 to 17 years of age with psoriasis, steady-state serum concentrations of ustekinumab were achieved by Week 28. At Week 28, the mean ±SD steady-state trough serum ustekinumab concentration was 0.54 ± 0.43 mcg/mL.

Drug Interaction Studies

The effects of IL-12 or IL-23 on the regulation of CYP450 enzymes were evaluated in an *in vitro* study using human hepatocytes, which showed that IL-12 and/or IL-23 at levels of 10 ng/mL did not alter human CYP450 enzyme activities (CYP1A2, 2B6, 2C9, 2C19, 2D6, or 3A4). However, the clinical relevance of *in vitro* data has not been established *[see Drug Interactions (7.3)]*.

No *in vivo* drug interaction studies have been conducted with STELARA®.

Population pharmacokinetic analyses indicated that the clearance of ustekinumab was not impacted by concomitant MTX, NSAIDs, and oral corticosteroids, or prior exposure to a TNF blocker in patients with psoriatic arthritis.

In patients with Crohn's disease and ulcerative colitis, population pharmacokinetic analyses did not indicate changes in ustekinumab clearance with concomitant use of corticosteroids or immunomodulators (AZA, 6-MP, or MTX); and serum ustekinumab concentrations were not impacted by concomitant use of these medications.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been conducted to evaluate the carcinogenic or mutagenic potential of STELARA®. Published literature showed that administration of murine IL-12 caused an anti-tumor effect in mice that contained transplanted tumors and IL-12/IL-23p40 knockout mice or mice treated with anti-IL-12/IL-23p40 antibody had decreased host defense to tumors. Mice genetically manipulated to be deficient in both IL-12 and IL-23 or IL-12 alone developed UV-induced skin cancers earlier and more frequently compared to wild-type mice. The relevance of these experimental findings in mouse models for malignancy risk in humans is unknown.

No effects on fertility were observed in male cynomolgus monkeys that were administered ustekinumab at subcutaneous doses up to 45 mg/kg twice weekly (45 times the MRHD on a mg/kg

basis) prior to and during the mating period. However, fertility and pregnancy outcomes were not evaluated in mated females.

No effects on fertility were observed in female mice that were administered an analogous IL-12/IL-23p40 antibody by subcutaneous administration at doses up to 50 mg/kg, twice weekly, prior to and during early pregnancy.

13.2 Animal Toxicology and/or Pharmacology

In a 26-week toxicology study, one out of 10 monkeys subcutaneously administered 45 mg/kg ustekinumab twice weekly for 26 weeks had a bacterial infection.

14 CLINICAL STUDIES

14.1 Psoriasis

Two multicenter, randomized, double-blind, placebo-controlled studies (Ps STUDY 1 and Ps STUDY 2) enrolled a total of 1996 subjects 18 years of age and older with plaque psoriasis who had a minimum body surface area involvement of 10%, and Psoriasis Area and Severity Index (PASI) score ≥12, and who were candidates for phototherapy or systemic therapy. Subjects with guttate, erythrodermic, or pustular psoriasis were excluded from the studies.

Ps STUDY 1 enrolled 766 subjects and Ps STUDY 2 enrolled 1230 subjects. The studies had the same design through Week 28. In both studies, subjects were randomized in equal proportion to placebo, 45 mg or 90 mg of STELARA®. Subjects randomized to STELARA® received 45 mg or 90 mg doses, regardless of weight, at Weeks 0, 4, and 16. Subjects randomized to receive placebo at Weeks 0 and 4 crossed over to receive STELARA® (either 45 mg or 90 mg) at Weeks 12 and 16.

In both studies, the endpoints were the proportion of subjects who achieved at least a 75% reduction in PASI score (PASI 75) from baseline to Week 12 and treatment success (cleared or minimal) on the Physician's Global Assessment (PGA). The PGA is a 6-category scale ranging from 0 (cleared) to 5 (severe) that indicates the physician's overall assessment of psoriasis focusing on plaque thickness/induration, erythema, and scaling.

In both studies, subjects in all treatment groups had a median baseline PASI score ranging from approximately 17 to 18. Baseline PGA score was marked or severe in 44% of subjects in Ps STUDY 1 and 40% of subjects in Ps STUDY 2. Approximately two-thirds of all subjects had received prior phototherapy, 69% had received either prior conventional systemic or biologic therapy for the treatment of psoriasis, with 56% receiving prior conventional systemic therapy and 43% receiving prior biologic therapy. A total of 28% of subjects had a history of psoriatic arthritis.

Clinical Response

The results of Ps STUDY 1 and Ps STUDY 2 are presented in Table 7 below.

Table 7: Clinical Outcomes Ps STUDY 1 and Ps STUDY 2

Week 12	Ps STUDY 1			Ps STUDY 2		
		STELARA®			STELARA®	
	Placebo	45 mg	90 mg	Placebo	45 mg	90 mg
Subjects randomized	**255**	**255**	**256**	**410**	**409**	**411**
PASI 75 response	8 (3%)	171 (67%)	170 (66%)	15 (4%)	273 (67%)	311 (76%)
PGA of Cleared or Minimal	10 (4%)	151 (59%)	156 (61%)	18 (4%)	277 (68%)	300 (73%)

Examination of age, gender, and race subgroups did not identify differences in response to STELARA® among these subgroups.

In subjects who weighed 100 kg or less, response rates were similar with both the 45 mg and 90 mg doses; however, in subjects who weighed greater than 100 kg, higher response rates were seen with 90 mg dosing compared with 45 mg dosing (Table 8 below).

Table 8: Clinical Outcomes by Weight Ps STUDY 1 and Ps STUDY 2

	Ps STUDY 1			Ps STUDY 2		
		STELARA®			STELARA®	
	Placebo	45 mg	90 mg	Placebo	45 mg	90 mg
Subjects randomized	**255**	**255**	**256**	**410**	**409**	**411**
PASI 75 response at Week 12*						
≤100 kg	4%	74%	65%	4%	73%	78%
	6/166	124/168	107/164	12/290	218/297	225/289
>100 kg	2%	54%	68%	3%	49%	71%
	2/89	47/87	63/92	3/120	55/112	86/121
PGA of Cleared or Minimal at Week 12*						
≤100 kg	4%	64%	63%	5%	74%	75%
	7/166	108/168	103/164	14/290	220/297	216/289
>100 kg	3%	49%	58%	3%	51%	69%
	3/89	43/87	53/92	4/120	57/112	84/121

* Patients were dosed with study medication at Weeks 0 and 4.

Subjects in Ps STUDY 1 who were PASI 75 responders at both Weeks 28 and 40 were re-randomized at Week 40 to either continued dosing of STELARA® (STELARA® at Week 40) or to withdrawal of therapy (placebo at Week 40). At Week 52, 89% (144/162) of subjects re-randomized to STELARA® treatment were PASI 75 responders compared with 63% (100/159) of subjects re-randomized to placebo (treatment withdrawal after Week 28 dose). The median time to loss of PASI 75 response among the subjects randomized to treatment withdrawal was 16 weeks.

14.2 Adolescent Subjects with Plaque Psoriasis

A multicenter, randomized, double blind, placebo-controlled study (Ps STUDY 3) enrolled 110 adolescent subjects 12 to 17 years of age with a minimum BSA involvement of 10%, a PASI score greater than or equal to 12, and a PGA score greater than or equal to 3, who were candidates for phototherapy or systemic therapy and whose disease was inadequately controlled by topical therapy.

Subjects were randomized to receive placebo (n = 37), the recommended dose of STELARA® (n = 36), or one-half the recommended dose of STELARA® (n = 37) by subcutaneous injection at Weeks 0 and 4 followed by dosing every 12 weeks (q12w). The recommended dose of STELARA® was 0.75 mg/kg for subjects weighing less than 60 kg, 45 mg for subjects weighing

60 kg to 100 kg, and 90 mg for subjects weighing greater than 100 kg. At Week 12, subjects who received placebo were crossed over to receive STELARA® at the recommended dose or one-half the recommended dose.

Of the adolescent subjects, approximately 63% had prior exposure to phototherapy or conventional systemic therapy and approximately 11% had prior exposure to biologics.

The endpoints were the proportion of patients who achieved a PGA score of cleared (0) or minimal (1), PASI 75, and PASI 90 at Week 12. Subjects were followed for up to 60 weeks following first administration of study agent.

Clinical Response

The efficacy results at Week 12 for Ps STUDY 3 are presented in Table 9.

Table 9: Summary of Efficacy Endpoints in the Adolescent Psoriasis Study at Week 12

	Ps STUDY 3	
	Placebo n (%)	**STELARA®* n (%)**
N	**37**	**36**
PGA		
PGA of cleared (0) or minimal (1)	2 (5.4%)	25 (69.4%)
PASI		
PASI 75 responders	4 (10.8%)	29 (80.6%)
PASI 90 responders	2 (5.4%)	22 (61.1%)

* Using the weight-based dosage regimen specified in Table 1 and Table 2.

14.3 Psoriatic Arthritis

The safety and efficacy of STELARA® was assessed in 927 patients (PsA STUDY 1, n=615; PsA STUDY 2, n=312), in two randomized, double-blind, placebo-controlled studies in adult patients 18 years of age and older with active PsA (≥5 swollen joints and ≥5 tender joints) despite non-steroidal anti-inflammatory (NSAID) or disease modifying antirheumatic (DMARD) therapy. Patients in these studies had a diagnosis of PsA for at least 6 months. Patients with each subtype of PsA were enrolled, including polyarticular arthritis with the absence of rheumatoid nodules (39%), spondylitis with peripheral arthritis (28%), asymmetric peripheral arthritis (21%), distal interphalangeal involvement (12%) and arthritis mutilans (0.5%). Over 70% and 40% of the patients, respectively, had enthesitis and dactylitis at baseline.

Patients were randomized to receive treatment with STELARA® 45 mg, 90 mg, or placebo subcutaneously at Weeks 0 and 4 followed by every 12 weeks (q12w) dosing. Approximately 50% of patients continued on stable doses of MTX (≤25 mg/week). The primary endpoint was the percentage of patients achieving ACR 20 response at Week 24.

In PsA STUDY 1 and PsA STUDY 2, 80% and 86% of the patients, respectively, had been previously treated with DMARDs. In PsA STUDY 1, previous treatment with anti-tumor necrosis factor (TNF)-α agent was not allowed. In PsA STUDY 2, 58% (n=180) of the patients had been previously treated with TNF blocker, of whom over 70% had discontinued their TNF blocker treatment for lack of efficacy or intolerance at any time.

Clinical Response

In both studies, a greater proportion of patients achieved ACR 20, ACR 50 and PASI 75 response in the STELARA® 45 mg and 90 mg groups compared to placebo at Week 24 (see Table 10). ACR 70 responses were also higher in the STELARA® 45 mg and 90 mg groups, although the difference was only numerical (p=NS) in STUDY 2. Responses were similar in patients regardless of prior TNFα exposure.

Table 10: ACR 20, ACR 50, ACR 70 and PASI 75 responses in PsA STUDY 1 and PsA STUDY 2 at Week 24

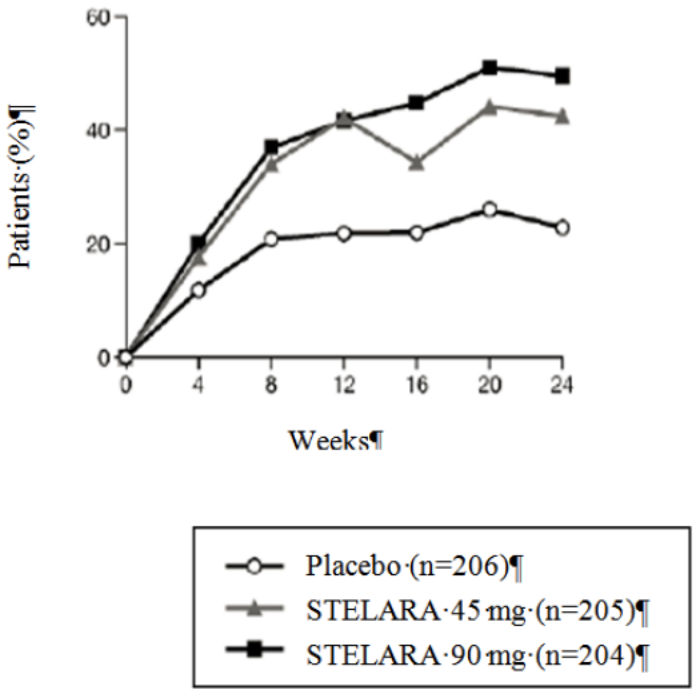
	PsA STUDY 1			PsA STUDY 2		
		STELARA®			STELARA®	
	Placebo	45 mg	90 mg	Placebo	45 mg	90 mg
Number of patients randomized	**206**	**205**	**204**	**104**	**103**	**105**
ACR 20 response, N (%)	47 (23%)	87 (42%)	101 (50%)	21 (20%)	45 (44%)	46 (44%)
ACR 50 response, N (%)	18 (9%)	51 (25%)	57 (28%)	7 (7%)	18 (17%)	24 (23%)
ACR 70 response, N (%)	5 (2%)	25 (12%)	29 (14%)	3 (3%)	7 (7%)	9 (9%)
Number of patients with ≥ 3% BSA[a]	**146**	**145**	**149**	**80**	**80**	**81**
PASI 75 response, N (%)	16 (11%)	83 (57%)	93 (62%)	4 (5%)	41 (51%)	45 (56%)

[a] Number of patients with ≥ 3% BSA psoriasis skin involvement at baseline

The percent of patients achieving ACR 20 responses by visit is shown in Figure 1.

Figure 1: Percent of patients achieving ACR 20 response through Week 24

PsA STUDY 1



The results of the components of the ACR response criteria are shown in Table 11.

Table 11: Mean change from baseline in ACR components at Week 24

	PsA STUDY 1		
		STELARA®	
	Placebo (N=206)	**45 mg (N= 205)**	**90 mg (N= 204)**
Number of swollen joints[a]			
Baseline	15	12	13
Mean Change at Week 24	-3	-5	-6
Number of tender joints[b]			
Baseline	25	22	23
Mean Change at Week 24	-4	-8	-9
Patient's assessment of pain[c]			
Baseline	6.1	6.2	6.6
Mean Change at Week 24	-0.5	-2.0	-2.6
Patient global assessment[c]			
Baseline	6.1	6.3	6.4
Mean Change at Week 24	-0.5	-2.0	-2.5
Physician global assessment[c]			
Baseline	5.8	5.7	6.1
Mean Change at Week 24	-1.4	-2.6	-3.1
Disability index (HAQ)[d]			
Baseline	1.2	1.2	1.2
Mean Change at Week 24	-0.1	-0.3	-0.4
CRP (mg/dL)[e]			
Baseline	1.6	1.7	1.8
Mean Change at Week 24	0.01	-0.5	-0.8

[a] Number of swollen joints counted (0-66)

[b] Number of tender joints counted (0-68)

[c] Visual analogue scale; 0= best, 10=worst.

[d] Disability Index of the Health Assessment Questionnaire; 0 = best, 3 = worst, measures the patient's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity.

[e] CRP: (Normal Range 0.0-1.0 mg/dL)

An improvement in enthesitis and dactylitis scores was observed in each STELARA® group compared with placebo at Week 24.

Physical Function

STELARA® treated patients showed improvement in physical function compared to patients treated with placebo as assessed by HAQ-DI at Week 24. In both studies, the proportion of HAQ-DI responders (≥0.3 improvement in HAQ-DI score) was greater in the STELARA® 45 mg and 90 mg groups compared to placebo at Week 24.

14.4 Crohn's Disease

STELARA® was evaluated in three randomized, double-blind, placebo-controlled clinical studies in adult patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] score of 220 to 450). There were two 8-week intravenous induction studies (CD-1 and CD-2) followed by a 44-week subcutaneous randomized withdrawal maintenance study (CD-

3) representing 52 weeks of therapy. Patients in CD-1 had failed or were intolerant to treatment with one or more TNF blockers, while patients in CD-2 had failed or were intolerant to treatment with immunomodulators or corticosteroids, but never failed treatment with a TNF blocker.

Studies CD-1 and CD-2

In studies CD-1 and CD-2, 1409 patients were randomized, of whom 1368 (CD-1, n=741; CD-2, n=627) were included in the final efficacy analysis. Induction of clinical response (defined as a reduction in CDAI score of greater than or equal to 100 points or CDAI score of less than 150) at Week 6 and clinical remission (defined as a CDAI score of less than 150) at Week 8 were evaluated. In both studies, patients were randomized to receive a single intravenous administration of STELARA® at either approximately 6 mg/kg, placebo (see Table 3), or 130 mg (a lower dose than recommended).

In Study CD-1, patients had failed or were intolerant to prior treatment with a TNF blocker: 29% patients had an inadequate initial response (primary non-responders), 69% responded but subsequently lost response (secondary non-responders) and 36% were intolerant to a TNF blocker. Of these patients, 48% failed or were intolerant to one TNF blocker and 52% had failed 2 or 3 prior TNF blockers. At baseline and throughout the study, approximately 46% of the patients were receiving corticosteroids and 31% of the patients were receiving immunomodulators (AZA, 6-MP, MTX). The median baseline CDAI score was 319 in the STELARA® approximately 6 mg/kg group and 313 in the placebo group.

In Study CD-2, patients had failed or were intolerant to prior treatment with corticosteroids (81% of patients), at least one immunomodulator (6-MP, AZA, MTX; 68% of patients), or both (49% of patients). Additionally, 69% never received a TNF blocker and 31% previously received but had not failed a TNF blocker. At baseline, and throughout the study, approximately 39% of the patients were receiving corticosteroids and 35% of the patients were receiving immunomodulators (AZA, 6-MP, MTX). The median baseline CDAI score was 286 in the STELARA® and 290 in the placebo group.

In these induction studies, a greater proportion of patients treated with STELARA® (at the recommended dose of approximately 6 mg/kg dose) achieved clinical response at Week 6 and clinical remission at Week 8 compared to placebo (see Table 12 for clinical response and remission rates). Clinical response and remission were significant as early as Week 3 in STELARA®-treated patients and continued to improve through Week 8.

Table 12: Induction of Clinical Response and Remission in CD-1* and CD-2**

	CD-1 n=741			**CD-2 n=627**		
	Placebo N=247	**STELARA®† N=249**	**Treatment difference and 95% CI**	**Placebo N=209**	**STELARA®† N=209**	**Treatment difference and 95% CI**
Clinical Response (100 point), Week 6	53 (21%)	84 (34%)[a]	12% (4%, 20%)	60 (29%)	116 (56%)[b]	27% (18%, 36%)
Clinical Remission, Week 8	18 (7%)	52 (21%)[b]	14% (8%, 20%)	41 (20%)	84 (40%)[b]	21% (12%, 29%)
Clinical Response (100 point), Week 8	50 (20%)	94 (38%)[b]	18% (10%, 25%)	67 (32%)	121 (58%)[b]	26% (17%, 35%)

70 Point Response, Week 6	75 (30%)	109 (44%)[a]	13% (5%, 22%)	81 (39%)	135 (65%)[b]	26% (17%, 35%)
70 Point Response, Week 3	67 (27%)	101 (41%)[a]	13% (5%, 22%)	66 (32%)	106 (51%)[b]	19% (10%, 28%)

Clinical remission is defined as CDAI score < 150; Clinical response is defined as reduction in CDAI score by at least 100 points or being in clinical remission: 70 point response is defined as reduction in CDAI score by at least 70 points

* Patient population consisted of patients who failed or were intolerant to TNF blocker therapy

** Patient population consisted of patients who failed or were intolerant to corticosteroids or immunomodulators (e.g., 6-MP, AZA, MTX) and previously received but not failed a TNF blocker or were never treated with a TNF blocker.

† Infusion dose of STELARA® using the weight-based dosage regimen specified in Table 3.

[a] $0.001 \leq p < 0.01$

[b] $p < 0.001$

Study CD-3

The maintenance study (CD-3), evaluated 388 patients who achieved clinical response (≥100 point reduction in CDAI score) at Week 8 with either induction dose of STELARA® in studies CD-1 or CD-2. Patients were randomized to receive a subcutaneous maintenance regimen of either 90 mg STELARA® every 8 weeks or placebo for 44 weeks (see Table 13).

Table 13: Clinical Response and Remission in CD-3 (Week 44; 52 weeks from initiation of the induction dose)

	Placebo* N=131†	**90 mg STELARA® every 8 weeks N=128†**	**Treatment difference and 95% CI**
Clinical Remission	47 (36%)	68 (53%)[a]	17% (5%, 29%)
Clinical Response	58 (44%)	76 (59%)[b]	15% (3%, 27%)
Clinical Remission in patients in remission at the start of maintenance therapy**	36/79 (46%)	52/78 (67%)[a]	21% (6%, 36%)

Clinical remission is defined as CDAI score < 150; Clinical response is defined as reduction in CDAI of at least 100 points or being in clinical remission

* The placebo group consisted of patients who were in response to STELARA® and were randomized to receive placebo at the start of maintenance therapy.

** Patients in remission at the end of maintenance therapy who were in remission at the start of maintenance therapy. This does not account for any other time point during maintenance therapy.

† Patients who achieved clinical response to STELARA® at the end of the induction study.

[a] $p < 0.01$

[b] $0.01 \leq p < 0.05$

At Week 44, 47% of patients who received STELARA® were corticosteroid-free and in clinical remission, compared to 30% of patients in the placebo group.

At Week 0 of Study CD-3, 34/56 (61%) STELARA® treated patients who previously failed or were intolerant to TNF blocker therapies were in clinical remission and 23/56 (41%) of these patients were in clinical remission at Week 44. In the placebo arm, 27/61 (44%) patients were in clinical remission at Week 0 while 16/61 (26%) of these patients were in remission at Week 44.

At Week 0 of Study CD-3, 46/72 (64%) STELARA® treated patients who had previously failed immunomodulator therapy or corticosteroids (but not TNF blockers) were in clinical remission and 45/72 (63%) of these patients were in clinical remission at Week 44. In the placebo arm, 50/70 (71%) of these patients were in clinical remission at Week 0 while 31/70 (44%) were in remission at Week 44. In the subset of these patients who were also naïve to TNF blockers, 34/52 (65%) of

STELARA® treated patients were in clinical remission at Week 44 as compared to 25/51 (49%) in the placebo arm.

Patients who were not in clinical response 8 weeks after STELARA® induction were not included in the primary efficacy analyses for Study CD-3; however, these patients were eligible to receive a 90 mg subcutaneous injection of STELARA® upon entry into Study CD-3. Of these patients, 102/219 (47%) achieved clinical response eight weeks later and were followed for the duration of the study.

14.5 Ulcerative Colitis

STELARA® was evaluated in two randomized, double-blind, placebo-controlled clinical studies [UC-1 and UC-2 (NCT02407236)] in adult patients with moderately to severely active ulcerative colitis who had an inadequate response to or failed to tolerate a biologic (i.e., TNF blocker and/or vedolizumab), corticosteroids, and/or 6-MP or AZA therapy. The 8-week intravenous induction study (UC-1) was followed by the 44-week subcutaneous randomized withdrawal maintenance study (UC-2) for a total of 52 weeks of therapy.

Disease assessment was based on the Mayo score, which ranged from 0 to 12 and has four subscores that were each scored from 0 (normal) to 3 (most severe): stool frequency, rectal bleeding, findings on centrally-reviewed endoscopy, and physician global assessment. Moderately to severely active ulcerative colitis was defined at baseline (Week 0) as Mayo score of 6 to 12, including a Mayo endoscopy subscore ≥2. An endoscopy score of 2 was defined by marked erythema, absent vascular pattern, friability, erosions; and a score of 3 was defined by spontaneous bleeding, ulceration. At baseline, patients had a median Mayo score of 9, with 84% of patients having moderate disease (Mayo score 6-10) and 15% having severe disease (Mayo score 11-12).

Patients in these studies may have received other concomitant therapies including aminosalicylates, immunomodulatory agents (AZA, 6-MP, or MTX), and oral corticosteroids (prednisone).

Study UC-1

In UC-1, 961 patients were randomized at Week 0 to a single intravenous administration of STELARA® of approximately 6 mg/kg, 130 mg (a lower dose than recommended), or placebo. Patients enrolled in UC-1 had to have failed therapy with corticosteroids, immunomodulators or at least one biologic. A total of 51% had failed at least one biologic and 17% had failed both a TNF blocker and an integrin receptor blocker. Of the total population, 46% had failed corticosteroids or immunomodulators but were biologic-naïve and an additional 3% had previously received but had not failed a biologic. At induction baseline and throughout the study, approximately 52% patients were receiving oral corticosteroids, 28% patients were receiving immunomodulators (AZA, 6-MP, or MTX) and 69% patients were receiving aminosalicylates.

The primary endpoint was clinical remission at Week 8. Clinical remission with a definition of: Mayo stool frequency subscore of 0 or 1, Mayo rectal bleeding subscore of 0 (no rectal bleeding), and Mayo endoscopy subscore of 0 or 1 (Mayo endoscopy subscore of 0 defined as normal or inactive disease and Mayo subscore of 1 defined as presence of erythema, decreased vascular pattern and no friability) is provided in Table 14.

The secondary endpoints were clinical response, endoscopic improvement, and histolologic-endoscopic mucosal improvement. Clinical response with a definition of (≥ 2 points and ≥ 30% decrease in modified Mayo score, defined as 3-component Mayo score without the Physician's Global Assessment, with either a decrease from baseline in the rectal bleeding subscore ≥1 or a rectal bleeding subscore of 0 or 1), endoscopic improvement with a definition of Mayo endoscopy subscore of 0 or 1, and histologic-endoscopic mucosal improvement with a definition of combined endoscopic improvement and histologic improvement of the colon tissue [neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue]) are provided in Table 14.

In UC-1, a significantly greater proportion of patients treated with STELARA® (at the recommended dose of approximately 6 mg/kg dose) were in clinical remission and response and achieved endoscopic improvement and histologic-endoscopic mucosal improvement compared to placebo (see Table 14).

Table 14: Proportion of Patients Meeting Efficacy Endpoints at Week 8 in UC-1

Endpoint	**Placebo** N = 319		**STELARA®†** N = 322		**Treatment difference and 97.5% CI** [a]
	N	**%**	**N**	**%**	
Clinical Remission*	**22**	**7%**	**62**	**19%**	12% (7%, 18%) [b]
Bio-naïve‡	14/151	9%	36/147	24%	
Prior biologic failure	7/161	4%	24/166	14%	
Endoscopic Improvement§	**40**	**13%**	**80**	**25%**	12% (6%, 19%) [b]
Bio-naïve‡	28/151	19%	43/147	29%	
Prior biologic failure	11/161	7%	34/166	20%	
Clinical Response†	**99**	**31%**	**186**	**58%**	27% (18%, 35%) [b]
Bio-naïve‡	55/151	36%	94/147	64%	
Prior biologic failure	42/161	26%	86/166	52%	
Histologic-Endoscopic Mucosal Improvement	**26**	**8%**	**54**	**17%**	9% (3%, 14%) [b]
Bio-naïve‡	19/151	13%	30/147	20%	
Prior biologic failure	6/161	4%	21/166	13%	

†Infusion dose of STELARA® using the weight-based dosage regimen specified in Table 3.

‡An additional 7 patients on placebo and 9 patients on STELARA® (6 mg/kg) had been exposed to, but had not failed, biologics.

* Clinical remission was defined as Mayo stool frequency subscore of 0 or 1, Mayo rectal bleeding subscore of 0, and Mayo endoscopy subscore of 0 or 1 (modified so that 1 does not include friability).

§ Endoscopic improvement was defined as Mayo endoscopy subscore of 0 or 1 (modified so that 1 does not include friability).

† Clinical response was defined as a decrease from baseline in the modified Mayo score by ≥30% and ≥2 points, with either a decrease from baseline in the rectal bleeding subscore ≥1 or a rectal bleeding subscore of 0 or 1.

‡ Histologic-endoscopic mucosal improvement was defined as combined endoscopic improvement (Mayo endoscopy subscore of 0 or 1) and histologic improvement of the colon tissue (neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue).

[a] Adjusted treatment difference (97.5% CI)

[b] $p < 0.001$

The relationship of histologic-endoscopic mucosal improvement, as defined in UC-1, at Week 8 to disease progression and long-term outcomes was not evaluated during UC-1.

Rectal Bleeding and Stool Frequency Subscores
Decreases in rectal bleeding and stool frequency subscores were observed as early as Week 2 in STELARA® treated patients.

Study UC-2

The maintenance study (UC-2) evaluated 523 patients who achieved clinical response 8 weeks following the intravenous administration of either induction dose of STELARA® in UC-1. These patients were randomized to receive a subcutaneous maintenance regimen of either 90 mg STELARA® every 8 weeks, or every 12 weeks (a lower dose than recommended), or placebo for 44 weeks.

The primary endpoint was the proportion of patients in clinical remission at Week 44. The secondary endpoints included the proportion of patients maintaining clinical response at Week 44, the proportion of patients with endoscopic improvement at Week 44, the proportion of patients with corticosteroid-free clinical remission at Week 44, and the proportion of patients maintaining clinical remission at Week 44 among patients who achieved clinical remission 8 weeks after induction.

Results of the primary and secondary endpoints at Week 44 in patients treated with STELARA® at the recommended dosage (90 mg every 8 weeks) compared to the placebo are shown in Table 15.

Table 15: Efficacy Endpoints of Maintenance at Week 44 in UC-2 (52 Weeks from Initiation of the Induction Dose)

Endpoint	**Placebo*** N = 175†		**90 mg STELARA® every 8 weeks** N = 176		**Treatment difference and 95% CI**
	N	**%**	**N**	**%**	
Clinical Remission**	**46**	**26%**	**79**	**45%**	19% (9%, 28%) [a]
Bio-naïve‡	30/84	36%	39/79	49%	
Prior biologic failure	16/88	18%	37/91	41%	
Maintenance of Clinical Response at Week 44†	**84**	**48%**	**130**	**74%**	26% (16%, 36%) [a]
Bio-naïve‡	49/84	58%	62/79	78%	
Prior biologic failure	35/88	40%	64/91	70%	
Endoscopic Improvement§	**47**	**27%**	**83**	**47%**	20% (11%, 30%) [a]
Bio-naïve‡	29/84	35%	42/79	53%	
Prior biologic failure	18/88	20%	38/91	42%	
Corticosteroid-free Clinical Remission‡	**45**	**26%**	**76**	**43%**	17% (8%, 27%) [a]
Bio-naïve‡	30/84	36%	38/79	48%	
Prior biologic failure	15/88	17%	35/91	38%	
Maintenance of Clinical Remission at Week 44 in patients who achieved clinical remission 8 weeks after induction	**18/50**	**36%**	**27/41**	**66%**	31% (12%, 50%) [b]

Bio-naïve[ɻ]	12/27	44%	14/20	70%	
Prior biologic failure	6/23	26%	12/18	67%	

[ɻ] An additional 3 patients on placebo and 6 patients on STELARA® had been exposed to, but had not failed, biologics.
[*] The placebo group consisted of patients who were in response to STELARA® and were randomized to receive placebo at the start of maintenance therapy.
[**] Clinical remission was defined as Mayo stool frequency subscore of 0 or 1, Mayo rectal bleeding subscore of 0, and Mayo endoscopy subscore of 0 or 1 (modified so that 1 does not include friability).
[†] Clinical response was defined as a decrease from baseline in the modified Mayo score by ≥30% and ≥2 points, with either a decrease from baseline in the rectal bleeding subscore ≥1 or a rectal bleeding subscore of 0 or 1.
[§] Endoscopic improvement was defined as Mayo endoscopy subscore of 0 or 1 (modified so that 1 does not include friability).
[‡] Corticosteroid-free clinical remission was defined as patients in clinical remission and not receiving corticosteroids at Week 44.
[a] p =<0.001
[b] p=0.004

Other Endpoints

Week 16 Responders to Ustekinumab Induction
Patients who were not in clinical response 8 weeks after induction with STELARA® in UC-1 were not included in the primary efficacy analyses for Study UC-2; however, these patients were eligible to receive a 90 mg subcutaneous injection of STELARA® at Week 8. Of these patients, 55/101 (54%) achieved clinical response eight weeks later (Week 16) and received STELARA® 90 mg subcutaneously every 8 weeks during the UC-2 trial. At Week 44, there were 97/157 (62%) patients who maintained clinical response and there were 51/157 (32%) who achieved clinical remission.

Histologic-Endoscopic Mucosal Improvement at Week 44
The proportion of patients achieving histologic-endoscopic mucosal improvement during maintenance treatment in UC-2 was 75/172 (44%) among patients on STELARA® and 40/172 (23%) in patients on placebo at Week 44. The relationship of histologic-endoscopic mucosal improvement, as defined in UC-2, at Week 44 to progression of disease or long-term outcomes was not evaluated in UC-2.

Endoscopic Normalization
Normalization of endoscopic appearance of the mucosa was defined as a Mayo endoscopic subscore of 0. At Week 8 in UC-1, endoscopic normalization was achieved in 25/322 (8%) of patients treated with STELARA and 12/319 (4%) of patients in the placebo group. At Week 44 of UC-2, endoscopic normalization was achieved in 51/176 (29%) of patients treated with STELARA® and in 32/175 (18%) of patients in placebo group.

15 REFERENCES

1 Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 6.6.2 Regs Research Data, Nov 2009 Sub (1973-2007) - Linked To County Attributes - Total U.S., 1969-2007 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2010, based on the November 2009 submission.

16 HOW SUPPLIED/STORAGE AND HANDLING

STELARA® (ustekinumab) Injection is a sterile, preservative-free, colorless to light yellow solution and may contain a few small translucent or white particles. It is supplied as individually packaged, single-dose prefilled syringes or single-dose vials.

For Subcutaneous Use

Prefilled Syringes

- 45 mg/0.5 mL (NDC 57894-060-03)
- 90 mg/mL (NDC 57894-061-03)

Each prefilled syringe is equipped with a 27 gauge fixed ½ inch needle, a needle safety guard, and a needle cover that contains dry natural rubber.

Single-dose Vial

- 45 mg/0.5 mL (NDC 57894-060-02)

For Intravenous Infusion

Single-dose Vial

- 130 mg/26 mL (5 mg/mL) (NDC 57894-054-27)

Storage and Stability

STELARA® vials and prefilled syringes must be refrigerated at 2ºC to 8ºC (36ºF to 46ºF). Store STELARA® vials upright. Keep the product in the original carton to protect from light until the time of use. Do not freeze. Do not shake.

17 PATIENT COUNSELING INFORMATION

Advise the patient and/or caregiver to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Infections

Inform patients that STELARA® may lower the ability of their immune system to fight infections and to contact their healthcare provider immediately if they develop any signs or symptoms of infection *[see Warnings and Precautions (5.1)]*.

Malignancies

Inform patients of the risk of developing malignancies while receiving STELARA® *[see Warnings and Precautions (5.4)]*.

Hypersensitivity Reactions

- Advise patients to seek immediate medical attention if they experience any signs or symptoms of serious hypersensitivity reactions and discontinue STELARA® *[see Warnings and Precautions (5.5)]*.
- Inform patients the needle cover on the prefilled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex *[see Dosage and Administration (2.4)]*

Immunizations

Inform patients that STELARA® can interfere with the usual response to immunizations and that they should avoid live vaccines *[see Warnings and Precautions (5.7)]*.

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)]*.

Administration

Instruct patients to follow sharps disposal recommendations, as described in the Instructions for Use.

Prefilled Syringe Manufactured by: Janssen Biotech, Inc., Horsham, PA 19044, US License No. 1864 at Baxter Pharmaceutical Solutions, Bloomington, IN 47403 and at Cilag AG, Schaffhausen, Switzerland

Vial Manufactured by: Janssen Biotech, Inc., Horsham, PA 19044, US License No. 1864 at Cilag AG, Schaffhausen, Switzerland

MEDICATION GUIDE
STELARA (stel ar' a)
(ustekinumab)
injection, for subcutaneous or intravenous use

What is the most important information I should know about STELARA?

STELARA is a medicine that affects your immune system. STELARA can increase your risk of having serious side effects, including:

Serious infections. STELARA may lower the ability of your immune system to fight infections and may increase your risk of infections. Some people have serious infections while taking STELARA, including tuberculosis (TB), and infections caused by bacteria, fungi, or viruses. Some people have to be hospitalized for treatment of their infection.

- Your doctor should check you for TB before starting STELARA.
- If your doctor feels that you are at risk for TB, you may be treated with medicine for TB before you begin treatment with STELARA and during treatment with STELARA.
- Your doctor should watch you closely for signs and symptoms of TB while you are being treated with STELARA.

You should not start taking STELARA if you have any kind of infection unless your doctor says it is okay.

Before starting STELARA, tell your doctor if you:

- think you have an infection or have symptoms of an infection such as:
  - fever, sweat, or chills
  - muscle aches
  - cough
  - shortness of breath
  - blood in phlegm
  - weight loss
  - warm, red, or painful skin or sores on your body
  - diarrhea or stomach pain
  - burning when you urinate or urinate more often than normal
  - feel very tired
- are being treated for an infection.
- get a lot of infections or have infections that keep coming back.
- have TB, or have been in close contact with someone with TB.

After starting STELARA, call your doctor right away if you have any symptoms of an infection (see above). STELARA can make you more likely to get infections or make an infection that you have worse.

People who have a genetic problem where the body does not make any of the proteins interleukin 12 (IL-12) and interleukin 23 (IL-23) are at a higher risk for certain serious infections. These infections can spread throughout the body and cause death. People who take STELARA may also be more likely to get these infections.

Cancers. STELARA may decrease the activity of your immune system and increase your risk for certain types of cancers. Tell your doctor if you have ever had any type of cancer. Some people who are receiving STELARA and have risk factors for skin cancer have developed certain types of skin cancers. During your treatment with STELARA, tell your doctor if you develop any new skin growths.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS). RPLS is a rare condition that affects the brain and can cause death. The cause of RPLS is not known. If RPLS is found early and treated, most people recover. Tell your doctor right away if you have any new or worsening medical problems including:

- headache
- seizures
- confusion
- vision problems

What is STELARA?

STELARA is a prescription medicine used to treat:

- adults and children 12 years and older with moderate or severe psoriasis who may benefit from taking injections or pills (systemic therapy) or phototherapy (treatment using ultraviolet light alone or with pills).
- adults 18 years and older with active psoriatic arthritis. STELARA can be used alone or with the medicine methotrexate.
- adults 18 years and older with moderately to severely active Crohn's disease.
- adults 18 years and older with moderately to severely active ulcerative colitis.

It is not known if STELARA is safe and effective in children less than 12 years of age.

Do not take STELARA if you are allergic to ustekinumab or any of the ingredients in STELARA. See the end of this Medication Guide for a complete list of ingredients in STELARA.

Before you receive STELARA, tell your doctor about all of your medical conditions, including if you:

- have any of the conditions or symptoms listed in the section "**What is the most important information I should know about STELARA**?"
- ever had an allergic reaction to STELARA. Ask your doctor if you are not sure.
- are allergic to latex. The needle cover on the prefilled syringe contains latex.
- have recently received or are scheduled to receive an immunization (vaccine). People who take STELARA should not receive live vaccines. Tell your doctor if anyone in your house needs a live vaccine. The viruses used in some types of live vaccines can spread to people with a weakened immune system, and can cause serious problems. **You should not receive the BCG vaccine during the one year before receiving STELARA or one year after you stop**

receiving STELARA.

- have any new or changing lesions within psoriasis areas or on normal skin.
- are receiving or have received allergy shots, especially for serious allergic reactions. Allergy shots may not work as well for you during treatment with STELARA. STELARA may also increase your risk of having an allergic reaction to an allergy shot.
- receive or have received phototherapy for your psoriasis.
- are pregnant or planning to become pregnant. It is not known if STELARA can harm your unborn baby. You and your doctor should decide if you will receive STELARA. There is a pregnancy registry for women who are treated with STELARA during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. If you are pregnant or become pregnant while receiving STELARA, talk to your doctor about how you can join this pregnancy registry or you may contact the registry at 1-877-311-8972 to enroll.
- are breastfeeding or plan to breastfeed. It is thought that STELARA passes into your breast milk in small amounts.
- Talk to your doctor about the best way to feed your baby if you receive STELARA.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine

How should I use STELARA?

- Use STELARA exactly as your doctor tells you to.
- **The needle cover on the STELARA prefilled syringe contains latex. Do not handle the needle cover if you are sensitive to latex.**
- Adults with Crohn's disease and ulcerative colitis will receive the first dose of STELARA through a vein in the arm (intravenous infusion) in a healthcare facility by a healthcare provider. It takes at least 1 hour to receive the full dose of medicine. You will then receive STELARA as an injection under the skin (subcutaneous injection) 8 weeks after the first dose of STELARA, as described below.
- Adults with psoriasis or psoriatic arthritis and children 12 years and older with psoriasis will receive STELARA as an injection under the skin (subcutaneous injection) as described below.
- **Injecting STELARA under your skin**
  - STELARA is intended for use under the guidance and supervision of your doctor. In children 12 years and older, it is recommended that STELARA be administered by a healthcare provider. If your doctor decides that you or a caregiver may give your injections of STELARA at home, you should receive training on the right way to prepare and inject STELARA. Your doctor will determine the right dose of STELARA for you, the amount for each injection, and how often you should receive it. Do not try to inject STELARA yourself until you or your caregiver have been shown how to inject STELARA by your doctor or nurse.
  - Inject STELARA under the skin (subcutaneous injection) in your upper arms, buttocks, upper legs (thighs) or stomach area (abdomen).
  - Do not give an injection in an area of the skin that is tender, bruised, red or hard.
  - Use a different injection site each time you use STELARA.
  - If you inject more STELARA than prescribed, call your doctor right away.
  - Be sure to keep all of your scheduled follow-up appointments.

Read the detailed Instructions for Use at the end of this Medication Guide for instructions about how to prepare and inject a dose of STELARA, and how to properly throw away (dispose of) used needles and syringes. The syringe, needle and vial must never be re-used. After the cap is punctured, STELARA can become contaminated by harmful bacteria which could cause an infection if re-used. Therefore, throw away any unused portion of STELARA.

What should I avoid while using STELARA?

You should not receive a live vaccine while taking STELARA. See **"Before you receive STELARA, tell your doctor about all of your medical conditions, including if you:"**

What are the possible side effects of STELARA?

STELARA may cause serious side effects, including:

- See "**What is the most important information I should know about STELARA?**"
- **Serious allergic reactions.** Serious allergic reactions can occur with STELARA. Stop using STELARA and get medical help right away if you have any of the following symptoms of a serious allergic reaction:
  - feeling faint
  - swelling of your face, eyelids, tongue, or throat
  - chest tightness
  - skin rash
- **Lung inflammation.** Cases of lung inflammation have happened in some people who receive STELARA, and may be serious. These lung problems may need to be treated in a hospital. Tell your doctor right away if you develop shortness of breath or a cough that doesn't go away during treatment with STELARA**.**

Common side effects of STELARA include:

- nasal congestion, sore throat, and runny nose
- upper respiratory infections
- fever
- redness at the injection site
- vaginal yeast infections
- urinary tract infections

- headache
- tiredness
- itching
- nausea and vomiting
- sinus infection
- stomach pain
- diarrhea

These are not all of the possible side effects of STELARA. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.
You may also report side effects to Janssen Biotech, Inc. at 1-800 JANSSEN (1-800-526-7736).

How should I store STELARA?

- Store STELARA prefilled syringes in a refrigerator between 36°F to 46°F (2°C to 8°C).
- Store STELARA vials standing up straight.
- Store STELARA in the original carton to protect it from light until time to use it.
- Do not freeze STELARA.
- Do not shake STELARA.

Keep STELARA and all medicines out of the reach of children.

General information about the safe and effective use of STELARA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use STELARA for a condition for which it was not prescribed. Do not give STELARA to other people, even if they have the same symptoms that you have. It may harm them. You can ask your doctor or pharmacist for information about STELARA that was written for health professionals.

What are the ingredients in STELARA?

Active ingredient: ustekinumab

Inactive ingredients: Single-dose prefilled syringe for subcutaneous use contains L-histidine, L-histidine monohydrochloride monohydrate, Polysorbate 80, and sucrose. **Single-dose vial for subcutaneous use** contains L-histidine, L-histidine hydrochloride monohydrate, Polysorbate 80 and sucrose. **Single-dose vial for intravenous infusion** contains EDTA disodium salt dihydrate, L-histidine, L-histidine hydrochloride monohydrate, L-methionine, Polysorbate 80, and sucrose.

Manufactured by: Janssen Biotech, Inc., Horsham, PA 19044, US License No. 1864

For more information, go to *www stelarainfo.com* or call 1-800-JANSSEN (1-800-526-7736).

This Medication Guide has been approved by the U.S. Food and Drug Administration Revised: 10/2019

INSTRUCTIONS FOR USE
STELARA (stel ar′ a**)**
(ustekinumab)
injection, for subcutaneous use

Instructions for injecting STELARA from a vial.

Read this Instructions for Use before you start using STELARA. Your doctor or nurse should show you how to prepare, measure your dose, and give your injection of STELARA the right way.

If you cannot give yourself the injection:

- ask your doctor or nurse to help you, or
- ask someone who has been trained by a doctor or nurse to give your injections.

Do not try to inject STELARA yourself until you have been shown how to inject STELARA by your doctor, nurse or health professional.

Important information:

- Before you start, check the carton to make sure that it is the right dose. You will have either 45 mg or 90 mg as prescribed by your doctor.
  - If your dose is 45 mg or less you will receive one 45 mg vial.
  - If your dose is 90 mg, you will receive two 45 mg vials **and you will need to give yourself two injections, one right after the other.**
- Children 12 years of age and older weighing less than 132 pounds require a dose lower than 45 mg.
- Check the expiration date on the vial and carton. If the expiration date has passed, do not use it. If the expiration date has passed, call your doctor or pharmacist, or call 1-800-JANSSEN (1-800-526-7736) for help.
- Check the vial for any particles or discoloration. Your vial should look clear and colorless to light yellow with few white particles.
- Do not use if it is frozen, discolored, cloudy or has large particles. Get a new vial.
- **Do not shake the vial at any time.** Shaking your vial may damage your STELARA medicine. If your vial has been shaken, do not use it. Get a new vial.
- Do not use a STELARA vial more than one time, even if there is medicine left in the vial. After the cap is punctured, STELARA can become contaminated by harmful bacteria which could cause an infection if re-used. Therefore, throw away any unused STELARA after you give your injection.
- Safely throw away (dispose of) STELARA vials after use.
- Do not re-use syringes or needles. See "**Step 6: Dispose of needles and syringes."**
- To avoid needle-stick injuries, **do not** recap needles.

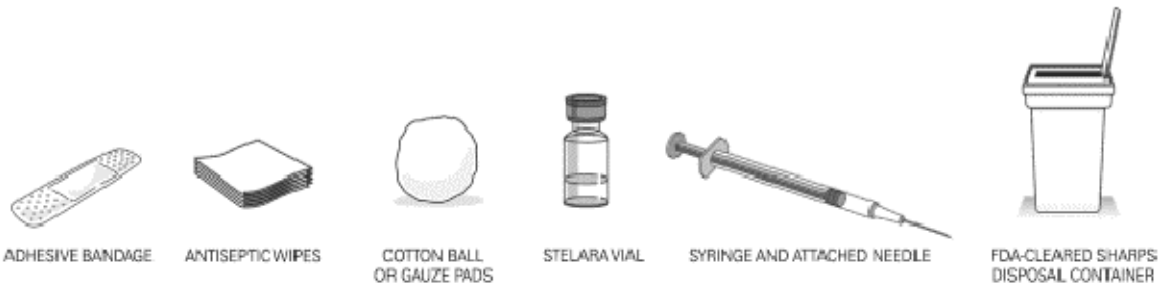
Gather the supplies you will need to prepare STELARA and to give your injection. (See Figure A)

You will need:

- a syringe with the needle attached, you will need a prescription from your healthcare provider to get syringes with the needles attached from your pharmacy.

- antiseptic wipes
- cotton balls or gauze pads
- adhesive bandage
- your prescribed dose of STELARA
- FDA-cleared sharps disposal container. See "**Step 6: Dispose of needles and syringes."**

Figure A



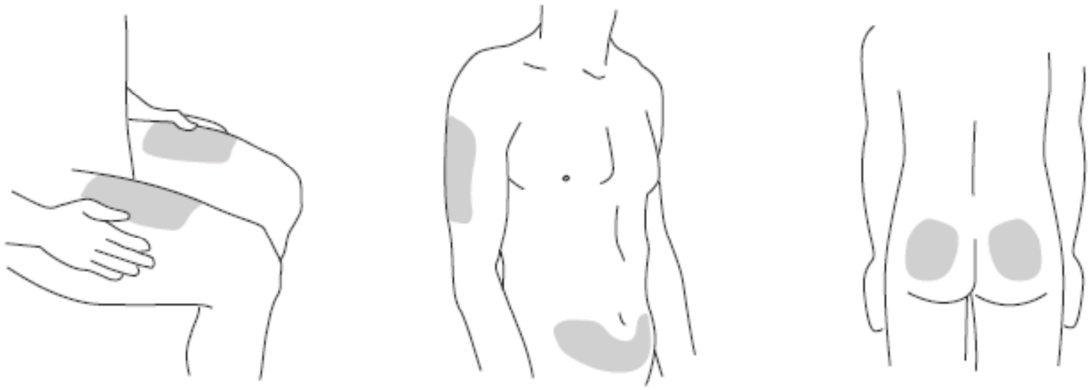
Step 1: Prepare the injection.

- Choose a well-lit, clean, flat work surface.
- Wash your hands well with soap and warm water.

Step 2: Prepare your injection site

- Choose an injection site around your stomach area (abdomen), buttocks, and upper legs (thighs).
  If a caregiver is giving you the injection, the outer area of the upper arms may also be used. **(See Figure B)**
- **Use a different injection site for each injection. Do not** give an injection in an area of the skin that is tender, bruised, red or hard.
- Clean the skin with an antiseptic wipe where you plan to give your injection.
- **Do not** touch this area again before giving the injection. Let your skin dry before injecting.
- **Do not** fan or blow on the clean area.

Figure B



*Areas in gray are recommended injection sites.

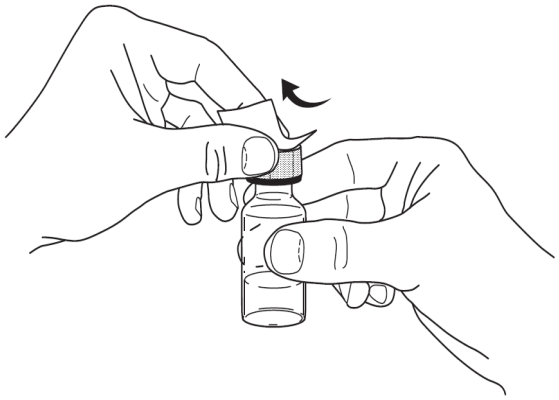
Step 3: Prepare the vial.

- Remove the cap from the top of the vial. Throw away the cap but do not remove the rubber stopper. **(See Figure C)**

Figure C

- Clean the rubber stopper with an antiseptic swab. **(See Figure D)**

Figure D

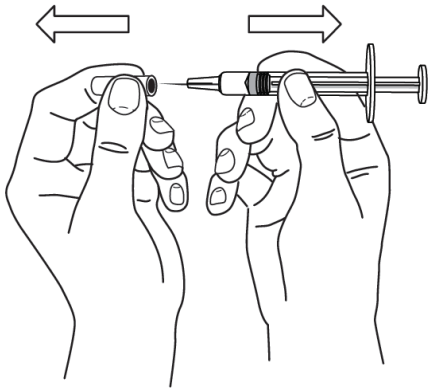


- Do not touch the rubber stopper after you clean it.
- Put the vial on a flat surface.

Step 4: Prepare the needle

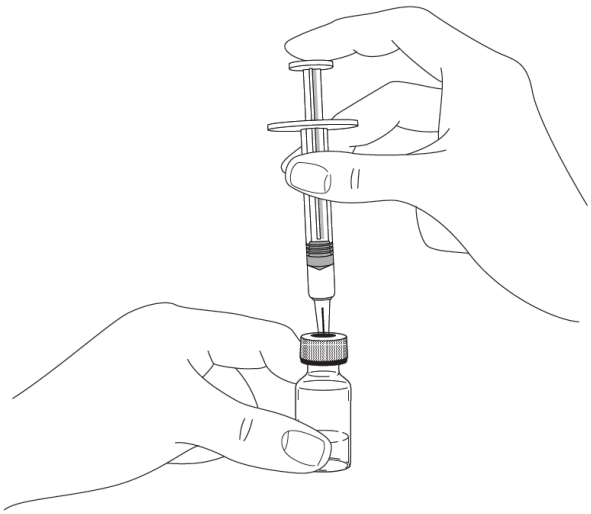
- Pick up the syringe with the needle attached.
- Remove the cap that covers the needle. **(See Figure E)**
- Throw the needle cap away. Do not touch the needle or allow the needle to touch anything.

Figure E



- Carefully pull back on the plunger to the line that matches the dose prescribed by your doctor.
- Hold the vial between your thumb and index (pointer) finger.
- Use your other hand to push the syringe needle through the center of the rubber stopper. **(See Figure F)**

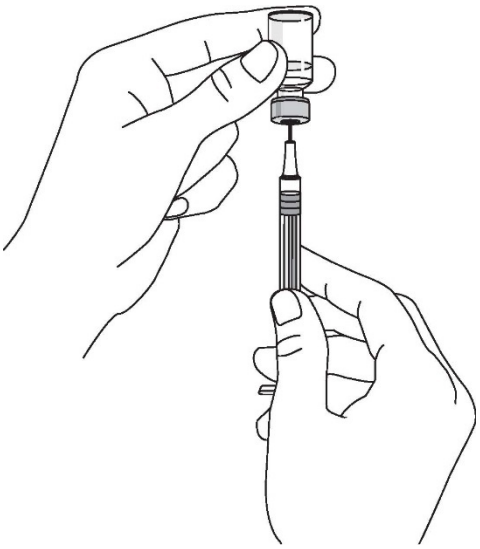
Figure F



- Push down on the plunger until all of the air has gone from the syringe into the vial.
- Turn the vial and the syringe upside down. **(See Figure G)**
- Hold the STELARA vial with one hand.
- It is important that the needle is always in the liquid in order to prevent air bubbles forming in the syringe.

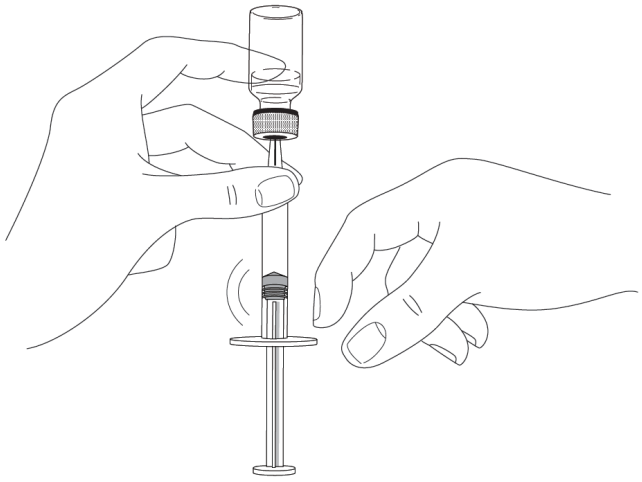
- Pull back on the syringe plunger with your other hand.
- Fill the syringe until the black tip of the plunger lines up with the mark that matches your prescribed dose.

Figure G



- **Do not remove the needle from the vial.** Hold the syringe with the needle pointing up to see if it has any air bubbles inside.
- If there are air bubbles, gently tap the side of the syringe until the air bubbles rise to the top. **(See Figure H)**
- Slowly press the plunger up until all of the air bubbles are out of the syringe (but none of the liquid is out).
- Remove the syringe from the vial. Do not lay the syringe down or allow the needle to touch anything.

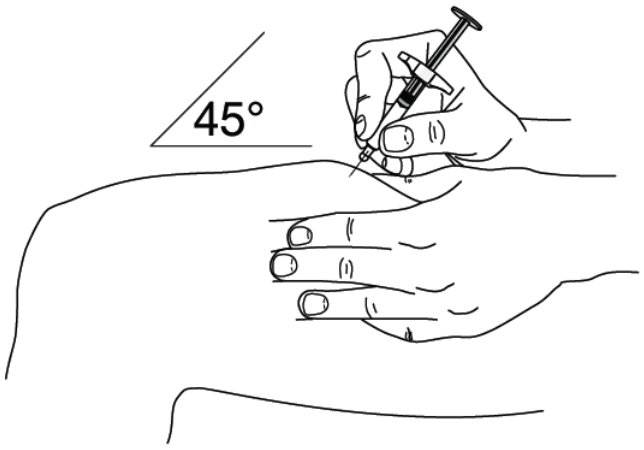
Figure H



Step 5: Inject STELARA

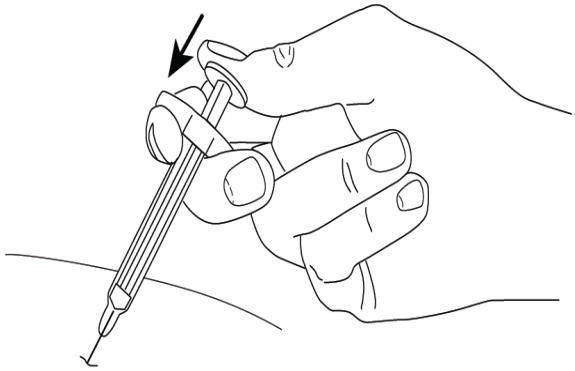
- Hold the barrel of the syringe in one hand, between the thumb and index fingers.
- **Do not** pull back on the plunger at any time.
- Use the other hand to gently pinch the cleaned area of skin. Hold firmly.
- Use a quick, dart-like motion to insert the needle into the pinched skin at about a 45-degree angle. **(See Figure I)**

Figure I



- Push the plunger with your thumb as far as it will go to inject all of the liquid. Push it slowly and evenly, keeping the skin gently pinched.
- When the syringe is empty, pull the needle out of your skin and let go of the skin. **(See Figure J)**

Figure J



- When the needle is pulled out of your skin, there may be a little bleeding at the injection site. This is normal. You can press a cotton ball or gauze pad to the injection site if needed. Do not rub the injection site. You may cover the injection site with a small adhesive bandage, if necessary.

If your dose is 90 mg, you will receive two 45 mg vials and you will need to give yourself a second injection right after the first. Repeat Steps 1-5 using a new syringe. Choose a different site for the second injection.

Step 6: Dispose of the needles and syringes.

- **Do not** re-use a syringe or needle.
- To avoid needle-stick injuries, do not recap a needle.
- Put your needles and syringes in a FDA-cleared sharps disposal container right away after use. **Do not throw away (dispose of) loose needles and syringes in your household trash.**
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - made of heavy-duty plastic
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out
  - upright and stable during use
  - leak-resistant,
  - and properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be local or state laws about how to throw away syringes and needles. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- Do not dispose of your sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your sharps disposal container.
- Throw away the vial into the container where you put the syringes and needles.

- If you have any questions, talk to your doctor or pharmacist.

Keep STELARA and all medicines out of the reach of children.

Vial Manufactured by: Janssen Biotech, Inc., Horsham, PA 19044, US License No. 1864 at Cilag AG, Schaffhausen, Switzerland

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Revised: 10/2019

INSTRUCTIONS FOR USE
STELARA (stel ar' a**)**
(ustekinumab)
injection, for subcutaneous use

Instructions for injecting STELARA using a prefilled syringe.

Read this Instructions for Use before you start using STELARA. Your doctor or nurse should show you how to prepare and give your injection of STELARA the right way.

If you cannot give yourself the injection:

- ask your doctor or nurse to help you, or
- ask someone who has been trained by a doctor or nurse to give your injections.

Do not try to inject STELARA yourself until you have been shown how to inject STELARA by your doctor, nurse or health professional.

Important information:

- Before you start, check the carton to make sure that it is the right dose. You will have either 45 mg or 90 mg as prescribed by your doctor.
  - If your dose is 45 mg, you will receive one 45 mg prefilled syringe.
  - If your dose is 90 mg, you will receive either one 90 mg prefilled syringe or two 45 mg prefilled syringes. **If you receive two 45 mg prefilled syringes for a 90 mg dose, you will need to give yourself two injections, one right after the other.**
- Children 12 years of age and older with psoriasis who weigh 132 pounds or more may use a prefilled syringe.
- Check the expiration date on the prefilled syringe and carton. If the expiration date has passed, do not use it. If the expiration date has passed call your doctor or pharmacist, or call 1-800-JANSSEN (1-800-526-7736) for help.
- Make sure the syringe is not damaged.
- **The needle cover on the prefilled syringe contains latex. Do not handle the needle cover on the STELARA prefilled syringe if you are allergic to latex.**
- Check your prefilled syringe for any particles or discoloration. Your prefilled syringe should look clear and colorless to light yellow with few white particles.
- Do not use if it is frozen, discolored, cloudy or has large particles. Get a new prefilled syringe.
- **Do not shake the prefilled syringe at any time.** Shaking your prefilled syringe may damage your STELARA medicine. If your prefilled syringe has been shaken, do not use it. Get a new prefilled syringe.
- To reduce the risk of accidental needle sticks, each prefilled syringe has a needle guard that is automatically activated to cover the needle after you have given your injection. Do not pull back on the plunger at any time.

Gather the supplies you will need to prepare and to give your injection. (See Figure A)

You will need:

- antiseptic wipes

- cotton balls or gauze pads
- adhesive bandage
- your prescribed dose of STELARA **(See Figure B)**
- FDA-cleared sharps disposal container. **See "Step 4: Dispose of the syringe."**

Figure A

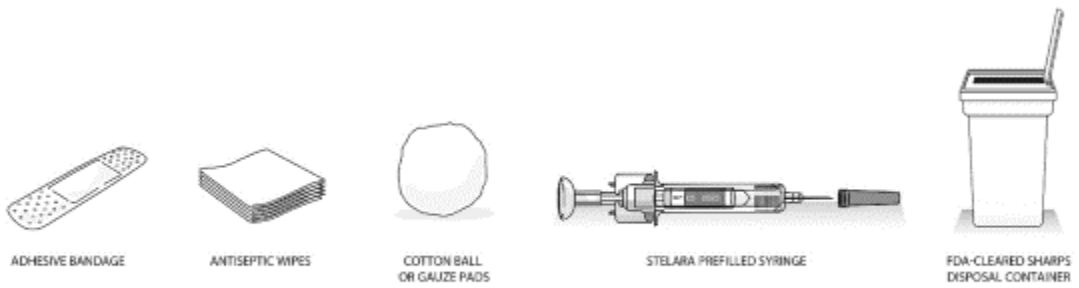
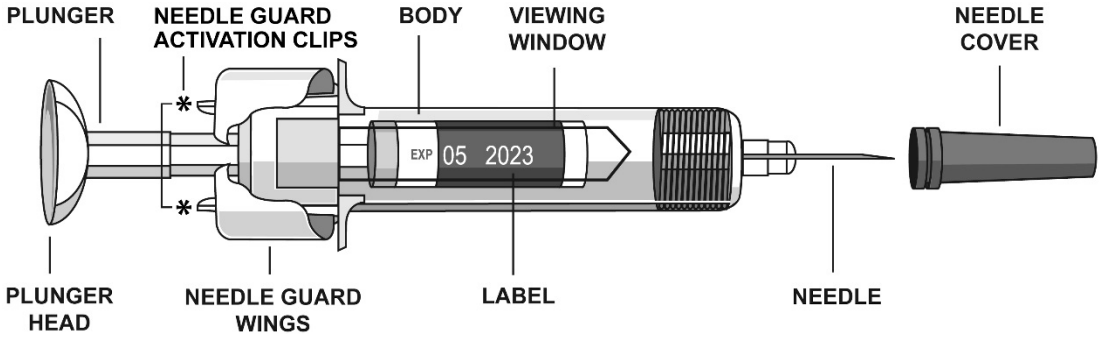


Figure B
To prevent early activation of the needle safety guard, do not touch the NEEDLE GUARD ACTIVATION CLIPS at any time during use.



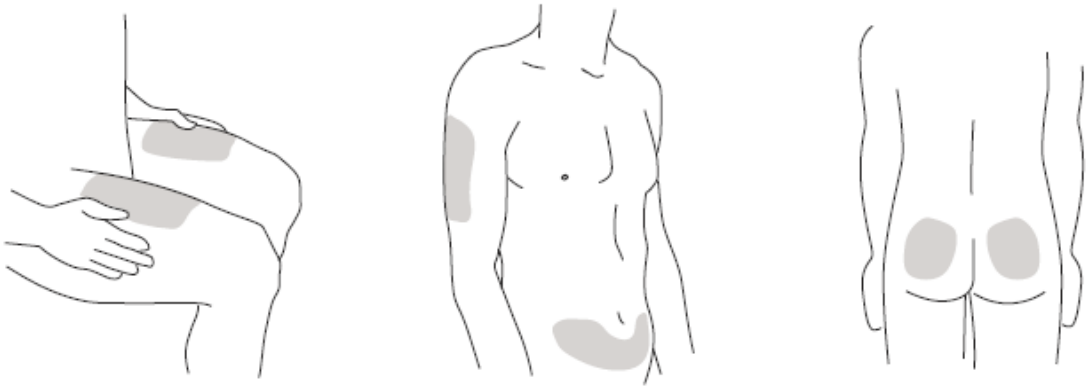
Step 1: Prepare the injection.

- Choose a well-lit, clean, flat work surface.
- Wash your hands well with soap and warm water.
- Hold the prefilled syringe with the covered needle pointing upward.

Step 2: Prepare your injection site

- Choose an injection site around your stomach area (abdomen), buttocks, upper legs (thighs). If a caregiver is giving you the injection, the outer area of the upper arms may also be used. **(See Figure C)**
- **Use a different injection site for each injection. Do not** give an injection in an area of the skin that is tender, bruised, red or hard.
- Clean the skin with an antiseptic wipe where you plan to give your injection.
- **Do not** touch this area again before giving the injection. Let your skin dry before injecting.
- **Do not** fan or blow on the clean area.

Figure C

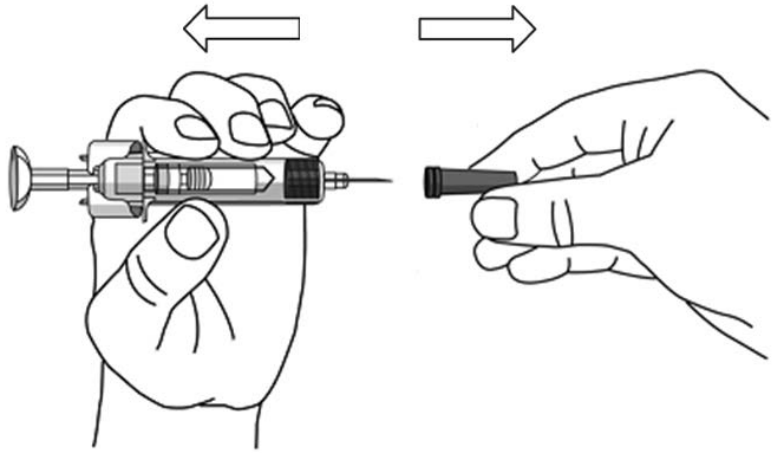


*Areas in gray are recommended injection sites.

Step 3: Inject STELARA

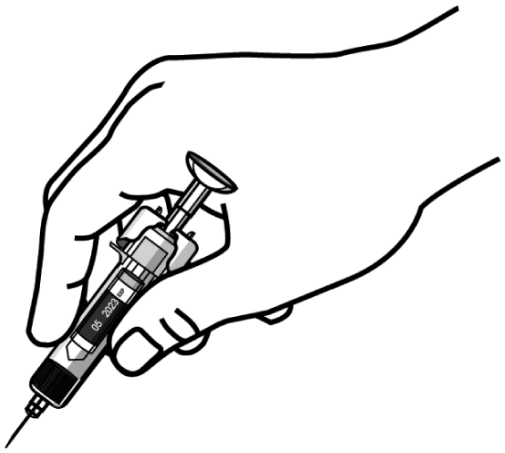
- Remove the needle cover when you are ready to inject your STELARA.
- **Do not** touch the plunger while removing the needle cover.
- Hold the body of the prefilled syringe with one hand, and pull the needle cover straight off. **(see Figure D)**
- Put the needle cover in the trash.
- You may also see a drop of liquid at the end of the needle. This is normal.
- **Do not** touch the needle or let it touch anything.
- **Do not** use the prefilled syringe if it is dropped without the needle cover in place. Call your doctor, nurse or health professional for instructions.

Figure D



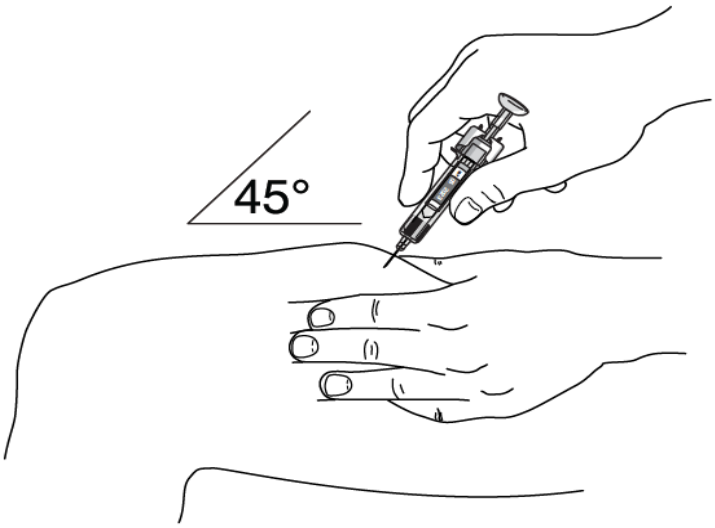
- Hold the body of the prefilled syringe in one hand between the thumb and index fingers. **(See Figure E)**

Figure E



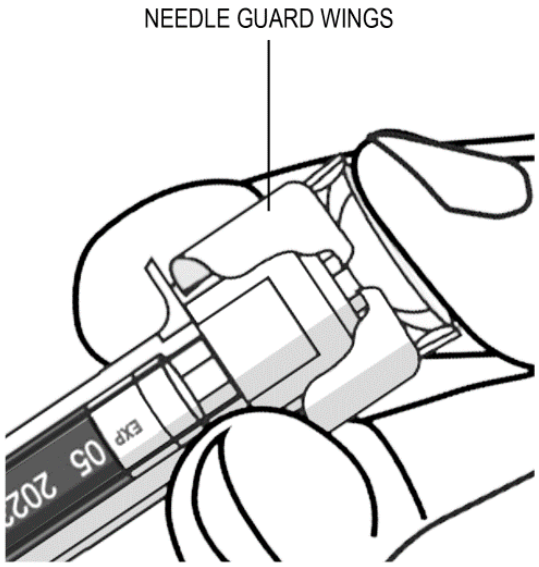
- **Do not** pull back on the plunger at any time.
- Use the other hand to gently pinch the cleaned area of skin. Hold firmly.
- Use a quick, dart-like motion to insert the needle into the pinched skin at about a 45-degree angle. **(See Figure F)**

Figure F



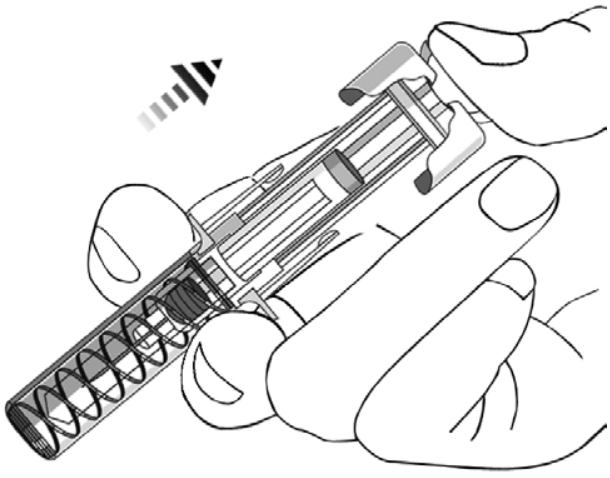
- Inject all of the liquid by using your thumb to push in the plunger until the plunger head is completely between the needle guard wings. **(See Figure G)**

Figure G



- When the plunger is pushed as far as it will go, keep pressure on the plunger head. Take the needle out of the skin and let go of the skin.
- Slowly take your thumb off the plunger head. This will let the empty syringe move up until the entire needle is covered by the needle guard. **(See Figure H)**

Figure H



- When the needle is pulled out of your skin, there may be a little bleeding at the injection site. This is normal. You can press a cotton ball or gauze pad to the injection site if needed. Do not rub the injection site. You may cover the injection site with a small adhesive bandage, if necessary.

If your dose is 90 mg, you will receive either one 90 mg prefilled syringe or two 45 mg prefilled syringes. If you receive two 45 mg prefilled syringes for a 90 mg dose, you will need to give yourself a second injection right after the first. Repeat Steps 1-3 for the second injection using a new syringe. Choose a different site for the second injection.

Step 4: Dispose of the syringe.

- Put the syringe in a FDA-cleared sharps disposal container right away after use. **Do not throw away (dispose of) loose syringes in your household trash.**
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - made of heavy-duty plastic.
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out.
  - upright and stable during use,
  - leak-resistant,
  - and properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be local or state laws about how to throw away syringes and needles. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- Do not dispose of your sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your sharps disposal container.
- If you have any questions, talk to your doctor or pharmacist.

Keep STELARA and all medicines out of the reach of children.

Prefilled Syringe Manufactured by:
Janssen Biotech, Inc., Horsham, PA 19044, US License No. 1864 at Baxter Pharmaceutical Solutions, Bloomington, IN 47403 and at Cilag AG, Schaffhausen, Switzerland

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Revised: 10/2019

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761044Orig1s003

MULTI-DISCIPLINE REVIEW

NDA/BLA Multidisciplinary Review and Evaluation

Application Type	Supplemental Biologics License Application (sBLA)
Application Number(s)	761044, supplement 3
Priority or Standard	Standard
Submit Date(s)	December 20, 2018
Received Date(s)	December 20, 2018
PDUFA Goal Date	October 20, 2019
Division/Office	Gastroenterology and Inborn Errors Products/ODEIII
Review Completion Date	October 17, 2019
Established/Proper Name	ustekinumab
(Proposed) Trade Name	Stelara
Pharmacologic Class	Human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody against the p40 subunit of the IL-12 and IL-23 cytokines (IL-12 and -23 antagonist)
Code name	CNTO1275
Applicant	Janssen Biotech, Inc.
Dosage form	Injectable
Applicant Proposed Dosing Regimen	A single intravenous infusion dose of Stelara® using the weight-based dosage regimen: • 55 kg or less: 260 mg • More than 55 kg to 85 kg: 390 mg • More than 85 kg: 520 mg The recommended maintenance dosage is a subcutaneous 90 mg dose administered 8 weeks after the initial intravenous dose, then every 8 weeks thereafter.
Applicant Proposed Indication(s)/Population(s)	Stelara is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (b) (4) (b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Stelara is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis
Recommended Dosing Regimen	A single intravenous infusion dose of Stelara® using the weight-based dosage regimen: • 55 kg or less: 260 mg • More than 55 kg to 85 kg: 390 mg • More than 85 kg: 520 mg The recommended maintenance dosage is a subcutaneous 90 mg dose administered 8 weeks after the initial intravenous dose, then every 8 weeks thereafter.

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Reviewers of Multidisciplinary Review and Evaluation

Regulatory Project Manager	Kelly Richards, RN, MSN
Nonclinical Reviewer	—
Nonclinical Team Leader	—
Office of Clinical Pharmacology Reviewer(s)	Anand Balakrishnan, PhD Justin Earp, PhD
Office of Clinical Pharmacology Team Leader(s)	Insook Kim, PhD Lian Ma, PhD
Clinical Reviewer	Frank A. Anania, MD
Clinical Team Leader	Juli Tomaino, MD
Statistical Reviewer/ Statistical Analyst	Shahla Farr, MS/Min Wang, MS
Statistical Team Leader	George Kordzakhia, PhD
Cross-Disciplinary Team Leader	Juli Tomaino, MD
Deputy Division Director (OB)	Gregory Levin, PhD
Division Director (OB)	Laura Lee Johnson, PhD
Division Associate Director (DGIEP) (designated signatory authority)	Jessica J. Lee, MD

Additional Reviewers of Application

OPQ	Steve Bowen, Maria Gutierrez-Lugo, PhD
Microbiology	—
OPDP	Adewale Adeleye, Pharm. D.
OSI	Susan Leibenhaut, MD, Susan Thompson, MD
OSE/DEPI	Joel Weissfeld, MD, MPH/Patricia Bright, MPH, PhD
OSE/DMEPA	Idalia Rychlik
OSE/DRISK	—
Other	Kelly Jackson

OPQ = Office of Pharmaceutical Quality
OPDP = Office of Prescription Drug Promotion
OSI = Office of Scientific Investigations
OSE = Office of Surveillance and Epidemiology
DEPI = Division of Epidemiology
DMEPA = Division of Medication Error Prevention and Analysis
DRISK = Division of Risk Management

Unireview Section Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Anand Balakrishnan, Ph.D.	OTS/OCP/DCPIII	Section 6	**Select one:** _X_ Authored ___ Approved
	Signature: Anand Balakrishnan -S Digitally signed by Anand Balakrishnan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001742021, cn=Anand Balakrishnan -S Date: 2019.10.10 12:10:34 -04'00'			
Clinical Pharmacology Team Leader	Insook Kim, Ph.D.	OTS/OCP/DCPIII	Section 6 Appendix 17.3	**Select one:** __ Authored _X_ Approved
	Signature: Insook Kim -S Digitally signed by Insook Kim -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Insook Kim -S, 0.9.2342.19200300.100.1.1=1300416436 Date: 2019.10.10 19:58:47 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Statistical Team Leader	George Kordzakhia, Ph.D.	OB/DBIII	Sections 8.1, Appendix 17.5	**Select one:** __X_ Authored _X_ Approved
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Deputy Director	Gregory Levin, Ph.D.	OB/DBIII	Sections 1, 7, 8, Appendix 17.5	**Select one:** ___ Authored _X_ Approved
	Signature: Gregory P. Levin -S Digitally signed by Gregory P. Levin -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001127703, cn=Gregory P. Levin -S Date: 2019.10.15 06:57:33 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Pharmacometrics Reviewer	Justin Earp, Ph.D.	OTS/OCP/DPM	Sections: 6 Appendix 17.3	**Select one:** _X_ Authored ___ Approved
	Signature: Justin C. Earp -S Digitally signed by Justin C. Earp -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Justin C. Earp -S, 0.9.2342.19200300.100.1.1=1300436664 Date: 2019.10.10 17:00:56 -04'00'			
Pharmacometrics Team Leader	Lian Ma, Ph.D.	OTS/OCP/DPM	Sections: 6 Appendix 17.3	**Select one:** ___ Authored _X_ Approved
	Signature: Lian Ma -S Digitally signed by Lian Ma -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lian Ma -S, 0.9.2342.19200300.100.1.1=2000825336 Date: 2019.10.10 17:04:21 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Frank Anania, M.D.	ODEIII/DGIEP	Sections: 2, 3, 7.1 Sections: 8.1.1; 8.2-8.10; 9-13; 17.1; 17.2	**Select one:** __X__ Authored _X_Approved
	Signature: Frank A. Anania -S Digitally signed by Frank A. Anania -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002405923, cn=Frank A. Anania -S Date: 2019.10.10 09:35:34 -04'00'			
Clinical Team Leader/CDTL	Juli Tomaino, M.D.	ODEIII/DGIEP	Authored: Sections 1, 2,3, 4.1, 7, 8, 9, 10, 11, 12, 13 Approved: all sections	**Select one:** _X_ Authored _X_ Approved (all sections)
	Signature: Juli A. Tomaino -S Digitally signed by Juli A. Tomaino -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001149989, cn=Juli A. Tomaino -S Date: 2019.10.16 12:47:04 -04'00'			
Associate Director	Jessica Lee, M.D., MMsc	ODEIII/DGIEP	Sections: 14 All sections approved	**Select one:** __X__ Authored _X_ Approved
	Signature: Jessica J. Lee -S Digitally signed by Jessica J. Lee -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jessica J. Lee -S, 0.9.2342.19200300.100.1.1=2000596373 Date: 2019.10.16 16:21:23 -04'00'			

Glossary

ADA	antidrug antibodies
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ARDS	acute respiratory distress syndrome
ARIA	Active Risk Identification and Analysis
5-ASA	5-aminosalicylate
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AZA	azathioprine
BLA	biologics license application
CD	Crohn's disease
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CMH	Cochran-Mantel-Haenszel
CMV	cytomegalovirus
CV	cardiovascular
CYP	cytochrome P450
DMC	data monitoring committee
DVT	deep venous thrombosis
eCRF	electronic case report form
EIM	extraintestinal manifestation
E-R	exposure-response
FDA	Food and Drug Administration
GS	Geboes Score
HHV-6	human herpesvirus-6
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICH	International Conference on Harmonisation
IgG1κ	human immunoglobulin G1 kappa
IL	interleukin
IND	investigational new drug
IV	intravenous
LTE	long-term extension
MACE	major adverse cardiovascular events
6-MP	6-mercaptopurine
MTX	methotrexate
NAbs	neutralizing antibodies
NDA	new drug application
NHI	Nancy Histologic Index
OFV	objective function value
OSI	Office of Scientific Investigation
PGA	Physician Global Assessment

PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PRO	patient-reported outcome
PSC	primary sclerosing cholangitis
Q8/12W	every 8/12 weeks
REMS	risk evaluation and mitigation strategy
RHI	Robarts Histology Index
RPLS	reversible posterior leukoencephalopathy syndrome
SAA	serum amyloid A
SAE	serious adverse event
SC	subcutaneous
SDC	Sponsor Decision Committee
TB	tuberculosis
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
UC	ulcerative colitis
ULN	upper limit of normal
WBC	white blood cell

1. Executive Summary

1.1. Product Introduction

Stelara® (ustekinumab) is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that is directed against the p40 subunit of interleukin (IL)-12 and IL-23 cytokines. The consequence of noncovalent IgG1κ-p40 association prevents both IL-12 and IL-23 from binding T helper cells and natural killer cells, thereby inhibiting downstream signal transduction events which prevents a robust inflammatory response.

Ustekinumab has been approved for adults with moderate to severe plaque psoriasis since 2009, adults with active psoriatic arthritis since 2013, and adolescents ages 12 to 17 years of age with psoriasis since 2017 (biologics license application (BLA) 125261).

In 2016, ustekinumab was approved for the treatment of adult patients with moderately to severely active Crohn's disease (CD) who have:

- Failed or were intolerant to treatment with immunomodulators or corticosteroids, but never failed treatment with a biologic (TNF antagonists or vedolizumab at the approved dose for UC) or
- Failed or were intolerant to treatment with one or more biologics (TNF antagonists or vedolizumab at the approved dose for UC)

The initial dose is administered intravenously (IV) using weight-based dosing (see table below).

Table 1. Initial Intravenous Dosage of Stelara

Body Weight of Patient at Time of Dosing	Dose	Number of 130 mg/26 mL (5 mg/mL) Stelara Vials
55 kg or less	260 mg	2
More than 55 kg to 85 kg	390 mg	3
More than 85 kg	520 mg	4

Maintenance dosing is 90 mg subcutaneously (SC) administered 8 weeks after induction and every 8 weeks thereafter.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The data submitted in this BLA establish a clinical benefit in adult patients with moderately to severely active ulcerative colitis (UC), and the use of Stelara (ustekinumab) is supported by evidence from adequate and well-controlled trials. The submitted evidence demonstrates the efficacy of ustekinumab for the treatment of patients with moderately to severely active ulcerative colitis and the evaluation of safety was adequate to support product approval and labeling. This product offers a new mechanism of action and another pharmacologic agent for the treatment of UC.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The data submitted in this supplemental BLA (sBLA) establish a clinical benefit in adult patients with moderately to severely active ulcerative colitis (UC), 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 UC and is already approved for the treatment of moderately to severely active Crohn's disease. In support of this sBLA, the Applicant conducted one 8-week induction trial and one 44-week maintenance trial (total duration of 52 weeks). At entry into the trial, roughly 50% of all patients across each treatment arm were defined as having failed prior biologic therapy ("biological failures").

The definition of clinical remission (primary endpoint) was selected while the Division's approach to endpoints was evolving and the Division did not object to the use of the Applicant's definition. Since that time, a Draft Guidance has been published describing the current endpoint approach for UC. Therefore, for both the induction and maintenance trials, the Applicant's definition differed from the Division's currently recommended definition. The results of the Applicant's efficacy analyses did not differ substantially from the FDA analyses using currently recommended endpoint definitions for clinical remission, endoscopic improvement, and clinical response. The Applicant included exploratory analyses using endpoint definitions that align with the Division's current recommendations. Therefore, the trial results described in this review (b) (4) (b) (4) are based on currently recommended approach to efficacy endpoints for clinical trials evaluating therapies for the treatment of UC. A comparison of the Applicant's primary efficacy endpoint definition (clinical remission) and secondary endpoint of clinical response with the Division's recommended definitions are below; note that the subscores refer to the subscores of the Mayo Score. The differences are shown in **bold** font.

Clinical Remission

- Applicant's definition: rectal bleeding subscore =0, **endoscopy subscore = 0 or 1**, **absolute stool number ≤3**, where the absolute stool number is the average number of stools per day over a 3-day period.
- Recommended definition: rectal bleeding subscore =0, **endoscopy subscore = 0 or 1 (modified so that 1 does not include friability), stool frequency subscore =0 or 1.**

Clinical Response

- Applicant's definition: a decrease from baseline in the **Mayo score of ≥3 points** and ≥30% and either a decrease in the rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1.
- Recommended definition: decrease in the **Mayo score (modified to exclude the Physician Global Assessment component) of ≥2 points** and ≥30% and either a decrease in the rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1.

Additionally, the Applicant's definition of clinical remission, endoscopic improvement, and histologic-endoscopic mucosal improvement (Applicant used the term, "mucosal healing" for this endpoint; the term "histologic-endoscopic mucosal improvement" will be used in this document (b) (4) (b) (4) each relied, in part, on an endoscopic subscore of 1. In the Applicant's prespecified analyses, an endoscopic subscore of 1 was not

modified to exclude the presence of friability. Therefore, the review team evaluated the additional analyses conducted by the Applicant in which patients with an endoscopic subscore of 1 and presence of friability were considered to be nonresponders for each endpoint that relied, in part, on an endoscopic subscore of 1 because the presence of friability (even if considered to be mild by the endoscopist/ central reader) is not consistent with *clinical remission*. There were no substantial differences that changed the interpretation of the trial results and similar to the primary endpoint, the trial results described in this review (b) (4) are based on currently recommended approach in which an endoscopic subscore of 1 is modified to exclude the presence of friability.

The data from the 8-week, multicenter, randomized, double-blind, placebo-controlled, parallel group trial in adult patients with moderately to severely active UC (defined by a Mayo score of 6 to 12 inclusive, including an endoscopy subscore ≥2 at baseline) evaluated a single intravenous infusion of three dose arms: a weight-based dose of approximately 6 mg/kg, 130 mg, or placebo. The trial results demonstrated statistical significance on multiple clinically relevant primary and ranked secondary endpoints. The trial evaluated 961 patients who failed or were intolerant to treatment with immunomodulators or corticosteroids, but never failed treatment with a biologic (TNF antagonists or vedolizumab at the approved dose for UC), or patients who failed or were intolerant to treatment with one or more biologics; at entry into the trial, roughly 50% of all patients across each treatment arm were defined as having failed prior biologic therapy ("biological failures"). Based on the primary analysis method, significantly greater proportions of patients in the ustekinumab 6 mg/kg and 130 mg groups achieved clinical remission (primary endpoint) at Week 8 (19.3% and 16.9%, respectively) when compared with patients in the placebo group (6.9%); p-values <0.001 for both comparisons. Similarly, in both biologic-naive and prior biological failure subgroups, the proportion of patients achieving remission was larger in the ustekinumab treatment groups compared to placebo. There were three multiplicity-controlled secondary endpoints evaluated at Week 8: endoscopic healing, clinical response, and histologic-endoscopic mucosal improvement. Both ustekinumab treatment arms achieved statistically significant improvement in all three secondary endpoints when compared to placebo. In both biologic-naive and prior biological failure subgroups, the proportion of patients achieving remission was larger in the ustekinumab treatment groups compared to placebo.

Patients who achieved at least clinical response 8 weeks after induction were eligible to be rerandomized into the 44-week "maintenance" trial. Patients were randomized to ustekinumab subcutaneous injection of 90 mg every 8 weeks (Q8W), 90 mg every 12 weeks (Q12W), or placebo. Clinical remission at Week 44 was the primary endpoint for the maintenance trial. At Week 44, both the ustekinumab 90 mg SC Q8W dose arm (44.9%; p<0.001) and the Q12W dose arm (38.4%; p=0.0121) were statistically significant compared to placebo (23.6%). Similarly, in both biologic-naive and prior biological failure subgroups, the proportion of patients achieving remission was larger in the ustekinumab treatments compared to placebo. There were four multiplicity-controlled secondary endpoints evaluated at the end of the double-blind period: maintenance of clinical response at Week 44, endoscopic improvement at Week 44, corticosteroid-free clinical remission at Week 44, and maintenance of clinical remission at Week 44 among patients who had achieved clinical remission at maintenance baseline. At Week 44, both the ustekinumab 90 mg SC Q8W dose arm and the Q12W dose arm were statistically significant compared to placebo on all four secondary endpoints. Similarly, in both biologic-naive and prior biological failure subgroups, the proportion of patients achieving these endpoints was larger in the ustekinumab treatments compared to placebo.

The histologic-endoscopic mucosal improvement endpoint was multiplicity-controlled at Week 8 of the induction but not at Week 44 in the maintenance trial. This endpoint is potentially clinically meaningful because improvement in the mucosa has been linked to improvements in

steroid use, hospitalizations, etc. However, correlation does not necessarily imply causation so there remains some uncertainty about whether drug effects on histologic endpoints will reliably predict drug effects on long-term clinical outcomes. The relationship of this histologic-endoscopic mucosal improvement endpoint, as defined in the clinical trials, with long-term clinical outcomes (e.g., reduction in hospitalization, colectomy, malignancy rates) was not evaluated. At Week 44, histologic-endoscopic mucosal improvement (modified so that patients with friability are considered as nonresponders) was also observed in a larger proportion of ustekinumab-treated patients compared to placebo.

The safety profile was generally comparable to the known safety profile already described in the product label for the psoriasis, psoriatic arthritis, and Crohn's disease indications, and overall similar to the safety profile of other immunosuppressant therapies used for the treatment of inflammatory bowel disease. The most common adverse reactions occurring in ≥3% of patients and at a higher rate than placebo during the induction trial included nasopharyngitis. In the maintenance trial, the most common adverse reactions occurring in ≥3% of patients and at a higher rate than placebo included nasopharyngitis, headache, abdominal pain, influenza, fever, diarrhea, sinusitis, fatigue, and nausea. Serious or other clinically significant infections included gastroenteritis, ophthalmic herpes zoster, pneumonia, and listeriosis.

Reversible posterior leukoencephalopathy syndrome (RPLS) and malignancy have been reported in other patient populations for which ustekinumab is indicated and are described in the Warnings and Precautions section of the current label. There were no cases of RPLS and a small number of malignancies identified during the phase 3 clinical trials in UC. There were 5 malignancies reported in the ustekinumab-treated patients and none in the placebo group. Although the specific types of nonmelanoma skin cancers are listed in the label under the psoriasis indication, the proportion of patients with nonmelanoma skin cancers in the UC (and CD) population was smaller compared to the proportion of patients in the psoriasis population with nonmelanoma skin cancers (1.5% of Stelara-treated patients with psoriasis versus 0.2% of patients with CD and 0.5% of patients with UC). Other malignancies reported during the phase 3 trials in patients with UC, including one patient with malignant melanoma, were associated with other confounding factors that made it difficult to establish causality to treatment with ustekinumab. Therefore, a description in the label of the specific types of malignancies does not seem warranted.

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 UC, there remains some uncertainty about the potential risk of malignancy in this patient population due to the small numbers of patients and short duration of exposure in controlled trials. In addition, (1) ustekinumab is a first-in-class therapy for UC, (2) patients with UC 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 UC includes introduction of an intravenous dose, followed by higher dosage regimen for chronic administration as compared to the doses previously approved for other non-inflammatory bowel disease 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 postmarketing setting. The Applicant is conducting a postmarketing study to evaluate these potential risks in patients with Crohn's disease and may also enroll patients with UC into the ongoing trial to meet the requirements of the postmarketing study.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Ulcerative colitis (UC), an inflammatory bowel disease (IBD), is a chronic, relapsing disease of the colonic mucosa. The typical age of onset is between the ages of 15 and 30. UC may affect as many as 907,000 Americans; the annual incidence rates of UC in the United States range from 1.55 to 15.0 cases per 100,000 person-years, and the prevalence ranges from 117 to 238 cases per 100,000 persons. Patients with UC most commonly present with bloody diarrhea, rectal bleeding, tenesmus, urgency, abdominal pain, and passage of mucus. Disease of moderate to severe activity may be associated with systemic symptoms, including fatigue, fever, anorexia, nausea, weight loss, and dehydration. Patients may also experience symptoms from anemia and hypoalbuminemia, including dyspnea and peripheral edema. UC is associated with many extraintestinal manifestations (EIMs), which have been reported to affect a wide variety of organ systems, most commonly joints, skin, eyes, kidneys, and hepatobiliary tract.	UC is a chronic, relapsing disease of the colonic mucosa. Patients with UC most commonly present with bloody diarrhea, rectal bleeding, tenesmus, urgency, abdominal pain, and passage of mucus. If left untreated or poorly treated with residual, ongoing inflammation, patients may suffer from significant morbidity and/or mortality.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	The overall goal in the treatment and management of UC is to "induce" and "maintain" remission. The choice of therapy is guided by the disease severity, extent of disease, 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 receptor blockers). 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 UC. There remains a need for novel therapies as not all patients will respond or have continued response to any given treatment.	Ustekinumab offers a new mechanism of action for the treatment of UC in patients who have failed prior therapies. Additional therapies are needed since many patients lose response over time to currently available therapies.
Benefit ***(continued below)***	The efficacy of ustekinumab was demonstrated in one 8-week induction" trial and one 44-week maintenance trial; total duration of 52 weeks. Data were submitted from one 8-week, multicenter, randomized, double-blind, placebo-controlled, parallel group trial in adult patients with active moderate to severe UC. Patients were randomized to a single weight-based intravenous (IV) infusion of approximately 6 mg/kg, 130 mg, or placebo.	One 8-week induction trial 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 therapy with corticosteroids, immunomodulators, or at least one biologic (TNF blockers or vedolizumab at the approved dose for UC).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit ***(continued below)***	The trial evaluated 961 patients who failed or were intolerant to treatment with immunomodulators or corticosteroids, but never failed treatment with a biologic (TNF antagonists or vedolizumab at the approved dose for UC), or patients who failed or were intolerant to treatment with one or more biologics; at entry into the trial, roughly 50% of all patients across each treatment arm were defined as having failed prior biologic therapy ("biological failures"). Based on the primary analysis method, significantly greater proportions of patients in the ustekinumab 6 mg/kg and 130 mg groups achieved clinical remission (primary endpoint) at Week 8 (19.3% and 16.9%, respectively) when compared with patients in the placebo group (6.9%); p-values <0.001 for both comparisons. Similarly, in both bio-naive and prior biological failure subgroups, the proportion of patients achieving remission was larger in the ustekinumab treatments compared to placebo. There were three multiplicity-controlled secondary endpoints evaluated at Week 8: endoscopic healing, clinical response, and histologic-endoscopic mucosal improvement. Both ustekinumab treatment arms achieved statistically significant improvement in all three secondary endpoints when compared to placebo. In both bio-naïve and prior biological failure subgroups, the proportion of patients achieving remission was larger in the ustekinumab treatment groups compared to placebo.	At Week 8, after a single weight-based IV infusion of 6 mg/kg, ustekinumab demonstrated statistical significance over placebo on multiple clinically relevant endpoints, including clinical remission, endoscopic healing, clinical response, and histologic-endoscopic mucosal improvement.

Benefit ***(continued below)***	Patients who achieved at least clinical response 8 weeks after the induction dose were eligible to be rerandomized into the 44-week "maintenance" trial. Patients were randomized to ustekinumab subcutaneous injection of 90 mg every 8 weeks (Q8W), 90 mg every 12 weeks (Q12W), or placebo. Clinical remission at Week 44 was the primary endpoint for the maintenance study. At Week 44, both the ustekinumab 90 mg subcutaneous (SC) Q8W dose arm (44.9%; p<0.001) and the Q12W dose arm (38.4%; p=0.0121) were statistically significant compared to placebo (23.6%). Similarly, in both biologic-naive and prior biological failure subgroups, the proportion of patients achieving remission was larger in the ustekinumab treatments compared to placebo. There were four multiplicity-controlled secondary endpoints evaluated at the end of the double-blind period: maintenance of clinical response at Week 44, endoscopic improvement at Week 44, corticosteroid-free clinical remission at Week 44, and maintenance of clinical remission at Week 44 among patients who had achieved clinical remission at maintenance baseline. The histologic-endoscopic mucosal improvement endpoint was multiplicity-controlled at Week 8 of the induction but not at Week 44 in the maintenance study. This endpoint is potentially clinically meaningful because improvement in the mucosa has been linked to improvements in steroid use, hospitalizations, etc. However, correlation does not necessarily imply causation so there remains some uncertainty about whether drug effects on histologic endpoints will reliably predict drug effects on long-term clinical outcomes. The relationship of this histologic-endoscopic mucosal improvement endpoint, as defined in the clinical trials, with long-term clinical outcomes (e.g., reduction in hospitalization, colectomy, malignancy rates) was not evaluated. At Week 44, histologic-endoscopic	At Week 44, ustekinumab 90 mg SC Q8W demonstrated statistical significance over placebo on multiple clinically relevant endpoints including, clinical remission at Week 44, maintenance of clinical response at Week 44, endoscopic improvement at Week 44, corticosteroid-free clinical remission at Week 44, and maintenance of clinical remission at Week 44 among patients who had achieved clinical remission at maintenance baseline.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	mucosal improvement (modified so that patients with friability are considered as nonresponders) was also observed in a larger proportion of Stelara-treated patients compared to placebo.	
Benefit *(continued)*	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 Q8W thereafter. The exposure-response (E-R) relationship also provides supportive evidence of clinical efficacy for the recommended dosing.	
Risk and Risk Management *(continued below)*	The safety profile was generally comparable to the known safety profile already described in the product label for the psoriasis, psoriatic arthritis, and Crohn's disease indications, and overall similar to the safety profile of other immunosuppressant therapies used for the treatment of inflammatory bowel disease. The most common adverse reactions occurring in ≥3% of patients and at a higher rate than placebo during the induction trial included nasopharyngitis. In the maintenance trial, the most common adverse reactions occurring in ≥3% of patients and at a higher rate than placebo included nasopharyngitis, headache, abdominal pain, influenza, fever, diarrhea, sinusitis, fatigue, and nausea. Serious or other clinically significant infections included gastroenteritis, ophthalmic herpes zoster, pneumonia, and listeriosis. Reversible posterior leukoencephalopathy syndrome (RPLS) was reported in other patient populations for which ustekinumab is indicated and is described in the Warning and Precautions section of the current label. There were no identified during the phase 3 clinical trials in UC.	The safety profile was generally comparable to the known safety profile already described in the product label for the approved 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 RPLS identified during the phase 3 clinical trials in UC. The safety concerns identified will be described in the product label.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management *(continued)*	Malignancy is also described in the Warnings and Precautions section of the current product label. There were 5 malignancies reported in the ustekinumab-treated patients and none in the placebo group. Although the specific types of nonmelanoma skin cancers are listed in the label under the psoriasis indication, the proportion of patients with nonmelanoma skin cancers in the UC (and CD) population was smaller compared to the proportion of patients in the psoriasis population with nonmelanoma skin cancers (1.5% of Stelara-treated patients with psoriasis versus 0.2% of patients with CD and 0.5% of patients with UC). Other malignancies reported during the phase 3 trials in patients with UC, including one patient with malignant melanoma, were associated with other confounding factors that made it difficult to establish causality to treatment with Stelara. Therefore, a description in the label of the specific types of malignancies does not seem warranted but malignancy will be further explored in the post-marketing setting.	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 UC, there is some uncertainty about the risk of malignancy about the potential effect on malignancy due to the small numbers of patients and short duration of exposure in controlled periods. In addition, (1) ustekinumab is a first-in-class therapy for ulcerative colitis, (2) patients with ulcerative colitis 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 ulcerative colitis includes introduction of an intravenous dose, following by higher dosage regimen for chronic administration as compared to the doses previously approved for other non-IBD indications. Therefore, longer term exposure in a larger patient population is necessary to evaluate the risk of malignancy. The Applicant is conducting a postmarketing study to evaluate these potential risks in patients with Crohn's disease and may also enroll patients with UC into the ongoing trial to meet the requirements of the postmarketing study. In addition, the safety, efficacy, and pharmacokinetics, as well as the long-term safety, of ustekinumab in pediatric patients 2 to 17 years of age with moderately severely active UC will be evaluated in two postmarketing commitments.

1.4. Patient Experience Data

Patient Experience Data Relevant to This Application (check all that apply)

X	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient-reported outcome (PRO)	Efficacy Section 8.1
		□	Observer-reported outcome (ObsRO)	
		□	Clinician-reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify):		
□	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	□	Input informed from participation in meetings with patient stakeholders		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Other: (Please specify):		
□	**Patient experience data was not submitted as part of this application.**			

2. Therapeutic Context

2.1. Analysis of Condition

Ulcerative colitis (UC), an IBD, is a chronic, intermittently relapsing disease of the colonic mucosa. The disease typically begins in the rectum and may extend proximally in an uninterrupted pattern into the colon, involving the entire colon (pancolitis), the left colon, or may manifest as isolated rectosigmoid disease. The typical age of onset is between the ages of 15 and 30 (Loftus et al. 2007). UC may affect as many as 907,000 Americans (Crohn's and Colitis Foundation). The annual incidence rates (IRs) of UC in the United States range from 1.55 to 15.0 cases per 100,000 person-years, and the prevalence ranges from 117 to 238 cases per 100,000 persons (Loftus et al. 2007; Kappelman et al. 2013).

While the pathogenesis of UC is not completely understood, it involves the complex interaction of genetic predisposition, epithelial barrier defects, dysregulated host immune responses, and environmental factors (Ungaro et al. 2017). Abnormal leukocyte trafficking to the gastrointestinal (GI) mucosa is believed to be an important component leading to colonic inflammation. Symptoms can vary depending on the severity of inflammation and extent of disease. Patients with UC most commonly present with bloody diarrhea, rectal bleeding, tenesmus, urgency, abdominal pain, and passage of mucus. Disease of moderate to severe activity may be associated with systemic symptoms, including fatigue, fever, anorexia, nausea, weight loss, and dehydration. Patients may also experience symptoms from anemia and hypoalbuminemia, including dyspnea and peripheral edema.

The clinical manifestations of UC are not limited to the colon. UC is associated with many extraintestinal manifestations (EIMs), which have been reported to affect a wide variety of organ systems, most commonly joints, skin, eyes, kidneys, and hepatobiliary tract (Vavricka et al. 2015). Renal manifestations of IBD may include nephrolithiasis, amyloidosis, tubulointerstitial nephritis, and glomerulonephritis (Oikonomou et al. 2011). Other EIMs may include ocular lesions, skin lesions, arthritis, and primary sclerosing cholangitis (PSC). PSC is one of the most important associated conditions that typically affects young males with UC and carries a significant risk of cholangiocarcinoma. Up to 47% of patients with IBD have at least one EIM, and up to one-quarter of those IBD patients with EIMs suffer from more than one EIM. While some EIMs, such as erythema nodosum and episcleritis, occur concurrently with flares of UC, others, including pyoderma gangrenosum, uveitis, and PSC, may occur and progress independently of the bowel inflammation. The former (those that occur with flares) typically improve with treatment of the bowel inflammation, while the latter do not respond to UC therapy (medically or surgically). Given the commonness and diversity of these disorders, EIMs represent a considerable source of morbidity and overall UC disease burden.

UC is a serious progressive disease that can be life-threatening (Torres et al. 2012). There is evidence that the disease extends proximally over time and may also be complicated by structural and functional damage beyond the mucosal layer, leading to giant pseudopolyposis, bridging fibrosis, dysmotility, anorectal incontinence, and possibly impaired gut permeability. Severe colitis can result in ischemic colitis requiring surgical colectomy, which is associated with significant morbidity, including recurrent disease in the rectal pouch (pouchitis) in up to 25% of patients, fecal incontinence, and female infertility. Severe UC also

carries a low, but significant risk (2.5%) of 'toxic megacolon (Marrero et al. 2008). The incidence of toxic megacolon substantially increases from 6% to 17% among those with UC who are hospitalized (Gan et al. 2003). The treatment for this fatal complication is total procto-colectomy, leaving patients with a colostomy for life.

This disease also carries with it an increased risk of colorectal cancer, partially due to chronic inflammation in patients with long-standing UC (Velayos et al. 2006). The goals of UC treatment are to induce and maintain remission of clinical symptoms and mucosal inflammation in order to improve quality of life, decrease hospitalizations, and reduce the risk of surgery and colon cancer (Hoentjen et al. 2011). With poorly controlled disease, the rate of developing colorectal cancer increases with time. Ten years after diagnosis, the cumulative probability of developing colorectal cancer is 2% and increases to 18% after 30 years. Overall, the risk of a patient with UC developing colorectal cancer is up to 23-fold higher compared with the general population (Triantafillidis et al. 2009).

2.2. Analysis of Current Treatment Options

The goals of UC treatment include reducing signs and symptoms, reducing long-term corticosteroid use, achieving "mucosal healing," reducing risk of colorectal carcinoma, and improving patient quality of life. For the treatment of mild to moderate UC, oral aminosalicylates, topical 5-ASA, such as mesalamine suppository and enemas, or topical steroids are used (Kornbluth et al. 2010). Topical medications are first-line treatment for distal colitis in those who are willing to use rectal therapy. Oral corticosteroids, such as budesonide or oral prednisone, may be required in patients who are refractory to topical therapies, or who are systemically ill and require more rapid treatment. Mesalamines and budesonide are FDA-approved treatments for mild to moderate UC. Immunomodulators, such as azathioprine and 6-mercaptopurine, can be considered for patients unresponsive to, or dependent on, oral corticosteroids, and for those experiencing disease relapse on aminosalicylates, but these are used off-label.

The currently approved therapies for the treatment of moderate to severe UC are summarized in Table 2 below.

Table 2. Currently Approved Treatments for Moderately to Severely Active UC

FDA Approved Treatments	Relevant Indication	Dosage & Administration	Efficacy Information	Important Safety and Tolerability Issues
Tumor necrosis factor blocker (TNF blocker)				
Infliximab[1] (Remicade®) BLA 103772 Infliximab Biosimilars: Inflectra® (Infliximab-DYYB) BLA 124544 Ixifi® (Infliximab-QBTX) BLA 761072 Renflexis® (Infliximab-ABDA) BLA 761054	Reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use	Intravenous (IV) 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks	69% and 62% of patients taking infliximab 5 mg/kg and 10 mg/kg respectively achieved clinical response at Week 8 39% and 32% of patients taking infliximab 5 mg/kg and 10 mg/kg, respectively, achieved clinical remission at Week 8 35% and 34% of patients taking infliximab 5 mg/kg and 10 mg/kg respectively achieved clinical remission at Week 54 62% and 59% of patients taking infliximab 5 mg/kg and 10 mg/kg respectively achieved mucosal healing at Week 8 45% and 47% of patients taking infliximab 5 mg/kg and 10 mg/kg respectively achieved mucosal healing at Week 54	Boxed Warning Serious infections that may lead to hospitalization or death (including tuberculosis, bacterial, viral, and other opportunistic infections, invasive fungal infections), malignancies (including lymphoma, hepatosplenic T-Cell lymphoma [HSTCL]). In addition, Warnings/Precautions include hepatitis B virus reactivation, hepatotoxicity, hematologic reactions, hypersensitivity (serious infusion reactions including anaphylaxis or serum sickness-like reactions), cardiovascular and cerebrovascular reactions, neurologic reactions. Most common adverse reactions: infections (e.g., upper respiratory, sinusitis, pharyngitis), infusion-related reactions, headache, and abdominal pain.

[1] (Food and Drug Administration 2015)
Abbreviations: BLA = biologics license application; UC = ulcerative colitis

Table 2. Currently Approved Treatments for Moderately to Severely Active UC (continued)

FDA Approved Treatments	Relevant Indication	Dosage & Administration	Efficacy Information	Important Safety and Tolerability Issues
Adalimumab[2] (Humira®) BLA 125057 Adalimumab Biosimilars: Amjevita® (Adalimumab-ATTO) BLA 761024 Cyltezo® (Adalimumab-ADBM) BLA 761058	Inducing and sustaining clinical remission in adult patients with moderately to severely active UC who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP). The effectiveness of HUMIRA has not been established in patients who have lost response to or were intolerant to TNF blocker.	SC Initial dose (Day 1): 160 mg Second dose 2 weeks later (Day 15): 80 mg 2 weeks later (Day 29): Begin a maintenance dose of 40 mg every other week.	Study I: 18.5% of patients receiving adalimumab 160/80 mg achieved clinical remission at Week 8 Study II: 16.5% of patients receiving adalimumab 160/80 mg achieved clinical remission at Week 8. 8.5% of patients receiving adalimumab 160/80 mg achieved sustained clinical remission (clinical remission at both Weeks 8 and 52).	Boxed Warning Serious infections that may lead to hospitalization or death (including tuberculosis, bacterial, viral, and other opportunistic infections, invasive fungal infections), malignancies (including lymphoma, hepatosplenic T-Cell lymphoma [HSTCL]). In addition, Warnings/Precautions include hepatitis B virus reactivation, hepatotoxicity, hematologic reactions, hypersensitivity (serious infusion reactions including anaphylaxis or serum sickness-like reactions), cardiovascular and cerebrovascular reactions, neurologic reactions. Most common adverse reactions: infections (upper respiratory, sinusitis), injection site reactions, headache and rash.

[2] (Food and Drug Administration 2017a)
Abbreviations: BLA = biologics license application; HSTCL = hepatosplenic T-Cell lymphoma; TNF = tumor necrosis factor; UC = ulcerative colitis

Table 2. Currently Approved Treatments for Moderately to Severely Active UC (continued)

FDA Approved Treatments	Relevant Indication	Dosage & Administration	Efficacy Information	Important Safety and Tolerability Issues
Golimumab[3] (Simponi®) BLA 125289	Indicated in adult patients with moderately to severely active UC who have demonstrated corticosteroid dependence or who have had an inadequate response to or failed to tolerate oral aminosalicylates, oral corticosteroids, azathioprine, or 6-mercaptopurine for: • inducing and maintaining clinical response • improving endoscopic appearance of the mucosa during induction • inducing clinical remission • achieving and sustaining clinical remission in induction responders	SC 200 mg initially administered by subcutaneous injection at Week 0, followed by 100 mg at Week 2 and then 100 mg every 4 weeks	Study I: 51% of patients receiving golimumab 200/100 mg achieved clinical response at Week 6 18% of patients achieved clinical remission at Week 6 42% of patients achieved improvement in endoscopic appearance of the mucosa at Week 6 Study II: 50% of patients receiving golimumab 100 mg achieved clinical response through Week 54 28% of patients achieved clinical remission at both Week 30 and Week 54	Boxed Warning Serious infections that may lead to hospitalization or death (including tuberculosis, bacterial, viral, and other opportunistic infections, invasive fungal infections), malignancies (including lymphoma, hepatosplenic T-Cell lymphoma [HSTCL]). In addition, Warnings/Precautions include hepatitis B virus reactivation, congestive heart failure, demyelinating disorders, hematologic cytopenias, hypersensitivity reactions (including anaphylaxis). Most common adverse reactions: upper respiratory tract infection, nasopharyngitis, and injection site reactions.

[3] (Food and Drug Administration 2017b)
Abbreviations: BLA = biologics license application; SC = subcutaneous; TB = tuberculosis; UC = ulcerative colitis

Table 2. Currently Approved Treatments for Moderately to Severely Active UC (continued)

FDA Approved Treatments	Relevant Indication	Dosage & Administration	Efficacy Information	Important Safety and Tolerability Issues
Anti-integrin agent				
Vedolizumab[4] (Entyvio®) BLA 125476	Adult patients with moderately to severely active UC who have had an inadequate response with, lost response to, or were intolerant to a TNF blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids	IV 300 mg infused intravenously over approximately 30 minutes at zero, two and 6 weeks, then every 8 weeks thereafter	Study I: 47% of patients achieved clinical response at Week 6 17% of patients achieved clinical remission at Week 6 Study II: 42% of patients achieved clinical remission at Week 52 57% of patients achieved clinical response at both Weeks 6 and 52 52% of patients achieved improvement of endoscopic appearance of the mucosa at Week 52	Warnings/Precautions include infusion-related reactions and hypersensitivity reactions, infections, (including serious infections anal abscess, sepsis (some fatal), tuberculosis, salmonella sepsis, Listeria meningitis, giardiasis, and cytomegaloviral colitis), progressive multifocal leukoencephalopathy, and liver injury. Most common adverse reactions: nasopharyngitis, headache, arthralgia, nausea, pyrexia, and upper respiratory tract infection.

[4] (Food and Drug Administration 2014)
Abbreviations: BLA = biologics license application; IV = intravenous; TNF = tumor necrosis factor; UC = ulcerative colitis

Table 2. Currently Approved Treatments for Moderately to Severely Active UC (continued)

FDA Approved Treatments	Relevant Indication	Dosage & Administration	Efficacy Information	Important Safety and Tolerability Issues
Tofacitinib[5] (Xeljanz®) NDA 203214	Adult patients with moderately to severely active UC, who had an inadequate response or who are intolerant to TNF blockers.	Induction: Tofacitinib 10 mg twice daily for 8 weeks; evaluate patients and transition to maintenance therapy depending on therapeutic response. If needed, continue 10 mg twice daily for a maximum of 16 weeks. Discontinue 10 mg twice daily after 16 weeks if adequate therapeutic response is not achieved. Maintenance: Tofacitinib 5 mg twice daily. Limit use of 10 mg twice daily beyond induction to those with loss of response and used for the shortest duration. Use the lowest effective dose of tofacitinib needed to maintain response.	Study UC-I Induction Study: 26% of patients achieved clinical remission at Week 8 who had not failed prior TNF blocker. 11% of patients achieved clinical remission at Week 8 who failed prior use of TNF blocker. Overall, 18% patients receiving tofacitinib achieved clinical remission compared to 8% of placebo-treated patients. Study UC-2 Induction Study: 22% of patients achieved a clinical remission who had no prior treatment with TNF blocker, compared to 8% of placebo-treated patients. 12% of patients had clinical remission failed prior treatment with TNF blocker compared to 0% of placebo-treated patients. Overall, 17% of patients achieved clinical remission compared to 4% of placebo-treated patients. Study UC-3 Maintenance Study: Of 179 patients who were in remission at baseline, 59 were taking placebo, 65 were taking 5 mg po bid of tofacitinib, and 55 patients were administered 10 mg po bid tofacitinib. 46% of patients taking 5 mg bid and 56% of patients treated with 10 mg bid maintained remission at Week 52 compared to 10% of placebo patients. *(continued below)*	Boxed Warning Serious infections that may lead to hospitalization and death: reported infections include active tuberculosis, invasive fungal infections, and bacterial, viral (including herpes zoster), and other infections due to opportunistic pathogens. Mortality: rheumatoid arthritis patients 50 years and older with at least one cardiovascular risk factor treated with Xeljanz 10 mg twice daily had a higher rate of all-cause mortality, including sudden CV death, compared to those treated with 5 mg twice daily or TNF blockers in a large, ongoing, postmarketing safety study. Malignancies: lymphoma and other malignancies have been observed in patients treated. Epstein Barr-Virus-associated post-transplant lymphoproliferative disorder has been observed at an increased rate in renal transplant patients treated with Xeljanz and concomitant immunosuppressive medications. *(continued below)*

FDA Approved Treatments	Relevant Indication	Dosage & Administration	Efficacy Information	Important Safety and Tolerability Issues
Tofacitinib[5] (Xeljanz®) NDA 203214 *(continued)*			Study UC-4 Open-label Extension Study: Of 322 patients who completed the induction study but did not achieve clinical response, at Week 52, 65 patients (20%) achieved remission based on local endoscopy reporting after continued treatment for 52 weeks of 10 mg BID.	Thrombosis: Thrombosis, including pulmonary embolism, deep venous thrombosis, and arterial thrombosis, has been observed at an increased incidence in rheumatoid arthritis patients who were 50 years of age and older with at least one CV risk factor treated with Xeljanz 10 mg twice daily compared to 5 mg twice daily or TNF blockers in a large, ongoing post-marketing safety study. Many of these events were serious and some resulted in death. Avoid Xeljanz in patients at risk. Adverse reactions in ≥5% of patients treated with tofacitinib, either 5 mg or 10 mg, and ≥1% greater than reported in patients receiving placebo in trials for the treatment of moderately to severely active UC include nasopharyngitis, elevated cholesterol levels, headache, upper respiratory tract infection, increased blood creatine phosphokinase, rash, diarrhea, herpes zoster, gastroenteritis, anemia, and nausea.

Source: Reviewer's table created from data in current prescribing information for relevant products and from the clinical review of sNDA 203214-018, tofacitinib (Xe janz®), Lesley S. Hanes, MD.
[5] (Food and Drug Administration 2018)
Abbreviations: BID = twice daily; NDA = new drug application; TNF = tumor necrosis factor; UC = ulcerative colitis

3. Regulatory

3.1. U.S. Regulatory Actions and Marketing History

The summary below includes a brief regulatory history from other approved conditions including (1) plaque psoriasis; (2) psoriatic arthritis; and (3) CD and focuses on the regulatory history as relevant to the current efficacy supplement for UC. For details on the regulatory history for the CD indication, refer to the clinical review by Kerry Jo Lee, MD, dated September 7, 2016.

Approved Indications of Ustekinumab Under BLA 125261: Plaque Psoriasis and Psoriatic Arthritis

Stelara (ustekinumab) was initially approved under BLA 125261 on September 25, 2009 for moderate to severe plaque psoriasis; the indication was expanded in 2017 to include adolescents ages 12 to 17 years of age with psoriasis. Stelara for this indication is available in 45 mg and 90 mg doses as a weight-based subcutaneously administered agent. At the time of marketing approval for this indication, the safety and efficacy of Stelara had not been evaluated beyond 2 years. This initial approval included a risk evaluation and mitigation strategy (REMS) to evaluate and mitigate the potential risks of serious infections, malignancy, and RPLS associated with Stelara. The REMS requirement was removed on February 15, 2017.

On September 20, 2013, Stelara was approved under BLA 125261 for psoriatic arthritis. The formulation and dosing were the same as for plaque psoriasis.

Approved Indication for Ustekinumab Under BLA 761044: Moderately to Severely Active CD

On September 23, 2016, Stelara was approved for adult patients with CD who failed or were intolerant to treatment with immunomodulators or corticosteroids, but who had never failed a tumor necrosis factor (TNF) blocker or who had failed or were intolerant to treatment with one or more TNF blockers. The recommended intravenous induction dosage for CD weight-based tiers are as follows: 260 mg (for patients weighing ≤55 kg), 390 mg (for patients weighing >55 kg to ≤85 kg), and 520 mg (for patients weighing >85 kg). The recommended maintenance dosage for CD is 90 mg subcutaneously administered 8 weeks after the initial intravenous dose and every 8 weeks thereafter.

3.2. Summary of Presubmission/Submission Regulatory Activity

Relevant discussion items from select presubmission meetings and regulatory activity are summarized below.

Pre-IND (PIND) Meeting, January 21, 2015

Clinical trial study design

- The Division agreed with the Applicant that it was acceptable to use the traditional Mayo Score for defining response for entry into the phase 3 clinical trial for UC.
- The Division encouraged the Applicant that the stratification variables for randomization in the maintenance trial include biologic failure status (yes or no) since some patients who failed prior treatment with biologics may respond differently to maintenance therapy compared to patients who failed prior therapy with corticosteroids or immunomodulators.

Primary efficacy endpoints

- The Division agreed that clinical remission was an acceptable primary endpoint and recommended that the definition of clinical remission include the following items from the Mayo Score: endoscopy subscore ≤1, stool frequency subscore of 0 or 1, and rectal bleeding subscore of 0. The Division agreed to utilizing a maximum score of 1 for stool frequency (b) (4) (b) (4)
- The Applicant claimed that exploratory data were available to support utilization of absolute stool frequency reduction to ≤3 stools/day instead of using the stool frequency subscore of the Mayo score that relies on recall of baseline or normal stool frequency.
- The Division reviewed the literature and further evaluated the Applicant's proposal to retain mild friability to define an endoscopy subscore of 1. The Division reiterated to the Applicant that any "friability," even if assessed through centrally-read endoscopies, should be classified as an endoscopy subscore of at least 2, which would exclude such patients as being classified as responders on the endpoint of endoscopic improvement, (b) (4) (b) (4)

Advice Letter to the Applicant, April 27, 2015

- On March 31, 2015, the Applicant submitted a revised definition of clinical remission (b) (4) The Applicant proposed the following definition of clinical remission: rectal bleeding score 0; endoscopy score 0 or 1; and an absolute stool number ≤3, where the absolute stool number is the average number of stools per day over a 3-day period.
- The Division did not object to the Applicant's definition and recommended that the protocol mandate documentation of what patients consider at baseline to be their "normal" stool frequency. Evidence that a substantial number of patients did not achieve their "normal" stool frequency (b) (4) (b) (4) In addition, the Division recommended that the Bristol Stool Scale should be used to record stool consistency and analyzed as an exploratory endpoint.

IND 124512/6 Submission and Feedback

The Applicant submitted an investigational new drug (IND) application on May 5, 2015, and the IND was deemed safe to proceed on June 4, 2015. The comments communicated in the study may proceed letter are summarized below:

- A single induction trial and a single maintenance trial would need to be both clinically meaningful and highly statistically persuasive.
- The recommendations to modify the Mayo endoscopy subscore so that a value of 1 does not include friability were reiterated.
- The protocol should specify how histologic healing was to be defined.
- The method of calculation rectal bleeding Mayo subscore was not clear from the protocol. The Applicant was asked to describe whether the average of the most recent consecutive 3-day period or the worse of the most recent consecutive 3-day period would be used to calculate the rectal bleeding Mayo subscore.
- The Division noted that dose levels for the induction and maintenance studies were based on data from trials conducted in patients with CD. It was not clear whether the proposed doses and dosing regimens would be acceptable for the treatment of UC in the absence of phase 2 data in this patient population to inform the appropriate doses and dosing regimens for phase 3. As was communicated to the Applicant during the pre-IND meeting, on February 18, 2015, the acceptability of the dose regimens would depend on the outcome of the trials.

Initial Pediatric Study Plan for UC

The Applicant submitted its initial Pediatric Study Plan (iPSP) on January 16, 2016, to the Division. However, Orphan Drug designation was granted on March 13, 2017, and the Applicant withdrew the iPSP.

Pre-sBLA Meeting February 20, 2018

On February 20, 2018, the Division sent the Applicant preliminary meeting responses. After receipt of the Division's preliminary comments, the Applicant cancelled the teleconference scheduled for February 27, 2018.

- The Division could not agree at the time of the premeeting minutes that the proposed analysis plans for mucosal healing is adequate (b) (4) (b) (4) based on endoscopic and histological assessments in accordance with current draft guidance for industry *Ulcerative Colitis: Clinical Trial Endpoints* (August 2016).[1] In general, the Geboes scoring system appeared reasonable to evaluate histology in inflammatory bowel disease but the determination of whether it could be used as a reliable endpoint to define histologic remission in clinical trials (b) (4) would be a review issue. The Division noted that the Inflammatory Bowel Disease Questionnaire (IBDQ) is not a validated instrument (b) (4)

[1] FDA updates guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm

Therefore, changes in the IBDQ (b) (4) that histologic changes reflect clinically meaningful changes in patient signs and symptoms. The sBLA submission should include a justification, based on available data, (b) (4) in the relevant patient population.

- The Applicant stated that mucosal healing at Week 44 (i.e., at the end of the maintenance study) would not be a multiplicity-controlled endpoint. However, the results of the exploratory analyses of the histologic outcomes at Week 44 (b) (4) (b) (4) given that histologic inflammation has been associated with disease relapse, need for surgery, and higher risk of cancer. If the data suggest that patients have a persistent or a recurrence of histologic inflammation at Week 44, (b) (4) (b) (4)
- As communicated to the Applicant in the Advice Letter, dated August 2, 2017, the Division reminded the Applicant of the following concerns that will be review issues for the sBLA. For the primary analyses of efficacy in both the induction and maintenance studies, the Applicant can use the proposed definition of clinical remission. Additional analyses based on the definition of clinical remission described below need to be conducted to further support the efficacy results. If the results differ significantly from the results based on the Applicant's proposed definition of clinical remission, it will be a review issue.
  - Applicant's proposed definition of clinical remission included:
    - Rectal bleeding subscore =0
    - Endoscopy score =0 or 1
    - Absolute stool number ≤3, where the absolute stool number is the average of stools per day over a 3-day period.
  - FDA Recommended definition of remission:
    - Rectal bleeding subscore =0
    - Endoscopy subscore =0 or 1 (modified, where 1 does not include friability) on Mayo Score
    - Stool Frequency subscore =0
- The Division reminded the Applicant that the "maintenance of remission" must be supported by favorable results of analyses in which the population rerandomized is limited to patients who were in remission at the end of the induction study.
- The Division generally agreed with the Applicant's overall pharmacokinetic (PK) and immunogenicity analyses proposed for inclusion in the clinical pharmacology package for the sBLA. Because this drug product has an orphan drug designation for pediatric UC, the Applicant is exempt from Pediatric Research Equity Act requirements and pediatric studies would likely be issued as postmarketing commitments if the adult indication was approved.

- The Division found acceptable the Applicant's proposal to cross-reference BLA 125261 for drug substance chemistry, manufacturing, and controls (CMC) information and BLA 761044 for drug product CMC information.

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

4.1. Office of Scientific Investigations

Inspections were conducted at three clinical sites. No significant regulatory findings or data integrity issues were noted. Overall, the data generated by these sites were found to be acceptable in support of the application. Refer to Clinical Inspection Summary by Dr. Susan Leibenhaut, MD, dated August 20, 2019.

4.2. Product Quality

The immunogenicity assay was reviewed by OBP. The antibody assays were the same as those used in the trials that supported the approval of the Crohn's disease indication. OBP recommends approval of this efficacy supplement. Please see OBP review by Drs. Steve Bowen and Maria Gutierrez-Lugo, dated September 23, 2019.

4.3. Clinical Microbiology

No new clinical microbiology data were submitted in this sBLA.

4.4. Devices and Companion Diagnostic Issues

No devices/companion diagnostic data were submitted in this sBLA.

5. Nonclinical Pharmacology/Toxicology

No new pharmacology/toxicology data were submitted in this sBLA.

6. Clinical Pharmacology

6.1. Executive Summary

Stelara (ustekinumab) is a human IgG1κ monoclonal antibody that is directed against the p40 subunit of IL-12 and IL-23 cytokines. Ustekinumab is a fully human IgG1κ monoclonal antibody (mAb) to the p40 subunit common to human IL-12 and IL-23. It binds to human IL-12 and IL-23 and neutralizes their bioactivity by preventing these cytokines from binding to their shared cell-surface receptor chain, IL-12Rβ1 (IL-12 receptor beta-1), expressed on the surface of immune cells.

Ustekinumab has been approved for adults with moderate to severe plaque psoriasis since 2009 (BLA 125261), adults with active psoriatic arthritis (BLA 125261) since 2013, and adolescents ages 12 to 17 years of age with psoriasis since 2017 (BLA 125261). In 2016, ustekinumab was approved for the treatment of adult patients with moderately to severely active Crohn's disease (BLA 761044).

The current efficacy supplement application is to include a new indication for Stelara for the treatment of adult patients with moderately to severely active ulcerative colitis (UC). The proposed dosing regimen for the treatment of UC is the same as previously approved for CD. The initial dose is administered IV using weight tiered dosing.

- ≤55 kg 260 mg
- >55 kg to ≤85 kg 390 mg
- >85 kg 520 mg

Maintenance dosing is 90 mg SC administered 8 weeks after induction and every 8 weeks thereafter regardless of body weight.

This sBLA contains efficacy and safety data from two phase 3 studies (an induction study and a randomized-withdrawal maintenance study) conducted under a single protocol, CNTO1275UCO3001 (hereafter referred to as UCO3001). The Applicant also included data from their clinical studies in patients with CD previously submitted for the approved Crohn's disease indication as supportive data for comparison of PK.

The key review findings with specific recommendations/comments are summarized below.

Table 3. Key Review Findings and Specific Recommendations

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The efficacy of Stelara for the treatment of moderate to severe ulcerative colitis is established based on an induction study and a randomized-withdrawal maintenance study (CNTO1275UCO3001). A positive dose-response and exposure-response relationship based on data from the phase 3 trials provide supportive evidence for effectiveness.
General dosing instructions	The proposed body weight tiered induction dosing regimen (<55 kg: 260 mg IV; 55-85 kg: 390 mg IV; >85 kg: 520 mg IV) and maintenance dosing regimen (90 mg SC every other week) are acceptable.
Dosing in patient subgroups (intrinsic and extrinsic factors)	Dose individualization based on intrinsic or extrinsic factors in addition to body weight is not recommended.
Labeling	The review team has specific content and formatting change recommendations. See Section 6.2 of this review
Immunogenicity	Among patients with UC in UCO3001 who received ustekinumab during both induction and maintenance, the incidence of antibodies of ustekinumab was 4.6%. Immunogenicity has a negative impact on systemic exposure of ustekinumab. In all randomized treatment groups, median serum ustekinumab concentrations were generally lower (ranging from no difference to up to 9-fold) over time in ADA^+ patients compared to ADA negative patients. The assessment of the impact of immunogenicity on clinical efficacy is inconclusive due to the small number of ADA^+ patients in the phase 3 studies.

Abbreviations: ADA = antidrug antibodies; IV = intravenous; SC = subcutaneous; UC = ulcerative colitis

6.1.1. Recommendations

From a clinical pharmacology standpoint, the information submitted in this supplemental BLA is acceptable to support the approval of Stelara (ustekinumab) for the treatment of adult patients with moderately to severely active ulcerative colitis.

6.1.2. Postmarketing Requirements and Commitment(s)

The Clinical Pharmacology review team recommends the following postmarketing commitment (PMC) study:

- Study: Conduct a clinical trial to assess whether ustekinumab alters the metabolism or pharmacokinetics of cytochrome P450 (CYP) substrates in patients with UC treated with ustekinumab (e.g., using a cocktail of relevant CYP probe drugs).
- Rationale: This recommendation is based on the current understanding that patients with UC have elevated levels of proinflammatory cytokines which can suppress the expression of some CYP enzymes and the CYP enzyme expression could be normalized upon the disease improvement following the ustekinumab treatment. The Applicant is currently conducting a clinical drug interaction study in patients with CD to satisfy a PMC (3112-4) under the original BLA 761044. However, it is unclear whether or not the underlying disease related mechanism will affect the CYP enzymes to a similar extent between in patients with CD and in patients with UC. Therefore, we recommend that the Applicant conduct a study to inform the potential for therapeutic protein-drug interaction in patients with UC. This study may be combined with the on-going study in patients with CD.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Pharmacokinetics of Ustekinumab in Patients With UC

The pharmacokinetics of ustekinumab in patients with moderately to severely active UC was generally comparable to those in patients with Crohn's disease.

Following a single IV administration of the 130 mg ustekinumab fixed dose (~2 mg/kg) or ~6 mg/kg ustekinumab at induction Week 0, median serum ustekinumab concentrations were approximately dose proportional and were detectable at all sampling time points through induction Week 8. Following the recommended IV induction dose, peak serum ustekinumab concentration was 129.1±27.6 mcg/mL (mean ± SD) in patients with UC, which is similar to the levels attained in patients with CD (125.2±33.6 mcg/mL).

The population PK of ustekinumab following IV and SC administration in patients with UC was adequately described by a 2-compartment linear PK model. The typical population estimates for clearance and steady-state volume of distribution were 0.186 L/day and 4.44 L, respectively, in patients with UC with an approximate body weight of 71 kg. The bioavailability following SC ustekinumab administration in patients with UC was estimated to be 87.2% and the median terminal elimination half-life of ustekinumab in patients with UC was approximately 19 days. Based on the population PK analysis, body weight, serum albumin level, and antibody to ustekinumab status were identified as major covariates affecting ustekinumab PK. The impact of these covariates on ustekinumab clearance was within ±20% of the population mean.

Steady-state ustekinumab concentrations were reached at approximately 8 weeks (16 weeks after IV induction) in patients receiving the recommended maintenance dose of ustekinumab (90 mg SC Q8W), and there was no apparent accumulation in ustekinumab concentration over time. Median steady-state trough serum ustekinumab concentrations over time in the ustekinumab 90 mg Q8W group ranged from 2.69 µg/mL to 3.09 µg/mL.

Drug Interactions

No formal drug-drug interaction studies or disease-drug-drug interaction studies were conducted for ustekinumab in UC. As monoclonal antibodies are not metabolized by CYP450 enzymes, conventional drug-drug interaction studies for evaluating the effects of CYP inhibitors or inducers on ustekinumab are not considered necessary. The concomitant use of immunomodulators including 6-MP, AZA and MTX did not appear to affect ustekinumab concentrations based on the population PK analysis.

On the other hand, patients with UC have elevated levels of pro-inflammatory cytokines which can suppress the expression of some CYP enzymes. The suppression of the CYP enzymes could be normalized upon the disease improvement following treatment with ustekinumab. As a result, the exposure of CYP substrates could be reduced when the disease is improved, and the pro-inflammatory cytokines are normalized (see Section 6.1.2 for PMC recommendation).

Immunogenicity and Its Impact on PK and Efficacy

Of the 635 patients in the ustekinumab groups with appropriate samples through Week 8 for the assessment of antibodies to ustekinumab during induction, four (0.6%) patients were positive for antibodies to ustekinumab through induction Week 8. Of these four patients, two were positive for neutralizing antibodies. Among all 680 treated patients in the UCO3001 maintenance study with appropriate samples for the assessment of antibodies to ustekinumab, 39 (5.7%) patients were positive for antibodies to ustekinumab at any time through Week 44. Of the 39 treated patients who were positive for antibodies to ustekinumab in the maintenance study 11 patients (overall incidence of 1.6% based on 680 patients) were positive for neutralizing antibodies (NAbs). Among the 505 randomized and nonrandomized patients in the UCO3001 maintenance study who received ustekinumab during both induction and maintenance, the incidence of antibodies to ustekinumab was 4.6% through Week 44.

The concomitant use of immunomodulators had an impact on immunogenicity. The proportion of antidrug antibody-positive (ADA^+) patients who received immunomodulators was lower (3.1%, 6 of 193 patients) compared with those who did not receive immunomodulators (6.8%, 33 of 487 patients).

Antibody formation was associated with lower serum concentrations of ustekinumab. Across the randomized treatment groups, median serum ustekinumab concentrations were lower (up to 9-fold) over time in patients who were positive for antibodies to ustekinumab compared with concentrations in patients who were negative for antibodies to ustekinumab. At the individual patient level, a clear trend was not observed when trough ustekinumab concentrations were compared in individual patients before and after the first samples showed ADAs against ustekinumab.

The assessment of the impact of immunogenicity on clinical efficacy is inconclusive because the number of patients who became ADA^+ was small in the phase 3 UC studies.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The Applicant has proposed a dosing regimen including a body weight-tiered induction dose (<55 kg: 260 mg IV; 55 to 85 kg: 390 mg IV; >85 kg: 520 mg IV) followed by flat maintenance dosing (90 mg SC every other week). The proposed regimens are supported by efficacy and safety data from a phase 3 induction study and a randomized maintenance study (CNTO1275UCO3001) and are acceptable.

The increase in clearance was observed by increasing body weight resulting in overlapping systemic exposure across weight tier under the proposed weight-tiered dose regimen studied in phase 3 trial (<55 kg: 260 mg IV; 55-85 kg: 390 mg IV; >85 kg: 520 mg IV). As such, a body weight tiered induction dosing regimen is appropriate for induction. A flat dose of 130 mg studied in phase 3 trial also showed a statistically significant greater proportion of clinical remitters compared to the placebo group; however, the overall response rate was numerically better with the weight-tiered dose regimen which provided 2-4 fold higher systemic exposure than 130 mg dose.

For the maintenance phase, the proposed flat dose of 90 mg SC is acceptable as the exposures at this dose yield exposures that fall in the plateau portion of the E-R relationship.

Refer to Section 7 of this review for additional efficacy findings supporting the recommended dosing regimen.

Therapeutic Individualization

No intrinsic or extrinsic factors that would require adjustment of the proposed dosing regimen have been identified.

Outstanding Issues

There are no outstanding issues that would preclude the approval of the current efficacy supplement from clinical pharmacology's perspective. However, we recommend a PMC to ensure that the Applicant conducts a clinical drug interaction study in patients with UC (see Section 6.1.2).

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Table 4. Pharmacology and Pharmacokinetic Characteristics of Ustekinumab

Pharmacology	
Mechanism of action	Ustekinumab is a human IgG1κ monoclonal antibody that binds to the p40 protein subunit used by both the IL-12 and IL-23 cytokines and neutralizes their bioactivity by preventing these cytokines from binding to their shared cell-surface receptor chain, IL-12Rβ1 (IL-12 receptor beta-1). IL-12 and IL-23 are naturally occurring cytokines that are involved in inflammatory and immune responses, such as natural killer cell activation and $CD4^+$ T-cell differentiation and activation. They are believed to be contributors to the chronic inflammation that is a hallmark of Crohn's disease and ulcerative colitis.
General Information	
Bioanalysis	Ustekinumab concentrations in human serum were quantified using a validated electrochemiluminescence immune assay (ECLIA) assay on a Meso Scale Discovery® platform that was also used in the previous BLA submission for Crohn's disease. The suitability of the assay was reviewed as a part of the previous BLA submission and was found to be acceptable. Refer to the clinical pharmacology review of BLA 761044 by Dr. Christine Hon, dated September 7, 2016.
PK in patients with UC	The pharmacokinetics of ustekinumab in patients with moderate to severe UC was generally comparable to these in patients with Crohn's disease. Following a single IV administration of the fixed dose of 130 mg ustekinumab (~2 mg/kg) or approximately 6 mg/kg using a body weight tiered dose (<55 kg: 260 mg; 55-85 kg: 390 mg; >85 kg: 520 mg) of ustekinumab at induction Week 0, median serum ustekinumab concentrations were detectable at all sampling time points through induction Week 8 and AUC or Cmax were approximately dose proportional. Following the recommended IV induction dose, peak serum ustekinumab concentration was 129.1±27.6 mcg/mL (mean ± SD) in patients with UC and was similar to the Cmax attained in patients with CD (125.2±33.6 mcg/mL). The bioavailability following SC ustekinumab administration in patients with UC was estimated to be 87.2% compared to IV administration. An estimated terminal elimination half-life is approximately 19 days in patients with UC. Using population PK analysis, the typical population estimates for clearance and total volume of distribution at steady-state were 0.186 L/day and 4.44 L, respectively, in patients with UC with an approximate body weight of 71 kg. Population PK analysis identified body weight as one of the covariates on ustekinumab CL, V2, V3, and Q, with these parameters increasing nonlinearly with body weight. The higher CL in heavier patients resulting in overlapping systemic exposure across weight tier was observed after administration of the weight-tiered dose (using a body weight tiered dose (<55 kg: 260 mg; 55-85 kg: 390 mg; >85 kg: 520 mg) in phase 3 trial.

Immunogenicity	
Incidence	Of the 635 patients in the ustekinumab groups with appropriate samples through Week 8 for the assessment of antibodies to ustekinumab during induction, four (0.6%) patients were positive for antibodies to ustekinumab through induction Week 8. Of these four patients, two were positive for neutralizing antibodies. Among all 680 treated patients in the UCO3001 maintenance study with appropriate samples for the assessment of antibodies to ustekinumab, 39 (5.7%) patients were positive for antibodies to ustekinumab at any time through Week 44. Of the 39 treated patients who were positive for antibodies to ustekinumab in the maintenance study, 11 (overall incidence of 1.6% based on 680 patients) patients were positive for NAbs. Among the 505 randomized and nonrandomized patients in the UCO3001 maintenance study who received ustekinumab during both induction and maintenance, the incidence of antibodies to ustekinumab was 4.6% through Week 44. The concomitant use of immunomodulators had an impact on immunogenicity. The proportion of ADA$^+$ patients who received immunomodulators was lower (3.1%, 6 of 193 patients) compared with those who did not receive immunomodulators (6.8%, 33 of 487 patients).
Impact on PK	Antibody formation was associated with lower serum concentrations of ustekinumab. Across the randomized treatment groups, median serum ustekinumab concentrations were lower over time in patients who were positive for antibodies to ustekinumab compared with concentrations in patients who were negative for antibodies to ustekinumab. At the individual patient level, a clear trend was not observed when the average trough ustekinumab levels were compared in individual patients before and after the first samples showed ADAs against ustekinumab.
Impact on efficacy	The assessment of the impact of immunogenicity on clinical efficacy is inconclusive because the number of patients who became ADA$^+$ was small in the phase 3 UC studies.

Abbreviations: ADA = antidrug antibodies; CD = Crohn's disease; E-R = exposure-response; IgG1κ = human immunoglobulin G1 kappa; Nabs = neutralizing ant bodies; PK = pharmacokinetic; SD = standard deviation; UC = ulcerative colitis

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. The dose- and exposure-response (E-R) relationships for efficacy (clinical remission at Week 8 or remission at Week 44) have provided supportive evidence of effectiveness.

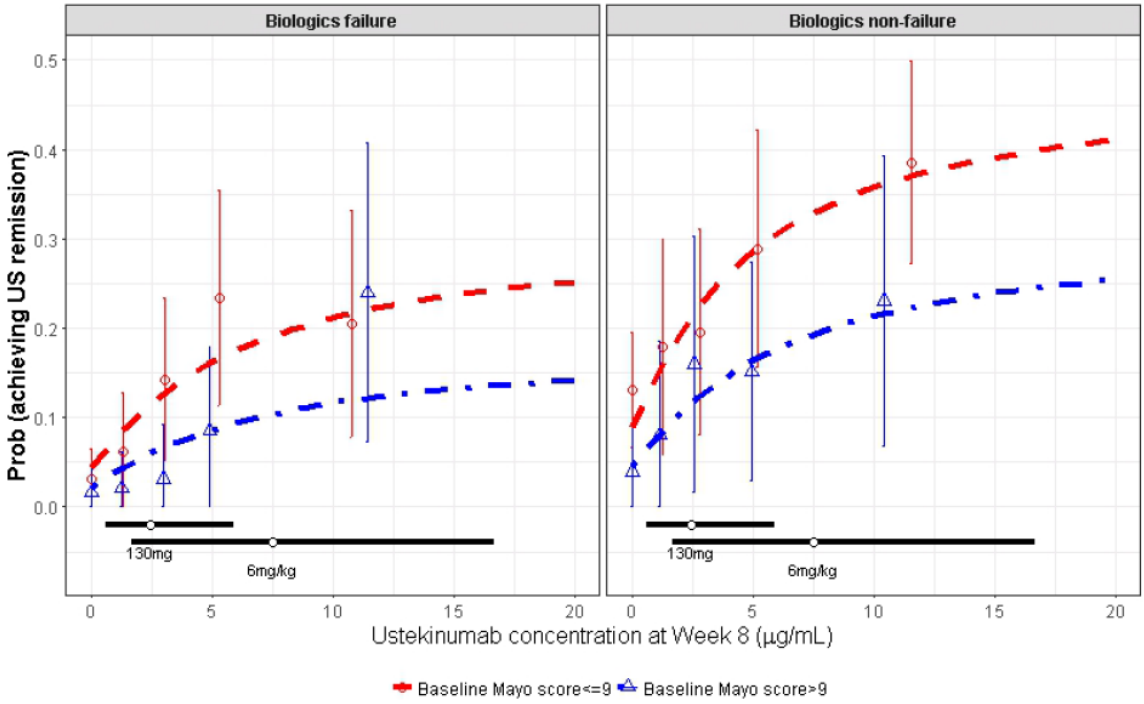
For the assessment of E-R relationships in patients with UC, the Applicant utilized a logistic regression modeling approach linking population PK model-predicted ustekinumab exposures and clinical efficacy outcomes during induction and maintenance therapy. Efficacy endpoints evaluated in Applicant's model-based E-R analysis were clinical remission, clinical response, and histologic-endoscopic improvement ("mucosal healing") (refer to Section 7 of this review for detailed definitions of clinical response, clinical remission and "mucosal healing").

Exposure-response at Week 8 after induction treatment

Based on the Applicant's analysis, a positive E-R relationship was observed between systemic ustekinumab exposure and all evaluated efficacy endpoints at Week 8 following induction treatment. Figure 1 depicts the relationship between the probability of achieving

clinical remission at Week 8 and the ustekinumab trough concentration at Week 8. A greater proportion of patients in the ~6 mg/kg induction group achieved concentrations in the upper portion of the E-R curve associated with the highest efficacy outcomes at Week 8 compared with patients in the 130 mg induction group. Similar trends also were observed for clinical response and "Mucosal healing" histologic-endoscopic mucosal improvement at Week 8. These results are presented further in Section 15.

Figure 1. Plot of Induction Exposure-Response Modeling Relating Ustekinumab Trough Concentration at Week 8 and Clinical Remission at Week 8; Stratified by Biologic-Failure Status* and Baseline Mayo Score

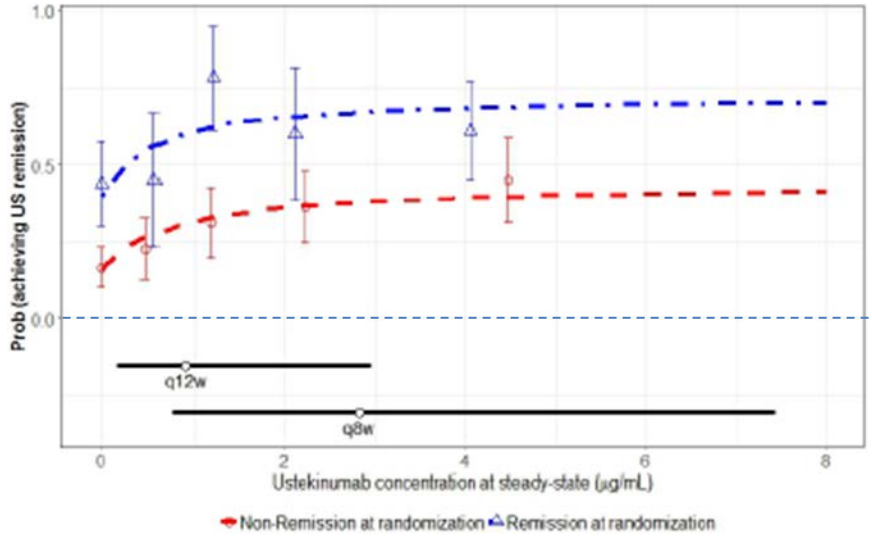


Source: Applicant's Population Pharmacokinetic-Pharmacodynamic Report, Figure 2
Abbreviation: Prob = probability
* Biologics non-failure subgroup reflects patients who are naïve to biologic therapy.

A positive E-R relationship was also observed between systemic ustekinumab exposure and the evaluated efficacy endpoints at Week 44 following maintenance treatment. Figure 2 depicts the relationship between the probability of achieving clinical remission at Week 44 and the trough ustekinumab concentration at steady state. The distribution of the steady-state trough ustekinumab concentrations on the E-R curve suggests that compared with the 90 mg Q12W regimen, the 90 mg Q8W regimen more effectively covers the portion of E-R curves associated with the highest clinical remission rates at Week 44.

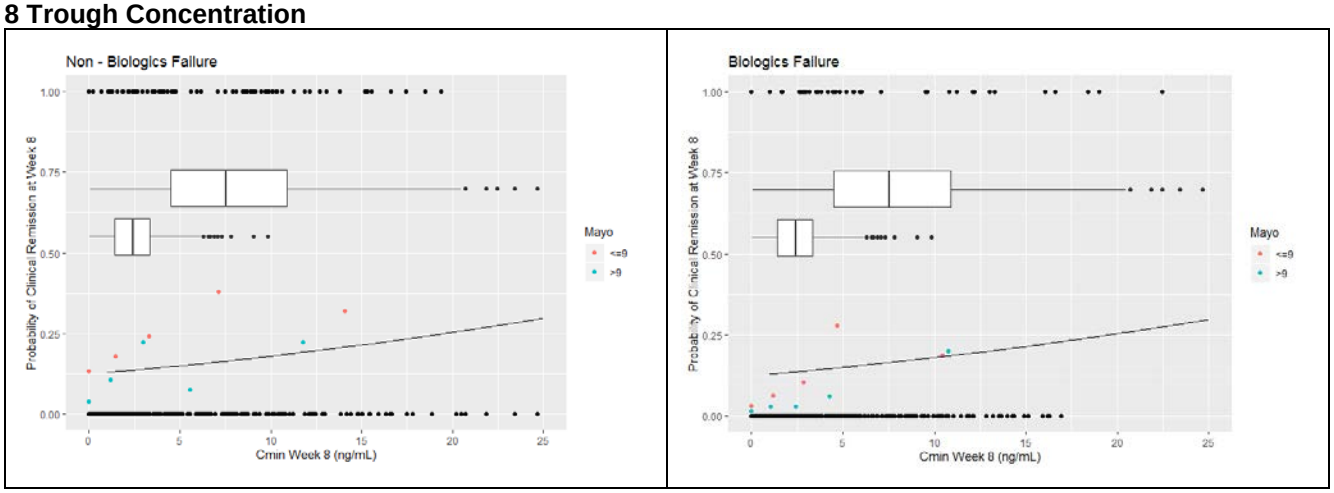
Since the Applicant 's definition for clinical remission differed from the FDA's currently recommended definition, the reviewer conducted independent E-R analysis using the FDA's definition for clinical remission at Week 8 and Week 44. Similar trends in E-R relationships were observed for clinical remission at both timepoints (see Section 15.3.1.2.4 for further details). The results for E-R at Week 8 is depicted in Figure 3.

Figure 2. Plot of Maintenance Phase Exposure-Response Model Relating Trough Concentration at Week 44 and Clinical Remission at Week 44; Stratified by Remission Status at Randomization



Source: Applicant's Population Pharmacokinetic-Pharmacodynamic Report, Figure 5
Abbreviations: Prob = probability; UC = ulcerative colitis

Figure 3. Exposure-Response Relationships for Clinical Remission (FDA Definition) at Week 8 vs. Week 8 Trough Concentration



Source: FDA analysis. See Appendix 15.3.1.2.
Colored circles depict the rate of remission per exposure quartile. Black circles indicate individual responses. The left panel ("Non-Biologics Failure") indicates results for patients naive to biologics. The right panel depicts results for patients with biologics failure. Color indicates baseline mayo score (red for ≤9 and blue for >9). Horizontal boxplots indicate the observed exposure range across all subjects in the 130 mg and ~6 mg/kg dose groups.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dosing regimen for induction and maintenance of clinical remission is appropriate. The supporting evidence includes primary efficacy and safety results in phase 3 studies which evaluated the proposed dose regimens and demonstrated efficacy across Week 8 to Week 44.

For induction treatment of patients with UC, treatment with a single dose of ustekinumab at both doses (~6 mg/kg and 130 mg) was associated with statistically significant improvement in the signs and symptoms of UC compared with placebo at Week 8 (Table 15). The proportion of patients in clinical remission at Week 8 (the primary endpoint) was numerically greater in the ~6 mg/kg group (19.3%) compared to 130 mg group (16.9%) (see Section 7 of this review for additional details). Further, a greater proportion of patients in the ~6 mg/kg group tended to achieve concentrations in the portion of the E-R curve associated with the highest clinical remission rates at Week 8 (Figure 3) in comparison to the 130 mg group supporting the use of ~6 mg/kg induction regimen in UC.

For maintenance phase treatment of patients with UC, treatment with ustekinumab at both dosage regimens (90 mg q8w and 90 mg q12w) was associated with statistically significant improvement in the signs and symptoms of UC compared with placebo (Table 15). The proportions of patients who achieved the clinical remission (primary) at Week 44 were greater in the ustekinumab Q8W (44.9%) and ustekinumab Q12W (38.4%) groups compared with the placebo group (26.3%), respectively. Further, the Q8W maintenance regimen also appears to yield higher and potentially more beneficial exposures compared to the Q12W dosing regimen supporting the use of the Q8W regimen (Figure 2).

The plateau in the response curve for both the induction and maintenance treatment suggests that higher doses than the proposed doses may not offer additional therapeutic benefit.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No. Other than body weight, no intrinsic factors were identified to require an alternative dose or dosing regimen for subpopulations.

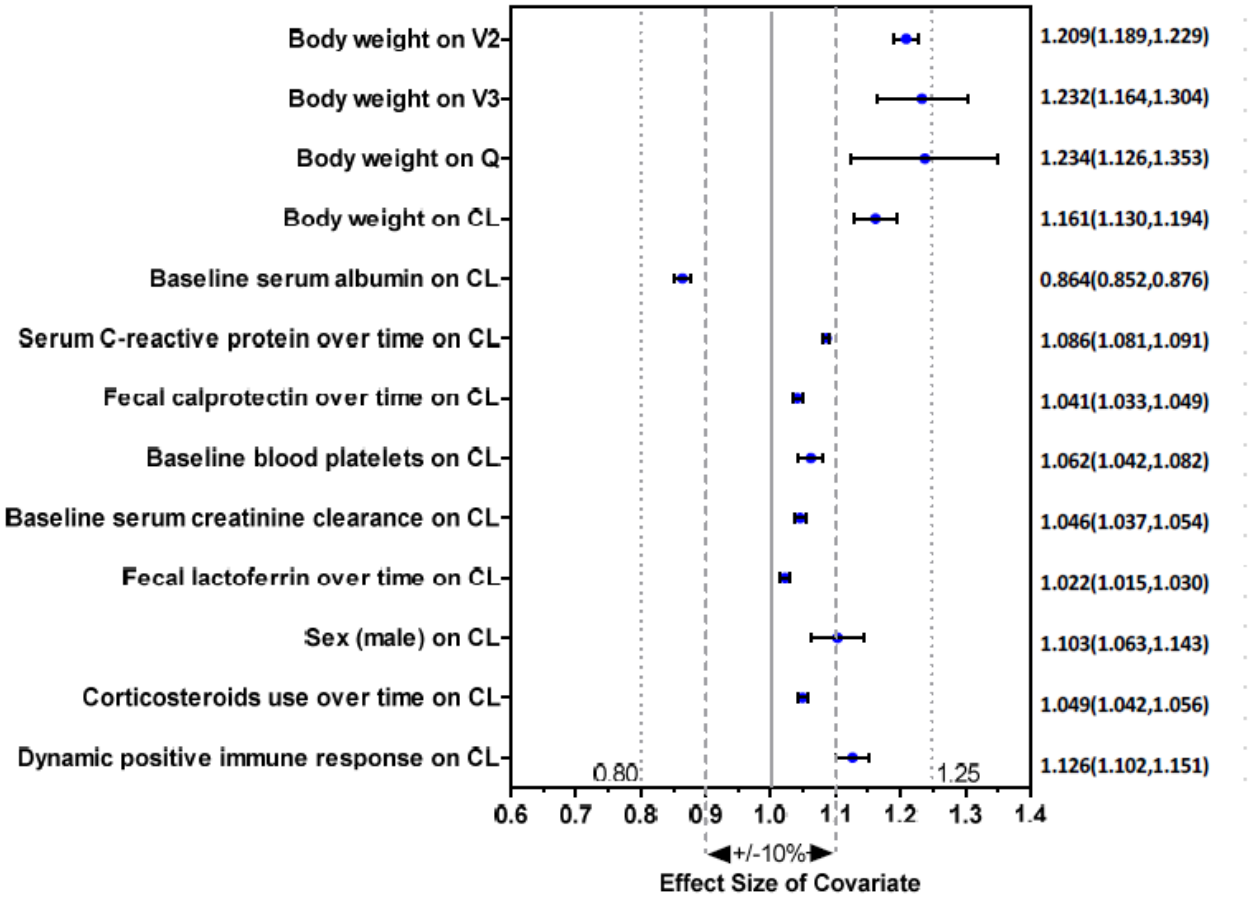
The Applicant evaluated various covariates including baseline body weight, race, age, sex, baseline disease characteristics, baseline serum albumin, use of concomitant medications, immunogenicity in the population PK analysis (Table 29). Among the covariates examined, body weight was a major covariate impacting ustekinumab CL, V2, V3, and Q, with these parameters increasing nonlinearly with body weight (Figure 4).

The proposed body weight-tiered dosing for induction (<55 kg: 260 mg IV; 55 to 85 kg: 390 mg IV; >85 kg: 520 mg IV corresponding to ~6 mg/kg) is taken into consideration the potential body weight effects on PK. Figure 5 shows the predicted ustekinumab PK metrics ($C_{trough,w8}$ and AUC_{0-8w}) following the proposed induction dose levels, suggesting that ustekinumab exposure during induction increased slightly as absolute induction doses increased, but are largely overlapping across the body weight groups.

In addition to body weight, patients with higher baseline serum albumin had lower clearance and the development of antibodies to ustekinumab was associated with an increase in ustekinumab clearance. However, the impact of these covariates was not considered to be clinically meaningful to require an alternative dosing regimen.

See Section 15.3.1.1.1 for additional details of the population PK analysis and covariate analysis results.

Figure 4. Effects of Covariates on Population Pharmacokinetic Parameters of Ustekinumab in Full Covariate Model



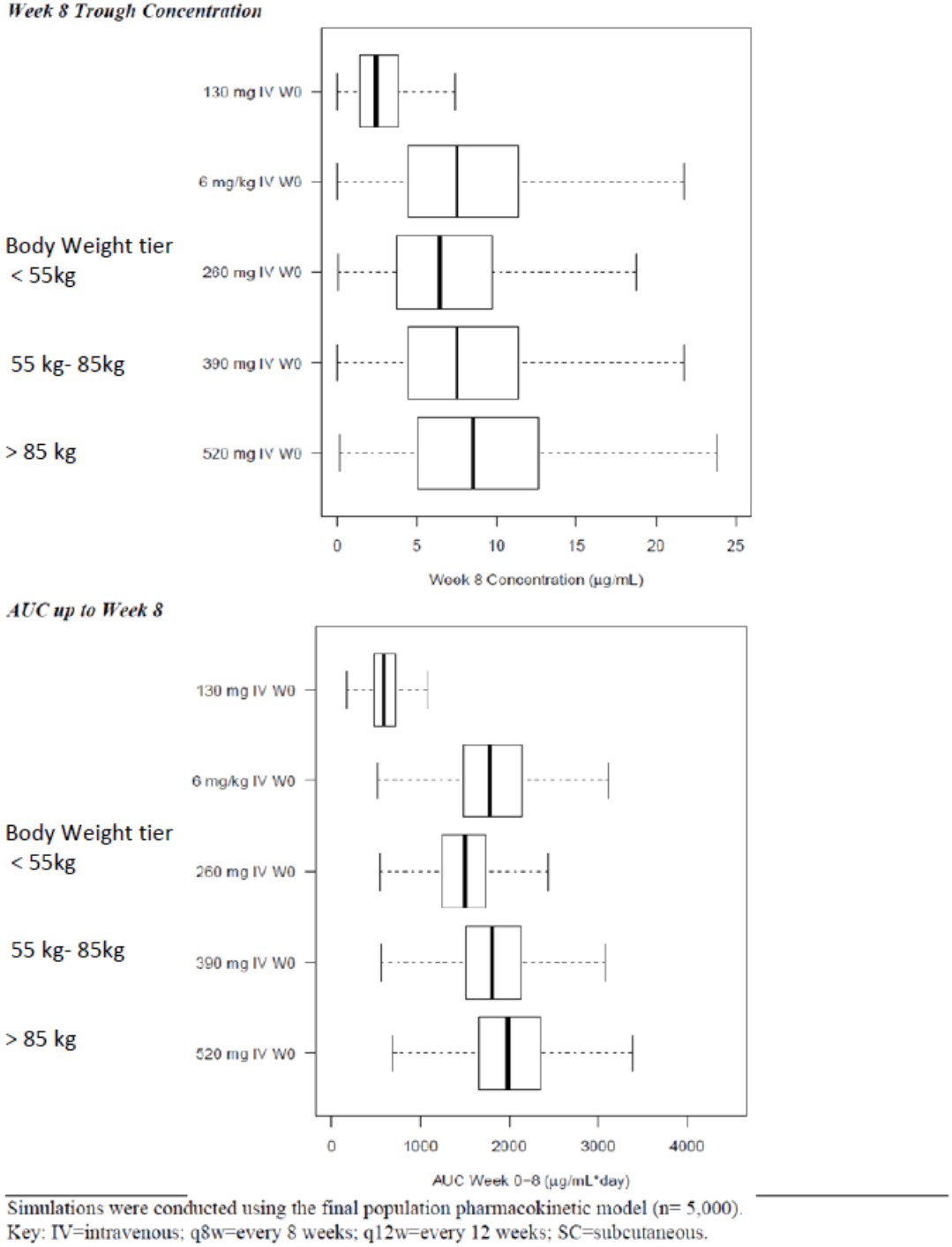
Effects of covariates assessed with the full covariate model. For discrete covariates, the covariate effects were the parameter estimates for status of 'Yes' relative to the reference of 'No'. For continuous covariates, the covariate effect was estimated as the ratio of E75/E25, where E25 and E75 represent PK parameter values corresponding to the covariate values at 25th percentile and 75th percentile of the population respectively.

Filled circles represent model predictions and solid line segments are the corresponding 90% confidence intervals. The associated values are shown on the right column. The gray vertical lines are the 80% to 125% bioequivalence intervals and the 90% to 110% significance interval.

Key: CL=clearance of the central compartment; Q=inter-compartmental clearance; V2=volume of distribution of the central compartment; V3=volume of distribution of the peripheral compartment.

Source: Applicant's Population PK Report, Figure 1

Figure 5. Simulated Ustekinumab PK Exposures in Induction Study



Simulations were conducted using the final population pharmacokinetic model (n= 5,000).
Key: IV=intravenous; q8w=every 8 weeks; q12w=every 12 weeks; SC=subcutaneous.

Source: Applicant's Population PK Report, Figure 6

Based on the exposure-efficacy analysis, baseline mayo score, remission status at randomization, and prior failure to other biologics status were identified as major covariates for E-R relationships for clinical response, clinical remission, and/or histologic-endoscopic improvement ("mucosal healing"). However, these patient characteristics appears to only

impact the levels of response, but not the exposure or the slope of E-R. For all subgroups of patients, the trend of greater rate of remission/response with higher exposure was observed. The proposed body weight tiered induction dosing regimen and the 90 mg SC dosing Q8W for maintenance resulted in a greater proportion of patients achieving concentrations in the portion of the E-R curve associated with the highest clinical response rates at Week 8 and Week 44 compared to lower dosage studied. See the pharmacometrics review in Section 15.3.1 for further details on these model results.

Are there clinically relevant drug-drug interactions, and what is the appropriate management strategy?

It is unknown at this time whether there are any relevant drug interactions as the Applicant has not conducted any clinical studies assessing the drug interaction potential for ustekinumab in patients with UC.

As monoclonal antibodies are not metabolized by CYP enzymes, the concomitant CYP enzyme inhibitors or inducers are not expected to affect the PK of ustekinumab.

However, the potential effects of ustekinumab on some CYP enzymes via modulation of pro-inflammatory cytokines in patients with UC cannot be ruled out. Briefly, patients with UC have elevated levels of pro-inflammatory cytokines which can suppress the expression of some CYP enzymes. The suppression of the CYP enzymes expression could be normalized upon the disease improvement following treatment with ustekinumab. As a result, the systemic exposure of CYP substrates could be reduced due to the increased CYP enzyme expression when the disease is improved, and the pro-inflammatory cytokines are normalized. One potential impact of the drug-drug interaction is the suboptimal efficacy of the concomitant CYP enzyme substrate drugs.

The potential effects of ustekinumab on PK of CYP enzyme substrates via modulation of pro-inflammatory cytokines in patients with UC should be further addressed in a clinical drug interaction study in patients with UC.

What is the overall incidence of immunogenicity to ustekinumab in patients with UC? What is the impact of immunogenicity on PK and efficacy?

Immunogenicity incidence

Among the 505 randomized and nonrandomized patients in the UCO3001 maintenance study who received ustekinumab during both induction and maintenance, the incidence of antibodies to ustekinumab was 4.6% through Week 44.

Of the 635 patients who received ustekinumab and had appropriate samples through Week 8 for the assessment of antibodies (ADAs) to ustekinumab during induction, four (0.6%) patients were positive for ADAs to ustekinumab. Of these four patients, two patients were positive for neutralizing antibodies.

Of the 822 patients who received ustekinumab at any time through Week 16 and had appropriate samples for the assessment of ADAs, 18 patients (2.2%) were positive for ADAs to ustekinumab through the final safety visit. Of these 18 patients, 15 patients were evaluated for NAbs and 4 (0.4%) were positive for NAbs through the final safety visit.

Among all 680 treated patients in the UCO3001 maintenance study with appropriate samples for the assessment of ADAs to ustekinumab, 39 (5.7%) patients were positive for antibodies to ustekinumab at any time through Week 44. Of the 39 treated patients who were positive for ADAs to ustekinumab in the maintenance study, 11 patients were positive for NAbs (overall incidence of 1.6% based on 680 patients).

The concomitant use of immunomodulators had an impact on immunogenicity. The proportion of ADA^+ patients who received immunomodulators was lower (3.1%, 6 of 193 patients) compared with those who did not receive immunomodulators (6.8%, 33 of 487 patients).

The immunogenicity incidence in patients with UC appears to be higher (4.6%; 23 of 505 subjects) compared to the incidence rates reported for patients with CD (2.9%; 19 of 663 subjects). However, this may also be due to the change in cut-point (resulting in a 1% false positive rate instead of the 0.1% false positive rate) in the ADA assay used in the current study. Refer to the OBP review in the current submission and original BLA review for additional details about the assays used for the assessment of immunogenicity.

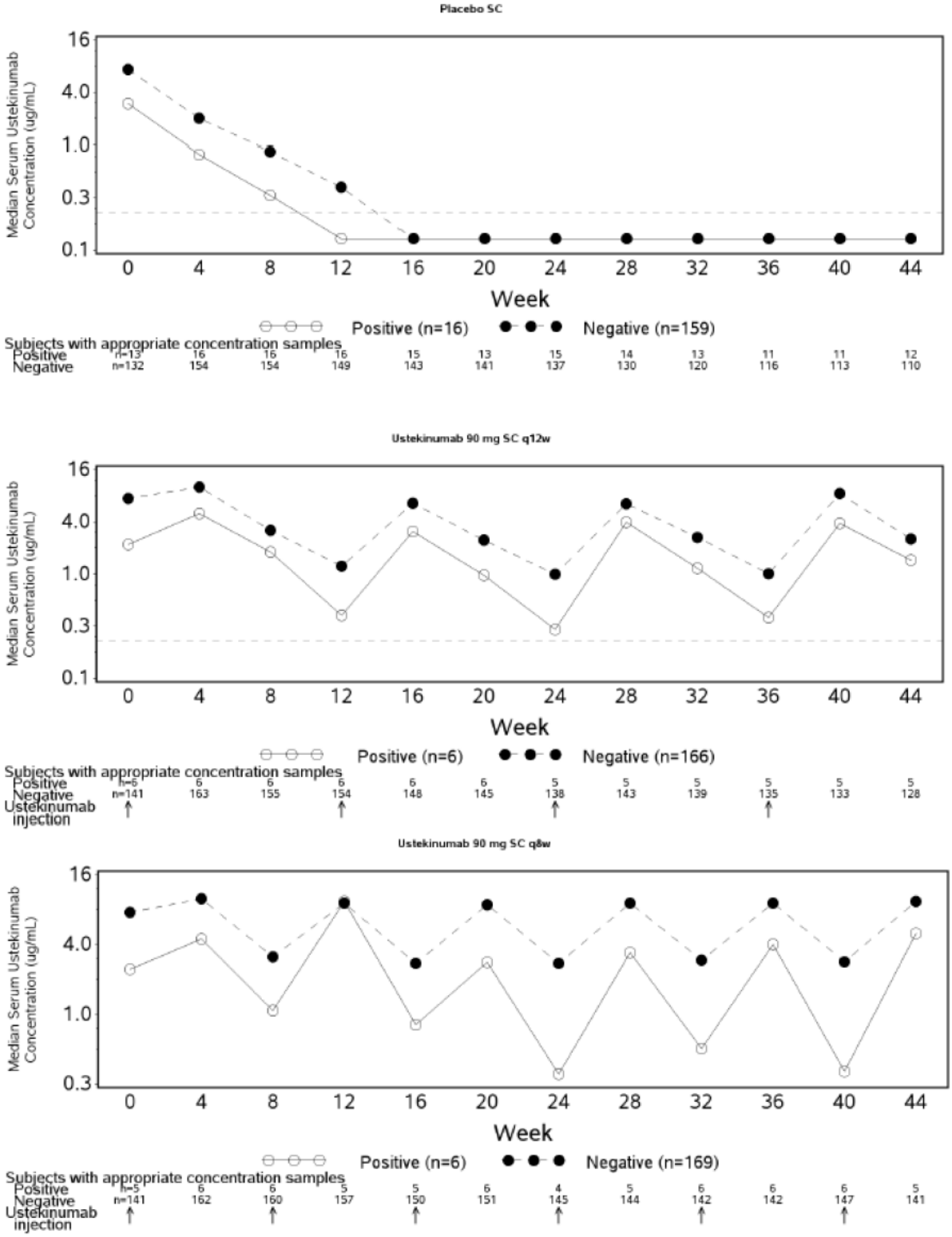
Impact of immunogenicity on PK

Antibody formation was associated with lower serum concentrations of ustekinumab. Across the randomized treatment groups, median serum ustekinumab concentrations were lower (up to 9-fold) over time in patients who were positive for antibodies to ustekinumab compared to concentrations in patients who were negative for antibodies to ustekinumab (Figure 6). At the individual patient level, a clear trend was not observed when trough ustekinumab concentrations in individual patients were compared before and after the first samples showed ADAs against ustekinumab.

Impact of immunogenicity on efficacy

The assessment of the impact of immunogenicity on clinical efficacy is inconclusive because the number of patients who became ADA^+ was small (n=39) in the phase 3 UC studies. Of the 635 ustekinumab-treated patients in the induction study with appropriate samples, four patients (0.6%) were positive for antibodies to ustekinumab from Week 0 through Week 8. No consistent trends on clinical remission were seen across these four individuals. Table 5 summarizes the impact of immunogenicity on efficacy responses at Week 44. However, due to the limited number of patients (n=28) who were positive for antibodies to ustekinumab at any time during maintenance treatment through Week 44, this analysis is inconclusive. We also note that while the Applicant's analysis of immunogenicity on efficacy is based on the Applicant's original definition of clinical remission. The overall conclusion remain unchanged even if we use Agency's definition of clinical remission.

Figure 6. Median Serum Ustekinumab Concentration (mcg/mL) Over Time by Antibody to Ustekinumab Status Through Week 44 of Maintenance Study; Randomized PK Analysis Set (CNTO1275UCO3001)*



Source: Applicant's clinical study report CNTO1275UCO3001 Maintenance, GPKIR01*
* Note that the Y-axis is not in log or linear scale.

Table 5. Number of Patients in Clinical Remission at Week 44, Clinical Response at Week 44, and With Endoscopic Healing at Week 44 by Antibody to Ustekinumab Status Through Week 44 in CNTO1275UCO3001 Maintenance Study; Randomized PK Analysis Set

	Placebo SC [a] (N=175)		Ustekinumab 90 mg SC q8w and q12w combined (N=348)	
	Positive for antibodies to ustekinumab at any time	Negative for antibodies to ustekinumab at any time	Positive for antibodies to ustekinumab at any time	Negative for antibodies to ustekinumab at any time
N	16	159	12	336
Subjects in clinical remission [b]	4 (25.0%)	39 (24.5%)	5 (41.7%)	138 (41.1%)
Subjects in clinical response [c]	6 (37.5%)	78 (49.1%)	9 (75.0%)	249 (74.1%)
Subjects with endoscopic healing [d]	5 (31.3%)	45 (28.3%)	6 (50.0%)	159 (47.3%)

IV=intravenous; PK=pharmacokinetics; q8w=every 8 weeks; q12w=every 12 weeks; SC=subcutaneous.
a: Subjects who were in clinical response to ustekinumab IV induction dosing and were randomized to placebo SC on entry into this maintenance study.
b: An absolute stool number ≤3, a Mayo rectal bleeding subscore of 0, and a Mayo endoscopy subscore of 0 or 1.
c: A decrease from baseline in the Mayo score by ≥30% and ≥3 points, with either a decrease from baseline in the rectal bleeding subscore ≥1 or a rectal bleeding subscore of 0 or 1.
d: A Mayo endoscopy subscore of 0 or 1.
Source: Applicant's Summary of Clinical Efficacy, Table 17
* The definition of clinical endpoints in this table is based on Applicant's original definition. However, the overall conclusion remain unchanged based on the Agency's definition of clinical remission as well.

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 6. Listing of Clinical Trials Relevant to BLA 761004-S003

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow-Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety								
2014-005606-38 induction study	02407236	Study 3: randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the efficacy of IV ustekinumab in inducing clinical remission in patients with moderately to severely active UC, and to evaluate the safety of IV ustekinumab	Randomized patients 1:1:1 to Fixed dose of ustekinumab 130 mg intravenously (IV) as a single infusion at Week 0, OR Weight-based dose of ustekinumab~6 mg/kg IV as a single infusion at Week 0 OR Placebo Single dose IV	Primary endpoint: In the United States, clinical remission was defined by absolute stool number ≤ 3, a rectal bleeding subscore of 0, and a Mayo endoscopy subscore of 0 or 1. Secondary Endpoints: Patients who achieved endoscopic healing (Mayo subscore of 0 or 1) Patients who achieve a clinical response defined as a decrease from the induction baseline Mayo score by ≥30% and >3 points, with either a decrease from induction baseline in the rectal bleeding subscore ≥1 or rectal bleeding subscore =0 or 1. Histologic-Endoscopic Mucosal Improvement at Week 8	Efficacy assessment at 8 weeks and rerandomized into maintenance study. Final safety assessment at 20 weeks	961	Males and females ≥18 years. With moderately to severely active UC who had an inadequate response or failed to tolerate either immunosuppressants (6-MP, AZA) or biologics.	AUS, AUT, BEL, BGR, CAN, CZE, DEU, DNK, FRA, GBR, HUN, ISR, ITA, JPN, KOR, NLD, NZL, POL, ROU, RUS, SRB, SVK, UKR, USA 244 centers 24 countries

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow-Up	No. of patients enrolled	Study Population	No. of Centers and Countries
2014-005606-38 maintenance study	02407236	Study 3: Randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate clinical remission for subcutaneous (SC) maintenance regimens of ustekinumab and to evaluate the safety of SC ustekinumab for 44 weeks.	Randomized Patients (N=523) 1:1:1 to Ustekinumab SC 90 mg Q12W OR Ustekinumab SC 90 mg Q8W OR Placebo SC either Q12 or Q8 weeks Nonrandomized Patients (N=260)[2] Ustekinumab SC 90 mg Q8W OR Placebo SC Q8W	Primary Endpoint: Clinical remission at Week 44, as defined in the induction study. Secondary Endpoints: Maintenance of clinical response at Week 44, as defined in the induction study. Patients achieving endoscopic healing (Mayo subscore of 0 or 1) Patients achieving clinical remission and not receiving corticosteroids at Week 44. Patients achieving clinical remission at Week 44 among those who achieved clinical remission at maintenance study baseline	44 weeks	783 (523: primary analysis population)	Males and females ≥18 years with moderately to severely active UC induced into clinical remission with ustekinumab in the induction study (2014-005606-38).	AUS, AUT, BEL, BGR, CAN, CZE, DEU, DNK, FRA, GBR, HUN, ISR, ITA, JPN, KOR, NLD, NZL, POL, ROU, RUS, SRB, SVK, URK, USA 201 centers 24 countries

Abbreviations: 6-MP = 6-mercaptopurine; AZA = azathioprine; IV = intravenous; Q8/12W = every 8/12 weeks; SC = subcutaneous; UC = ulcerative colitis
Nation abbreviations: AUS = Australia; AUT = Austria; BEL = Belgium; BGR = Bulgaria; CAN = Canada; CZE = Czech Republic; DEU = Germany; DNK = Denmark; FRA = France; GBR = Great Britain; HUN = Hungary; ISR = Israel; ITA = Italy; JPN = Japan; KOR = Korea; NLD = Netherlands; NZL = New Zealand; POL = Poland, ROU = Romania; RUS = Russia; SRB = Serbia; SVK = Slovakia; UKR = Ukraine; USA = United States

[2] This population included 157 patients who were delayed-responders to ustekinumab. Delayed-responders were defined as patients who were not in clinical response to ustekinumab IV at Week 8 of the induction study but were in clinical response at Week 16 following 90 mg SC administration of ustekinumab at Week 8 of the induction trial. The other 103 patients in the nonrandomized population were patients who were in clinical response to placebo IV induction dosing and received placebo SC on entry into the maintenance study.

7.2. Review Strategy

We reviewed the data in the submission from the single induction trial and single maintenance trial separately. No pooling of results for efficacy was conducted. In the maintenance trial, only the randomized population was assessed for efficacy. The team identified several review issues relevant to the evaluation of efficacy (Section 8 below):

1. The definition of clinical remission (primary endpoint) was evolving at the time that these trials were designed; therefore, the Applicant's definition differed from the Division's currently recommended definition and we communicated that it would be a review issue if the trial results differed from the results of exploratory analyses using our recommended definitions. We considered whether the results using the Applicant's endpoint definitions differed from the results using our currently recommended definition for clinical remission. The Applicant's primary endpoint definition of clinical remission and our currently recommended definition are shown below; note that the subscores refer to the subscores of the Mayo Score.
    a. Applicant's definition: rectal bleeding subscore =0, endoscopy subscore =0 or 1, absolute stool number ≤3, where the absolute stool number is the average number of stools per day over a 3-day period.
    b. Currently recommended definition: rectal bleeding subscore =0, endoscopy subscore =0 or 1 (modified so that 1 does not include friability), stool frequency subscore =0 or 1.
2. The Applicant's definition of clinical remission, endoscopic improvement, and histologic-endoscopic mucosal improvement ("mucosal healing" per the Applicant) each relied, in part, on an endoscopic subscore of 1. In the Applicant's prespecified analyses, an endoscopic subscore of 1 was not modified to exclude the presence of friability. However, the presence of friability (even if considered to be mild by the endoscopist/ central reader) is not consistent with *clinical remission.* Therefore, we evaluated the additional analyses conducted by the Applicant in which patients with an endoscopic subscore of 1 and presence of friability were considered to be nonresponders for each endpoint that relied, in part, on an endoscopic subscore of 1.
3. Maintenance of remission will be supported by favorable results of analyses of remission at the end of the maintenance study in which the population is limited to patients who were in remission at the end of the induction study. The Applicant included a prespecified endpoint in the maintenance trial and performed this analysis.
4. (b) (4) (b) (4) This endpoint was prespecified at Week 8 of the induction trial and was exploratory at Week 44 of the maintenance trial. The Applicant included additional data in the sBLA submission to support the proposed definition of histologic healing, included as part of the endpoint definition. We evaluated the Applicant's "Histologic and Mucosal Healing Position Paper" to assess whether: (1) available data are adequate to support that the Geboes scoring system can reliably define histologic remission, and (2) the definition of histologic remission reflects a clinically meaningful change in the relevant patient population (b) (4)

5. We reviewed the totality of the data submitted to determine whether a single induction and single maintenance trial are adequate to support product approval and labeling.
6. There were several other endpoints (b) (4) that were assessed and will be discussed in the following sections of this document (normalization of stool frequency and rectal bleeding, histologic improvement, endoscopic normalization).

Our efficacy assessment primarily focused on the evaluation of the versions of the primary and secondary endpoints that are consistent with the currently recommended endpoint approach.

8. Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Design, Endpoints, and Analysis Plan of CNTO1275UCO3001

8.1.1.1. Trial Design for Induction and Maintenance Studies

The Applicant conducted a single randomized, double-blind, placebo-controlled, parallel group, multisite international induction study (CNTO1275UCO3001IND) and a single maintenance study (CNTO1275UCO3001MAIN). The induction study duration was 8 weeks with a final safety visit at Week 20, and the maintenance study duration was 44 weeks, followed by a final safety visit at Week 52. The total duration of dosing was 52 weeks (8-week induction and 44-week maintenance). The Applicant is also currently conducting a 3-year long-term extension (LTE).

The induction study design randomized patients in a 1:1:1 ratio to one of three treatment groups:

- Placebo IV (placebo group)
- Stelara (ustekinumab) 130 mg IV (130 mg group)
- Stelara (ustekinumab) weight-tiered dosing approximating 6 mg/kg IV
  - Ustekinumab 260 mg (body weight ≤55 kg)
  - Ustekinumab 390 mg (body weight >55 kg and ≤85 kg)
  - Ustekinumab 520 mg (body weight >85 kg)

Randomized patients received a single IV dose of ustekinumab or placebo at Week 0. At Week 8, all patients were assessed for clinical response/remission. Patients who achieved at least clinical response 8 weeks after induction were eligible to enter the maintenance trial for an additional 44 weeks (52 weeks total). These patients were included in the randomized patient population, the primary analysis population for the maintenance trial. Patients who were in clinical response to placebo IV induction received placebo SC in the maintenance trial and were not included in the primary analysis population.

In the maintenance trial, patients were randomized in a 1:1:1 ratio to one of three treatment groups at the Week 0/maintenance baseline:

- Placebo SC
- Stelara (ustekinumab) 90 mg SC every 12 weeks (Q12W)
- Stelara (ustekinumab) 90 mg SC every 8 weeks (Q8W)

In addition, patients who did not achieve clinical response at Week 8 could receive ustekinumab as outlined below:

- Patients randomized to placebo at Week 0 received one dose of ustekinumab approximately 6 mg/kg IV plus placebo SC to maintain the blind at Week 8.
- Patients who were randomized to ustekinumab at Week 0 received one dose of ustekinumab 90 mg SC plus placebo IV to maintain the blind at Week 8.

Of these patients, those who achieved at least clinical response at Week 16 were eligible to enter the maintenance trial and continued for 44 weeks (the duration of the maintenance trial). However, these patients were considered as the **nonrandomized patient population** and were followed for efficacy and safety, but were not included in the primary analysis population.

Patients who did not achieve clinical response by Week 16 did not enter the maintenance trial and were followed for approximately 20 weeks after their last dose of study drug for safety.

Enrollment Criteria

The target population included male and female adults, aged 18 or older, with a clinical diagnosis of UC that should have been made at least 3 months prior to screening. At screening, patients had moderately to severely active UC, as defined by a Mayo score of 6 to 12 inclusive, including an endoscopy subscore ≥2 at baseline (Week 0) of the induction study, based on the Mayo endoscopy subscore assigned during the central reading of the video endoscopy. Enrolled patients also met *at least one* of the following criteria:

- Failed biologic therapy (i.e., received treatment with one or more TNF antagonists or vedolizumab at a dose approved for the treatment of UC) and have documented history of failure to respond to or tolerate such treatment.

  OR

- Naïve to biologic therapy (e.g., TNF antagonist or vedolizumab) or not have demonstrated a history of failure to respond to, or tolerate, a biologic and have a prior or current UC medication history that includes at least one of the following:
  - Inadequate response to or failed to tolerate current treatment with oral corticosteroids or immunomodulators (6-MP or AZA)

    OR
  - History of failure to respond to, or tolerate, at least one of the following: oral or IV corticosteroids or immunomodulators (6-MP or AZA)

    OR
  - History of corticosteroid dependence (i.e., an inability to successfully taper corticosteroids without a return of the symptoms of UC)

    A minimum of 40% but not more than 50% of the total number of patients enrolled in the induction study were to have been biologic failures as defined above.

Patients were excluded if they met any of the following:

- Severe extensive colitis
- UC limited to the rectum only or to <20cm of the colon
- Presence of a stoma or fistula or history of a fistula.
- Received treatment with a biologic therapy targeted at IL-12 and/or IL-23, natalizumab or agents that deplete B or T cells within 12 months of first study drug administration.
- Positive stool culture for an enteric pathogen, including *Clostridium difficile*, in the previous 4 months unless a repeat exam is negative and there are no signs of ongoing infection.
- Active infections, including active tuberculosis (TB), history of latent or active granulomatous infection, history of/ongoing/chronic or recurrent infectious disease. An exception was made for patients with a history of latent TB who were receiving treatment for latent TB, would initiate treatment before the first dose of study drug, or have documented completion of appropriate treatment within 3 years before the first dose of study drug. Patients with a history of latent TB who have not been treated were excluded. Patients with signs or symptoms suggestive of active TB or patients who have had close contact with a person with active TB were excluded.
- Known malignancy of history of malignancy (with the exception of basal cell carcinoma, squamous cell carcinoma in situ of the skin, or cervical carcinoma in situ that has been treated with no evidence of recurrence, or squamous cell carcinoma of the skin that has been treated with no evidence of recurrence within 5 years prior to screening).

Patients randomized into the maintenance study were required to be in at least clinical response to treatment in the induction study. This criterion included two groups of patients: (1) those randomized to ustekinumab who were in at least clinical response at Week 8 of the induction study; and (2) patients who were randomized to placebo and who were not in clinical response at Week 8 of the induction study, but were in clinical response at Week 16 after receiving an induction dose of ustekinumab 6 mg/kg IV at Week 8.

8.1.1.2. Long-Term Extension (LTE)

Patients who completed the safety and efficacy evaluations at Week 44 of the maintenance study and who would benefit from continued ustekinumab therapy were eligible to participate in the long-term extension which began after completion of Week 44 assessments of the maintenance study and are to continue to Week 220. In the LTE, patients were to receive the same dose regimen as during the maintenance study (either placebo or ustekinumab 90 mg SC Q8W or Q12W). Patients would then be assessed for worsening of disease activity based on clinical judgement of the investigator. Patients whose disease worsened during the LTE would be eligible for a single dose adjustment that would include switching to ustekinumab 90 mg SC Q8W. Induction placebo responders and delayed-responders (who were already receiving ustekinumab 90 mg SC Q8W) would not be eligible for a dose adjustment during the LTE. Available data from the LTE were submitted in the 120-day safety update.

8.1.1.3. Efficacy Endpoint Definitions

As mentioned previously, the Applicant's endpoint definitions differed from the Division's currently recommended definitions. For the endpoint definitions that differed, the FDA recommended endpoint definitions are show in *italic text* below each of the Applicant's definitions. For endpoints that included an endoscopic component, patients underwent either a sigmoidoscopy or full colonoscopy and the score was based on the worst findings identified in the colon. The biopsies were obtained from the most representative area 15 to 20 cm from the anal verge at screening, Week 8, Week 16 (if applicable), Week 44, and at a clinical flare visit (if applicable); if possible, a tattoo was placed at the area from which the biopsy was taken. If this pre-defined region is not representative of the disease activity, then the biopsies were taken from a representative area and follow up biopsies were collected from that same location.

- **Induction baseline:** Week 0 of induction study (I-0 visit)
- **Maintenance baseline:** Week 0 of maintenance study (M-0 visit)
- **Clinical remission:**
  - **U.S. definition of clinical remission:** Absolute stool number ≤3 with a rectal bleeding subscore of 0 and a Mayo endoscopy score of 0 or 1 (a score of 1 includes the presence of friability).
    - *FDA currently recommended definition: rectal bleeding subscore =0, endoscopy subscore =0 or 1 (modified so that 1 does not include friability), stool frequency subscore =0 or 1.*
  - Global (outside of the United States): Mayo endoscopy score ≤2 with no individual subscores >1 (note: the results using the global definition were not relied upon in our efficacy assessment to support product approval and labeling)
- **Clinical response:** A decrease from induction baseline in the Mayo score by ≥30% and ≥3 points, with either a decrease from baseline in the rectal bleeding subscore ≥1 or a rectal bleeding subscore of 0 or 1.
  - *FDA currently recommended definition: A decrease from induction baseline in the Mayo score (excluding the PGA) by ≥30% and ≥2 points, with either a decrease from baseline in the rectal bleeding subscore ≥1 or a rectal bleeding subscore of 0 or 1.*
  - [Note: the definition of clinical response used to evaluate patients at Week 8 to determine eligibility for randomization into the maintenance study was based on the following: a decrease from induction baseline in the full Mayo score by ≥30% and ≥3 points (using the Mayo endoscopy subscore assigned by the local endoscopist), with either a decrease from baseline in the rectal bleeding subscore ≥1 or a rectal bleeding subscore of 0 or 1.]
- **Endoscopic improvement** ("healing" per the Applicant) (i.e., improvement in the endoscopic appearance of the mucosa): Endoscopy subscore of the Mayo score =0 or 1 (a score of 1 includes the presence of friability).
  - *FDA currently recommended definition: endoscopy subscore =0 or 1 (modified so that 1 does not include friability).*
- **Normal or inactive mucosal disease:** Endoscopy subscore =0

- **Histologic-endoscopic mucosal improvement** ("Mucosal healing" per the Applicant): Endoscopic healing with an endoscopy subscore of 0 or 1 and histologic healing (referred to as "histologic-endoscopic improvement" in this document (b) (4)
- **Histologic improvement** ("healing" per the Applicant): Histologic improvement is based on the Geboes score (Geboes et al. 2000) and is defined as <5% neutrophils in epithelium and no crypt destruction, erosions, ulcerations or granulations. For details on the Geboes scoring system, see Appendix, Figure 23. Geboes Score.
- **Symptomatic remission:** Mayo stool frequency subscore of 0 or 1 and rectal bleeding subscore of 0.
- **Final reported endoscopy subscore:** Agreed upon subscore defined when both the central reader and local endoscopist agree on the endoscopic subscore. The analysis of endpoints related to the endoscopy subscore, including the Mayo subscore, and except when noted, will be based on the final reported endoscopic subscore.
- **Maintenance of symptomatic remission:** Achieving symptomatic remission at ≥80% of all visits from Week 4 to Week 40 (at least 8 out of 10 visits) and in symptomatic remission at last visit (Week 44) among patients who had achieved symptomatic remission at maintenance baseline.
- **Durable partial Mayo remission:** Achieving partial Mayo remission at ≥80% of all visits (at least 9 out of 11 visits) prior to Week 44 and in partial Mayo remission at last visit (Week 44)

8.1.1.4. Study Endpoints

Induction Study

Primary U.S. clinical endpoint

At Week 8, defined as absolute stool frequency ≤3 stools/day; a Mayo rectal bleeding subscore of 0, and a Mayo endoscopy subscore of 0 or 1.

Multiplicity-controlled secondary endpoints (for United States) in the following hierarchical order:

(1) Endoscopic improvement ("healing") at Week 8
(2) Clinical response at Week 8
(3) Histologic-endoscopic mucosal improvement ("mucosal healing") at Week 8, defined as endoscopic improvement and histologic improvement

Additional clinical endpoints

The following additional clinical endpoints, of interest to the Agency, were not controlled for multiplicity:

(1) Histologic-endoscopic mucosal improvement ("mucosal healing") at Week 8, including both endoscopic and histologic improvement, with a patient considered as a nonresponder if friability was present on endoscopy
(2) Histologic improvement at Week 8
(3) Remission at Week 8 based on a stool frequency subscore of 0 or 1, a rectal bleeding

subscore of 0, and an endoscopy subscore of 0 or 1; nonresponder would include a patient if friability was present on endoscopy.

(4) Remission at Week 8 based on a stool frequency subscore of 0, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1, since this clinical endpoint would support the definition of normalization of stool frequency and no rectal bleeding. This definition allowed for the presence of friability in an endoscopy subscore of 1. The Applicant also performed this analysis in which an endoscopic subscore of 1 excluded the presence of friability.

Maintenance Study

Primary U.S. clinical endpoint

At Week 44, defined as absolute stool frequency ≤3 stools/day, a Mayo rectal bleeding subscore of 0, and a Mayo endoscopy subscore of 0 to 1.

- Primary endpoint subgroup analysis by induction dose will support efficacy based on induction dose stratification.

Secondary endpoints

Secondary endpoints in the maintenance study as prespecified in the statistical analysis plan for the "randomized" population and controlled for multiplicity:

(1) Maintenance of clinical response at Week 44
(2) Endoscopic improvement at Week 44
(3) Clinical remission and not receiving concomitant corticosteroids (corticosteroid-free clinical remission) at Week 44
(4) Maintenance of clinical remission at Week 44 among the patients who had achieved clinical remission at maintenance baseline.

The endpoints above were also analyzed by subgroups of biologic failure status (i.e., bio naïve/bio failure) and are proposed by the Applicant (b) (4)

Other clinical endpoints

Other clinical endpoints summarized in the maintenance study of interest to the Agency but were not controlled for multiplicity:

- Durable partial Mayo remission through Week 44 (Mayo Score ≤2 at least through 80% of visits through Week 44).
- Symptomatic remission based on achieving a Mayo stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0.
- Remission at Week 44 based on a stool frequency subscore of 0 or 1, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1 (nonresponder if friability present on endoscopy).
- Histologic-endoscopic mucosal improvement ("mucosal healing") at Week 44 (nonresponder if friability present on endoscopy).
- Normal or inactive mucosal disease at Week 44 (endoscopy subscore of 0).

- Patients in clinical remission at Week 44 and not receiving corticosteroids for at least 90 days prior to Week 44.
- Patients in clinical remission at Week 44 and not receiving corticosteroids for at least 30 days prior to Week 44.

The endoscopic subscore was assessed by the investigator (i.e., local endoscopist) during the endoscopy procedure and by a central reader reviewing a video of the endoscopy. The central readers were blinded to local endoscopist scores, treatment assignment, and study visit (except for the initial or the final endoscopy videos when the central readers know that these videos are or are not from the screening visit). If the local endoscopist and the central reader agreed on the endoscopic subscore, the agreed score was the final reported endoscopic subscore. If there was a discrepancy between the local endoscopist and the central reader subscores, the video endoscopy was submitted to a second central reader designated for adjudication. The adjudicator was blinded to the scores of the local and first central reader. From the three Mayo endoscopic subscores, the score with which two readers agreed was reported as the final Mayo endoscopic subscore. In the unlikely event that no two readers agreed on the Mayo endoscopic subscore, the median score of the three completed reads (i.e., local read, central read #1 and central read #2 designated for adjudication) was chosen as the final reported endoscopic subscore. The analysis of endpoints related to the endoscopy subscore, including the Mayo score was based on the final reported endoscopic subscore.

8.1.1.5. Statistical Analysis Plan

Efficacy Analysis Populations

In the *induction study*, the efficacy analysis population consisted of all randomized patients.

Analogously, the efficacy analysis population for the *maintenance study* consisted of all patients randomized at Week 0 of the maintenance study. Unless otherwise specified, all efficacy analyses were based on the intent-to-treat principle. That is, patients were analyzed according to the treatment group to which they were assigned regardless of the treatment they actually received.

Safety Analysis Population

The safety analysis population included patients who received at least one dose of study drug, including a partial dose, and were analyzed according to the actual treatment received. Therefore, the safety population differs slightly from the efficacy analysis population because one patient was randomized to the 130 mg group but did not receive study drug (not included in the safety analysis population), and two patients were randomized to the ~6 mg/kg group, but received a ustekinumab dose that was closer to 130 mg. These two patients were included in the 130 mg group for the safety analyses. For comparison, the efficacy analysis population includes 961 total patients (319 in the placebo arm, 320 in the 130-mg dose arm, and 322 in the 6 mg/kg dose arm), whereas the safety analysis population includes 960 total patients (319 in the placebo arm, 321 in the 130-mg dose arm, and 320 in the 6 mg/kg dose arm).

Statistical Analysis Methods

The primary and major secondary binary endpoints in the induction and maintenance studies were compared between each ustekinumab treatment group and the placebo group using a stratified Cochran-Mantel-Haenszel (CMH) chi-square test. In the induction study, the CMH test was stratified by biologic failure status (yes or no) and region (Eastern Europe, Asia, or Rest of World). In the maintenance study, stratification factors for the analysis were clinical remission status at baseline (yes or no as determined by the Interactive Web Response System based on the Applicant's definition) and induction treatment.

The adjusted treatment difference (with CMH weight) between each ustekinumab treatment group and the placebo group were calculated together with the associated confidence intervals (95% or 97.5% confidence intervals depending on the multiplicity adjustment).

Handling Missing Data

For dichotomous endpoints, patients with missing data were considered as not achieving the respective endpoints.

Stool frequency and rectal bleeding subscores

The electronic case report forms (eCRFs) capture 7 days of rectal bleeding data and the number of stools per day prior to each visit at which the partial Mayo score or Mayo score is collected. Absolute stool number is the average of the daily stool number over the 3 days, and rectal bleeding subscores are calculated using the average rectal bleeding number for the 3 days. If 3 consecutive days are not available, the sites are instructed to choose 2 consecutive days and the closest nonconsecutive day. If 2 consecutive days are not available, then 3 nonconsecutive days closest to the visit should be chosen. If 3 days (within the week prior to the indicated visit) that meet the criteria defined above are not available, then the absolute stool number, stool frequency subscore, and rectal bleeding subscore cannot be calculated and will be missing in the eCRF.

Endoscopy subscore

If the final reported endoscopic subscore was not available, the corresponding central endoscopy score (central read #1) was used, if available. If the central endoscopy score (central read #1) was also missing, then the local endoscopy score was used, if available. If the local endoscopy score was also not available, then the endoscopy subscore for the analysis was left missing.

Treatment failure rules overrode missing data rules. This meant that if a patient had an event of treatment failure, baseline values were assigned from the point of treatment failure onward for continuous endpoints, and patients were considered as not achieving the respective endpoints for dichotomous endpoints, regardless of whether the data were observed or

missing. Patients who had any of the following events were considered to be a treatment failure from the time of the event onward:

- Ostomy or colectomy (partial or total)
- Prohibited change in UC medication, which included initiation, increase in dose, or change from one product to another of corticosteroids, 5-ASA products, or immunomodulators.

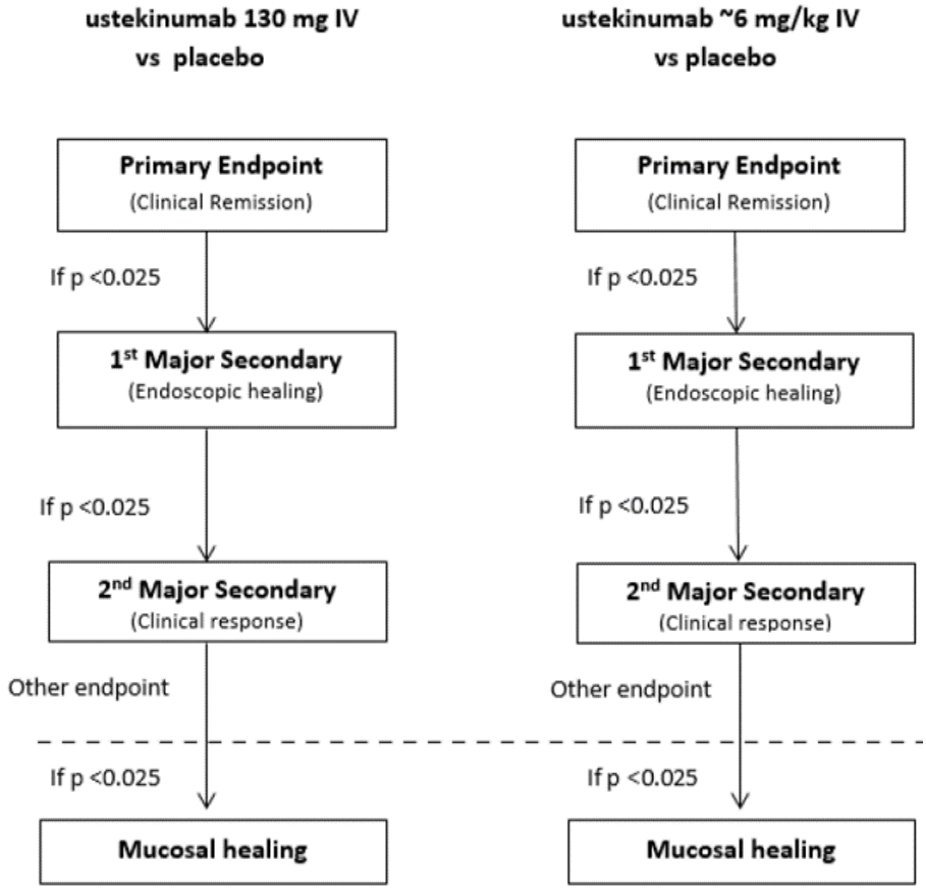
Multiplicity Adjustment (U.S.-Specific Testing Procedures)

The Applicant prespecified different multiple testing strategies to control the overall Type 1 error for the United States as compared to other regions. In this review we only discuss the multiplicity adjustment approach used for the submission to FDA.

Induction study

The overall Type 1 error rate was controlled at the two-sided 0.05 significance level across the primary and three secondary endpoints (endoscopic improvement at Week 8, clinical response at Week 8, and histologic-endoscopic improvement ("mucosal healing") at Week 8) for the two ustekinumab dose arms. As depicted in Figure 7, the primary and three multiplicity-controlled secondary endpoints were tested in a hierarchical manner within each ustekinumab group at the two-sided 0.025 level of significance.

Figure 7. Multiple Testing Procedure in Induction Study (U.S.-Specific)

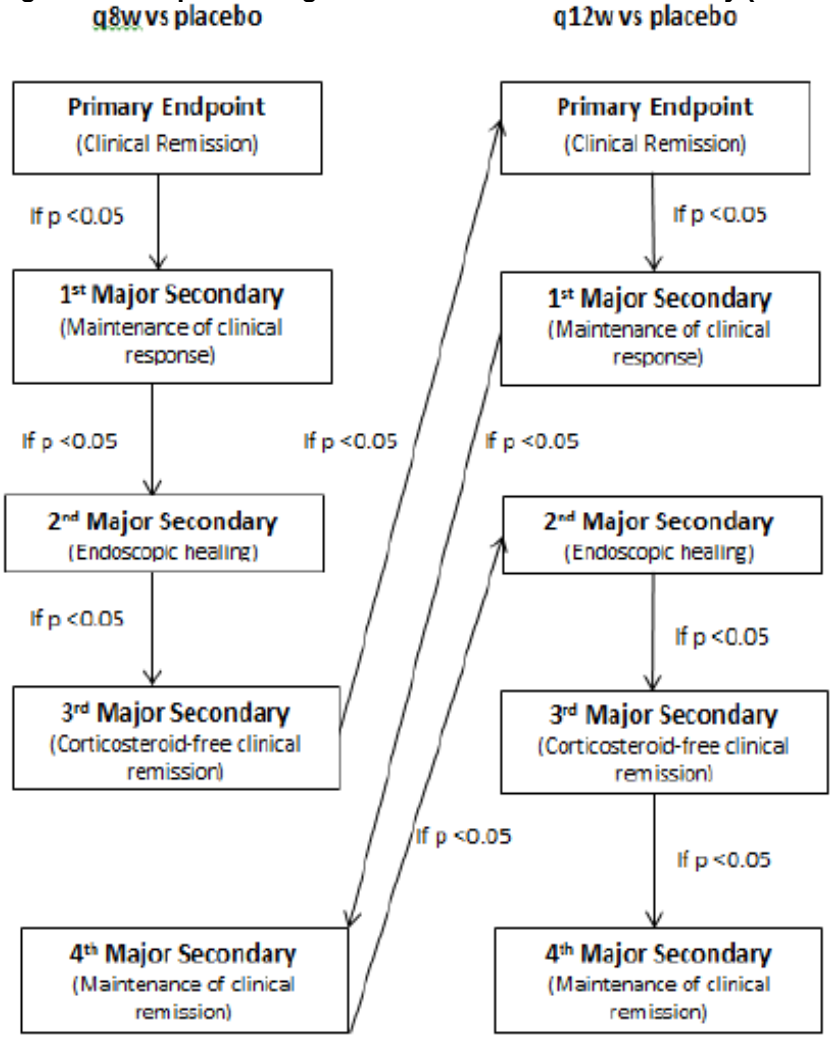


Source: Applicant statistical analysis plan cnto1275uco3001ind.pdf, p. 31. Fig. 5 (U.S.-specific testing proc.)

Maintenance study

The overall Type 1 error rate was controlled across the primary and four secondary endpoints (maintenance of clinical response, endoscopic improvement at Week 44, corticosteroid-free clinical remission at Week 44, and maintenance of clinical remission) for the two ustekinumab dose arms. All tests were performed at the two-sided 0.05 level following a fixed sequence procedure (i.e., following the prespecified order) as depicted in Figure 8. If a test for any hypothesis was not significant, all subsequent tests were not to be performed.

Figure 8. Multiple Testing Procedure in Maintenance Study (U.S.-Specific)



Source: Applicant statistical analysis plan cnto1275uco3001main.pdf, p. 34
Abbreviation: Q8/12W = every 8/12 weeks

8.1.1.6. Interim Analysis (Induction Study)

A futility analysis based on the primary endpoint of clinical remission at Week 8 was planned when the first 30% of randomized patients had either completed the Week 8 visit or had terminated study participation before Week 8. If the conditional power on both ustekinumab doses was less than 20%, the study could have been stopped for futility. Per the Agency's recommendation, the Applicant allocated a small α of 0.00001 for this interim analysis.

The futility analysis and the unblinding of the treatment assignments for the futility analysis were to be handled by an external statistical support group. To decide whether to stop the study for futility, the Data Monitoring Committee (DMC) reviewed the futility analysis results provided by the statistical support group and provide a recommendation to the Sponsor Decision Committee (SDC) based on the prespecified decision rules. The SDC then reviewed the DMC's recommendation and made a final decision concerning the futility analysis.

Determination Based on the Futility Interim Analysis Results

Following the futility analysis, the DMC recommended continuing the trial, and the SDC accepted the DMC recommendation without reviewing the unblinded results per the guiding principle. The Applicant claims that they did not have access to the unblinded results at the time of futility analysis.

8.1.1.7. Protocol Amendments

The original protocol for UC was available on March 17, 2015. The Applicant submitted an amended protocol on July 14, 2015, and a second amended protocol on April 20, 2016. The majority of the amendments made by the Applicant were applied to the maintenance trial although several modifications were made to the induction trial. For example, the Bristol Stool Form Scale was also added for exploratory analysis in the induction study. The substantive changes adopted in protocol for the induction and maintenance trials are summarized here.

First amended protocol, July 14, 2015

(1) Serum sample for anti-ustekinumab antibodies was added to Week 4 of the maintenance study and moved from Week 2 to Week 4 in the induction study.
(2) The first dose of ustekinumab in the LTE study was moved from Week 44 to Week 48; no study agent was to be administered at Week 52.
(3) The global definition of clinical remission would be used to stratify patients randomized into the maintenance study.
(4) CMH test would be used for the primary and major secondary efficacy analyses for both the induction study and the maintenance study.
(5) The definition of failure to respond to corticosteroids was clarified.

Second amended protocol, April 20, 2016

(1) U.S.-specific definition of clinical remission was clarified to be used to support only the U.S. submission, and each definition would be applied to all patients in the analysis population.
(2) Stool consistency data using the Bristol Stool Form Scale was added for exploratory analyses in the induction and maintenance studies.

(3) The order of the third and fourth secondary objectives/major secondary endpoints in the maintenance study was reversed. In addition, the analysis population for the objective/endpoint of corticosteroid-free remission at Week 44 (now the third secondary objective/major secondary endpoint) was updated to include all patients randomized into the maintenance study, regardless of corticosteroid use at the M-0 visit (instead of being limited to only patients who were receiving corticosteroids at the M-0 visit). The previous endpoint of corticosteroid-free remission at Week 44 in patients induced into clinical response with ustekinumab and receiving corticosteroids at Week 0 of maintenance was moved to the Other Secondary Endpoints section.
(4) Maintaining clinical remission in patients induced into clinical remission with ustekinumab (now the fourth secondary objective/major secondary endpoint) was retained.
(5) Clarifying language was added for which endoscopy score would be used to determine patient eligibility at baseline and for primary and major secondary endpoints involving the endoscopy subscore.
(6) Statistical methods were revised to incorporate a fixed-sequence testing procedure that would be used in the United States.
(7) Extended-release corticosteroids were added to use of corticosteroids and to enhance clarity in the definition of corticosteroid dependence.

8.1.2. Study Results

8.1.2.1. Compliance with Good Clinical Practices

The Applicant states that all studies included in the submission were conducted and reported in accordance with the ethical principles originating in the Declaration of Helsinki and in accordance with International Conference for Harmonisation (ICH) good clinical practice guidelines, applicable regulatory requirements, and in compliance with the respective protocols.

Good clinical practice deviations were noted during monitoring visits for sites US00041 and US00123. The deviations were primarily related to principal investigator oversight. Efforts were made to bring the sites back into compliance; however, due to ongoing deviations, both sites were closed and reported to the Office of Scientific Investigations.

- Site US00041: One patient remained in the study and was offered the option to transfer to another investigational site but declined and a final study visit was conducted. Data (efficacy, safety and PK) from two patients who were randomized at the site were used in the analyses; however, the patients' efficacy data were excluded in the per-protocol sensitivity analysis.
- Site US00123: One patient was randomized but was lost to follow-up prior to site closure. Data (efficacy, safety and PK) from the randomized patients were used in the analyses; however, the patient efficacy data were excluded in the per-protocol sensitivity analysis.

8.1.2.2. Financial Disclosure

The Applicant adequately disclosed financial arrangements with the clinical investigators. These arrangements do not raise concern over the integrity of the data. See Section 15.2, Appendix: Financial Disclosure, for further discussion and tables detailing financial disclosures.

8.1.2.3. Patient Disposition

Randomized Population

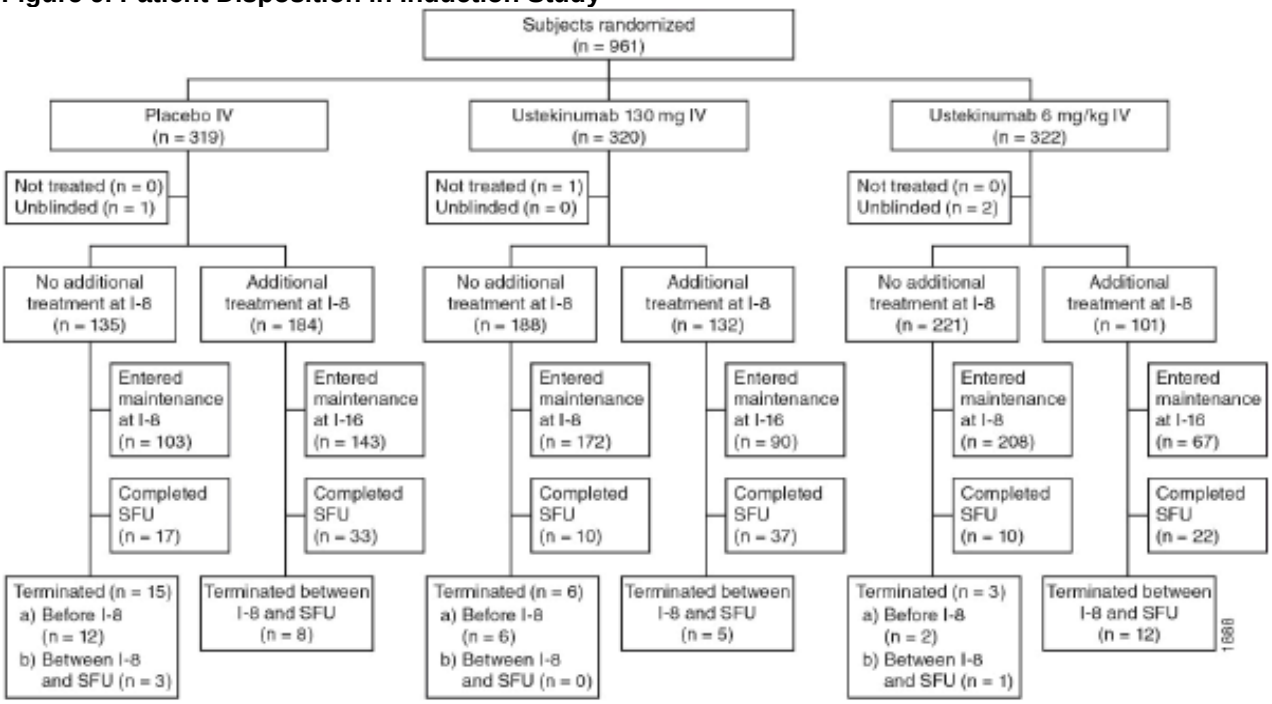
A total of 961 patients from 244 sites were randomized in 1:1:1 ratio to two ustekinumab dose arms and placebo. All but three randomized patients received the treatment to which they were assigned at Week 0. One patient was randomized to the 130 mg group but did not receive study agent. Two patients were randomized to the ~6 mg/kg group but received a ustekinumab dose that was closer to 130 mg; these two patients were included in the 130 mg group for the safety analyses.

Five-hundred twenty-three patients were in clinical response to IV ustekinumab induction at week 8 and were randomized into the maintenance study. There were 208 patients from the 6 mg/kg IV dose arm and 172 patients from the 130 mg dose arm who were in clinical response at Week 8 after the single IV induction dose and entered the maintenance phase. In addition, patients in the placebo IV induction arm who were not in clinical response were eligible to receive a blinded 6 mg/kg IV induction dose at Week 8. These patients were eligible to enter the maintenance phase as part of the randomized population if they were in clinical response 8 weeks later at Week 16; they were followed for a total of 44 weeks in the maintenance phase to allow for the same duration of exposure as patients who received the ustekinumab IV induction dose. Of these patients, 143 patients who received placebo IV induction were in clinical response 8 weeks later at Week 16 and entered the maintenance phase.

Forty-nine patients (5.1%) terminated the induction trial prematurely; 20 patients (2.1%) terminated study participation prior to Week 8 (2 in the 6 mg/kg group, 6 in the 130 mg group, and 12 in the placebo group). The most common reason for termination before Week 8 was withdrawal of consent, which was reported for a total of 14 patients (1.5%); 0 patients in the ~6 mg/kg group, 5 patients [1.6%] in the 130 mg group, and 9 patients [2.8%] in the placebo group. Of the remaining 29 patients who terminated study participation, four patients terminated at Week 8, and 25 patients terminated after Week 8. Details of the patient disposition for the induction study are shown below in Figure 9 and Table 7.

Details of the patient disposition for the maintenance study are shown below in Figure 10 and Table 8. In the maintenance trial, 43/172 (24.6%), 24/175 (14%), and 18/176 (10.2%) patients on the placebo, 90 mg Q12W, and 90 mg Q8W arms discontinued treatment early, respectively.

Figure 9. Patient Disposition in Induction Study



I-8 = Induction, Week 8 I-16 = Induction, Week 16 IV = Intravenous SFU = Safety follow-up

Source: Attachment TSIDS01, Attachment TSIDS02, Attachment LSIPD01

Table 7. Induction Study Participation Status at Week 8

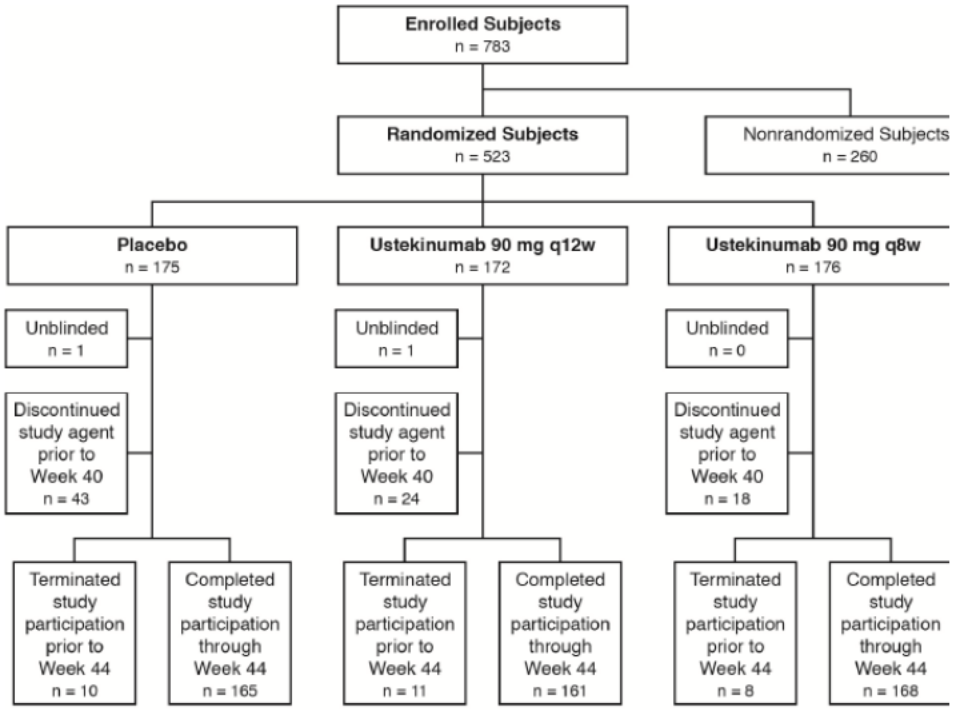
	Placebo IV	Ustekinumab IV 130 mg	Ustekinumab IV 6 mg/kg [a]	Ustekinumab IV Combined	Total
Primary Efficacy Analysis Set	319	320	322	642	961
Subjects who entered maintenance study at Week 8	103 (32.3%)	172 (53.8%)	208 (64.6%)	380 (59.2%)	483 (50.3%)
Subjects who did not enter maintenance study at Week 8	216 (67.7%)	148 (46.3%)	114 (35.4%)	262 (40.8%)	478 (49.7%)
Subjects who received study agent at Week 8	184 (57.7%)	132 (41.3%)	101 (31.4%)	233 (36.3%)	417 (43.4%)
Subjects in safety follow-up	17 (5.3%)	10 (3.1%)	10 (3.1%)	20 (3.1%)	37 (3.9%)
Subjects who terminated prior to Week 8	12 (3.8%)	6 (1.9%)	2 (0.6%)	8 (1.2%)	20 (2.1%)
Reasons for termination					
Adverse event	2 (0.6%)	0	0	0	2 (0.2%)
Withdrawal of consent	9 (2.8%)	5 (1.6%)	0	5 (0.8%)	14 (1.5%)
Lost to follow up	0	0	1 (0.3%)	1 (0.2%)	1 (0.1%)
Sponsor decision	0	1 (0.3%)	0	1 (0.2%)	1 (0.1%)
Death	0	0	1 (0.3%)	1 (0.2%)	1 (0.1%)
Other	1 (0.3%)	0	0	0	1 (0.1%)
Subjects who terminated at Week 8	3 (0.9%)	0	1 (0.3%)	1 (0.2%)	4 (0.4%)
Reasons for termination					
Adverse event	1 (0.3%)	0	0	0	1 (0.1%)
Withdrawal of consent	2 (0.6%)	0	1 (0.3%)	1 (0.2%)	3 (0.3%)
Lost to follow up	0	0	0	0	0
Sponsor decision	0	0	0	0	0
Death	0	0	0	0	0
Other	0	0	0	0	0

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

[TSIDS01.RTF] [/SAS/2709/CNTO1275UCO3001/FILES/RE/CSRINDUCTIONFINAL/PROGRAMS/TSIDS01.SAS] 06FEB2018. 05:02

Source: Applicant submission, sBLA 761044, Study Report CNTO1275UCO3001 Induction, Table TSIDS01, page 724/853

Figure 10. Patient Disposition in Maintenance Study (Randomized Population)



Source: Applicant submission, sBLA 761044, Study Report CNTO1275UCO3001 Maintenance, Figure 7, page 70/1560

Table 8. Maintenance Study Participation; Maintenance Baseline Through Week 44 (Randomized Population)

	Placebo SC N=175		Ustekinumab 90 mg SC Q12W N=172		Ustekinumab 90 mg SC Q8W N=176	
Disposition Event	**n**	**%**	**n**	**%**	**n**	**%**
Patients who discontinued study drug prior to Week 40 (last study drug administration visit)	43	24.6	24	14.0	18	10.2
Reason for discontinuation						
Lack of efficacy	15	8.6	7	4.1	6	3.4
Adverse event—worsening of UC	16	9.1	4	2.3	0	0.0
Adverse event other than worsening of UC	3	1.7	4	2.3	4	2.3
Not in partial mayo response 16 weeks following initiation of rescue meds	4	2.3	2	1.2	0	0.0
Other	5	2.9	7	4.1	8	4.5
Patients terminated study participation prior to Week 44 and did not complete safety follow up prior to Week 44	10	5.7	11	6.4	8	4.5
Reason for termination						
Lost to follow-up	1	0.6	0	0.00	1	0.6
Sponsor Decision	1	0.6	0	0.0	1	0.6
Withdrawal of Consent	8	4.6	10	5.8	5	2.8
Other	0	0.0	1	0.6	1	0.6

Source: Adapted from Applicant submission, sBLA 761044, Study Report CNTO1275UCO3001 Maintenance, pages 1278-79/1560, Table TSIDS01, and reviewer analysis of ADDS dataset from CNTO1275UCO3001 maintenance data 5.3.5.1.
Abbreviations: Q8/12W = every 8/12 weeks; SC = subcutaneous; UC = ulcerative colitis

Non-Randomized Population

A total of 417 patients who were not in clinical response at Week 8 received an additional dose of study agent at Week 8 (referred to as the "**nonrandomized population**" by the Applicant; data obtained from these patients were analyzed separately from the primary efficacy and safety populations):

- At Week 8, 184 patients who received placebo at Week 0 received one dose of ustekinumab 6 mg/kg IV.
- At Week 8, 233 patients who received ustekinumab at Week 0 received one dose of ustekinumab 90 mg SC as follows:
  - 132 patients who received ustekinumab 130 mg IV at Week 0 received one dose of ustekinumab 90 mg SC at Week 8.
  - 101 patients who received ustekinumab ~6 mg/kg IV at Week 0 received one dose of ustekinumab 90 mg SC at Week 8.

Among the patients who received additional treatment at Week 8, 392 patients (94%) completed study participation: 300 patients (71.9%) entered maintenance at Week 16, and 92 patients (22.1%) who did not enter maintenance completed the final safety visit. Twenty-five patients (6.0%) terminated study participation between Week 8 and the final safety visit (4.3% in the placebo → ~6 mg/kg group; 3.8% in the 130 mg → 90 mg SC group; and 11.9% in the ~6 mg/kg → 90 mg SC group).

8.1.2.4. Protocol Violations/Deviations

Induction Study

Of the 961 randomized patients enrolled in the induction study from Week 0 to Week 8, 138 (14.4%) had a major protocol violation/deviation, the majority of whom (92; 9.6% of the randomized population) entered the study but did not meet enrollment criteria. One patient (0.1%) took a rectal preparation of 5-ASA during the induction but remained in the study even though 5-ASA products were disallowed. This patient was randomized to the ustekinumab 6 mg/kg IV induction treatment arm and failed to achieve clinical remission or response at Week 8. Therefore, the patient was counted as a treatment failure for the efficacy analyses at Week 8 and was not included in the primary analysis population. The use of rectal 5-ASA, although prohibited, did not appear to bias the efficacy results in favor of the study drug. The patient received 90 mg SC ustekinumab at Week 8 but failed to achieve clinical remission or response at Week 16. Four patients (0.4%) received either the wrong treatment or the incorrect dose at Week 0 and are discussed previously in the disposition section.

Deviations from study entry criteria were categorized as related to UC disease criteria, medication criteria, laboratory criteria, medical history criteria, and other. Deviations due to study entry criteria were identified during monitoring visits or data review by the Applicant. On identification of deviations to study entry criteria, sites were requested to provide follow-up information and assessment to confirm a patient's eligibility to continue study agent administration. The absence of documentation confirming a patient's eligibility at randomization was considered a deviation even if subsequent follow-up confirmed that the patient would have met the specific entry criterion.

Nine (0.9%) patients did not meet UC disease criteria:

- Five patients did not have a Mayo score of 6 to 12 inclusive, at randomization. One of these patients was identified as not meeting this criterion due to the absence of a confirmation that the Mayo endoscopy score was ≥2 as assessed during central review of the video of the endoscopy. However, subsequent follow-up confirmed the patient's eligibility based on the Mayo score at randomization and the endoscopy subscore provided during central review. The baseline Mayo score was not lower than 5 for any of the patients with available baseline Mayo scores, and the majority of these patients were not responders at Week 8. Therefore, inclusion of these patients with slightly more mild disease does not appear to have influenced the trial results overall.
- One additional patient was randomized without confirmation that the Mayo endoscopy score was ≥2 as assessed during central review of the video of the endoscopy, subsequent follow-up confirmed eligibility.
- Two patients were randomized with a prior history of fistula; a UC diagnosis was confirmed for both patients.
- One patient was diagnosed with UC less than 3 months prior to study entry.

Overall, the small number of patients with protocol deviations and type of deviations, including the additional follow-up to confirm whether the patients met enrollment criteria, are unlikely to have influenced the results of the trials.

Twenty-six patients (2.7%) were reported to have not met medication criteria (one patient did not meet two of the medication criteria), 21(3.3%) of whom were randomized to either ustekinumab treatment arms:

- Eleven patients did not discontinue vedolizumab 4 months prior to the first dose of study agent. Eight of these patients were randomized to ustekinumab treatment. Of the 11 patients, four patients entered the maintenance phase in the randomized population.
- Two patients did not discontinue anti-TNF therapy for at least 8 weeks prior to the first dose of study agent. One patient achieved response at Week 8 and one did not.
  - The patients who did not discontinue vedolizumab or anti-TNF therapy were permitted to continue in study provided the full washout period for these agents was achieved by the next scheduled dosing visit (Week 8 induction/Week 0 maintenance study). Information on the timing of when the vedolizumab or anti-TNF therapy was initially started in relation to the study start date was not available.
- Eight patients did not discontinue other treatments for UC for the duration prior to the first administration of study agent as specified per protocol.
  - Three patients did not discontinue antibiotics.
  - Two patients did not discontinue rectal 5-ASA or rectal corticosteroid.
  - One patient each did not discontinue the use of an immunomodulator, oral 5-ASA or corticosteroid, or total parenteral nutrition.
- Five patients failed to maintain stable doses of concomitant medications (oral corticosteroid, 5-ASA, or immunomodulator) prior to the first dose of study agent.

- One patient continued treatment with 6-thioguanine, was directed to discontinue the study, and did not enter the maintenance study.

The proportion of patients with protocol deviations related to concomitant medication was small and unlikely to influence the outcomes of the trial because the patients were symptomatic at baseline (met criteria for moderately to severely active UC) despite therapy with these other treatments. Only one of the patients who did not meet the medication enrollment criteria also failed to meet the UC disease enrollment criteria (this patient did not achieve clinical response at Week 8).

There were 51 (5.3%) other deviations/violations that are classified as follows:

At or after Week 8, one patient (0.1%) met the withdrawal criteria but did not withdraw (the patient used a rectal 5-ASA prior to Week 16, completed the induction study and did not enter the maintenance study). Three patients received the wrong treatment or incorrect dose of the study drug at Week 8, and nine patients were reported to have “other” protocol deviations/violations. None of these protocol violations at or after Week 8 were associated with medication violations at enrollment, randomization, or at Week 0 of the induction trial.

The major protocol deviations committed in the induction study laboratory assessments that were not obtained or not available prior to next dose administration (12 patients, 1.5%). The patients who were identified to have not met laboratory assessment enrollment criteria that could raise safety concerns underwent additional testing and/or follow-up to ensure the safety of the patients enrolled in the trial or did not continue in the trial if additional information was not available.

Thirty-five patients who had deviations that called into question their inclusion in the target population, or the assessment of clinical response at Week 8, were excluded in a prespecified per-protocol analysis. The per-protocol analysis was consistent with the results from the primary analysis population. Finally, patients with deviations related to concomitant medications were identified as treatment failures.

Maintenance Study

In the maintenance study, 40/523 patients (7.6%) of the randomized population and 19/260 (7.3%) of the non-randomized population were identified as having met protocol violations in the maintenance study. These deviations do not appear to represent a consistent pattern of deficiency in the conduct of the clinical trial across multiple sites.

Two patients (0.3%), both in the randomized population, were reported to have met withdrawal criteria but were not withdrawn (pregnancy and squamous cell carcinoma). Two patients (0.3%) missed doses of medication (one patient at Week 8 in the nonrandomized population and a second patient at Week 36) in the randomized population in the ustekinumab q12 cohort. Five patients (0.6%) initiated a corticosteroid (prednisone, rectal steroid, or budesonide) during the trial, which was disallowed; one of these patients initiated Anusol for hemorrhoids and was included in the efficacy analyses but the other four patients initiated a corticosteroid for a disease flare and were considered to be treatment failures in the efficacy analyses. One patient missed a follow-up clinical visit due to noncompliance and early termination. The other 47 protocol violations listed by the Applicant included most frequently in the category of “Other” included Week 44 visit conducted outside of the allowed

protocol visit window (11 patients); induction visit at Week 8 or Week 16 performed outside of the allowed protocol window (eight patients); and lab assessments at various week intervals not taken or not available (nine patients).

Overall, the totality of these violations in both the induction and maintenance studies are unlikely to have impacted the assessment of the efficacy, nor pose significant risk to the patients enrolled in these trials.

8.1.2.5. Demographic Characteristics

Baseline demographics and baseline UC disease characteristics were similar across all treatment groups. Most patients were male (60.6%) and white (76.0%). The median age was 41.0 years, and the median weight was 71.2 kg. Approximately 14% of randomized patients were from Asia, 38% were from Eastern Europe, and 48% were from the rest of world (including North America, Western Europe, Israel, Australia, and New Zealand); 18.6% were from the United States.

The median duration of disease was 5.97 years, and 45.7% of patients had extensive disease. The median Mayo score was 9.0; 84.4% of patients had moderate UC (i.e., a Mayo score ≥6 and ≤10) and 15.3% had severe disease (Mayo score >10); 51.1% of patients had a history of biologic failure. Demographic characteristics of the induction study are summarized in Table 9.

Table 9. Patient Demographics for Induction Study (All Randomized Patients)

Characteristic	Placebo (N=319)	Ustekinumab 130 mg (N=320)	Ustekinumab 6 mg/kg (N=322)	Total (N=961)
Sex, n (%)				
Male	197 (61.8)	190 (59.4)	195 (60.6)	582 (60.6)
Female	122 (38.2)	130 (40.6)	127 (39.4)	379 (39.4)
Race, n (%)				
White	248 (77.7)	239 (74.7)	243 (75.5)	730 (76.0)
Black or African American	3 (0.9)	6 (1.9)	0	9 (0.9)
Asian	48 (15.0)	46 (14.4)	49 (15.2)	143 (14.9)
American Indian or Alaska Native	0	0	1 (0.3)	1 (0.1)
Native Hawaiian or Pacific Islander	0	0	0	0
Other	8 (2.5)	9 (2.8)	12 (3.7)	29 (3.0)
Unknown	0	2 (0.6)	1 (0.3)	3 (0.3)
Not reported	12 (3.8)	18 (5.6%)	16 (5.0)	46 (4.8)
Region, n (%)				
Asia	44 (13.8)	44 (13.8)	45 (14.0)	133 (13.8)
Eastern Europe	122 (38.2)	123 (38.4)	123 (38.2)	368 (38.3)
Rest of world	153 (48.0)	153 (47.8)	154 (47.8)	460 (47.9)
Age (yrs)				
Mean (SD)	41.2 (13.5)	42.2 (13.9)	41.7 (13.7)	41.7 (13.7)
Median	40.0	42.0	41.0	41.0
IQ range	(30.0; 51.0)	(31.0; 51.0)	(30.0; 52.0)	(30.0; 51.0)
Range	(18; 79)	(18; 84)	(18; 77)	(18; 84)

Characteristic	Placebo (N=319)	Ustekinumab 130 mg (N=320)	Ustekinumab 6 mg/kg (N=322)	Total (N=961)
Weight (kg)				
Mean (SD)	72.9 (16.8)	73.7 (16.8)	73.0 (19.3)	73.2 (17.6)
Median	70.0	72.0	71.8	71.2
IQ range	(61.4; 83.6)	(62.1; 83.8)	(58.5; 83.0)	(60.5; 83.5)
Range	(38.3; 126.6)	(36.5; 168.2)	(38.8; 177.2)	(36.5; 177.2)
Height (cm)				
Mean (SD)	172.3 (10.0)	171.3 (9.3)	171.5 (9.7)	171.7 (9.7)
Median	172.5	171.5	171.3	172.0
IQ range	(165.0; 180.0)	(165.00; 178.0)	(164.50; 178.0)	(165.00; 179.0)
Range	(145.0; 197.0)	(147.3; 198.5)	(149.6; 205.7)	(145.0; 205.7)

Source: Clinical Study Report CNTO1275UCO3001 Induction Table 2 (pg. 65)
Abbreviations: IQ = interquartile; SD = standard deviation

Table 10. Patient Demographics for Maintenance Study (All Randomized Patients)

Characteristic	Placebo (N=175)	ustekinumab Q12W (N=172)	ustekinumab Q8W (N=176)	Total (N=523)
Sex, n (%)				
Male	107 (61.1)	96 (55.8)	94 (53.4)	297 (56.8)
Female	68 (38.9)	76 (44.2)	82 (46.6)	226 (43.2)
Race, n (%)				
White	125 (71.4)	135 (78.5)	127 (72.2)	387 (74.0)
Black or African American	3 (1.7)	0	3 (1.7)	6 (1.1)
Asian	34 (19.4)	24 (14.0)	29 (16.5)	87 (16.6)
American Indian or Alaska Native	0	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0	0
Other	3 (1.7)	9 (5.2)	5 (2.8)	17 (3.3)
Not reported	9 (5.1)	3 (1.7)	12 (6.8)	24 (4.6)
Unknown	1 (0.6)	1 (0.6)	0	2 (0.4)
Region, n (%)				
Asia	31 (17.7)	21 (12.2)	26 (14.8)	78 (14.9)
Eastern Europe	68 (38.9)	80 (46.5)	67 (38.1)	215 (41.1)
Rest of world	76 (43.4)	71 (41.3)	83 (47.2)	230 (44.0)
Age (yrs)				
Mean (SD)	42.0 (13.9)	40.7 (13.5)	39.5 (13.3)	40.8 (13.6)
Median	42.0	39.0	39.0	40.0
IQ range	(30.0; 52.0)	(30.0; 50.5)	(29.0; 48.0)	(29.0; 50.0)
Range	(18; 72)	(18; 79)	(18; 84)	(18; 84)
Weight (kg)				
Mean (SD)	71.7 (14.6)	73.3 (18.9)	72.0 (19.1)	72.3 (17.6)
Median	71.0	70.0	70.0	70.0
IQ range	(60.9; 81.5)	(59.7; 83.5)	(58.2; 83.0)	(59.6; 83.0)
Range	(38.8; 113.0)	(41.0; 141.9)	(36.5; 168.2)	(36.5; 168.2)
Height (cm)				
Mean (SD)	171.0 (10.1)	171.3 (9.7)	170.9 (10.0)	171.1 (9.9)
Median	170.2	171.0	170.8	170.5
IQ range	(164.0; 178.0)	(164.0; 178.0)	(163.2; 178.0)	(164.0; 178.0)
Range	(149.6; 198.5)	(151.5; 205.7)	(150.0; 195.0)	(149.6; 205.7)

Source: Clinical Study Report CNTO1275UCO3001 Maintenance Table TSIDEM02 (pg. 1257)
Abbreviations: IQ = interquartile; SD = standard deviation

8.1.2.6. Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

The baseline disease characteristics were comparable across the treatment arms. The median duration of disease at baseline was 5.97 years, the median Mayo score was 9.0. Approximately 85% of patients had moderate disease based on their respective baseline Mayo composite score, while approximately 15% had severe disease by the composite Mayo score. Nearly 30% of patients had an extraintestinal manifestation of UC (range 26% in the placebo arm to 30% in the ustekinumab 6 mg/kg arm) upon entering the trial. The most common extraintestinal manifestation was arthralgia (20%). The mean C-reactive protein concentration was slightly higher in the ustekinumab 6 mg/kg arm (12 mg/L), compared to the mean in the placebo arm (10 mg/L) and the ustekinumab 130 mg arm (10 mg/L). However, there was no difference in the medians of C-reactive protein concentration among the treatment groups. The small difference in the mean values is unlikely to be clinically relevant. Approximately two-thirds of all patients entering the ustekinumab study never smoked, and a range of 4% to 6% of patients were active smokers at enrollment.

At entry into the trial, roughly 50% of all patients across each treatment arm were defined as having failed prior biologic therapy ("biological failures").

Over 90% of patients at baseline, regardless of treatment group or placebo arm, were either refractory to, dependent on, or intolerant to corticosteroids (80.7%), or 6-MP/AZA (55.2%). A summary of UC disease characteristics at baseline is included below in Table 11.

Table 11. Baseline Disease Characteristics in Induction Study (Primary Analysis Population)

		Ustekinumab IV			
	Placebo IV	130 mg	6 mg/kg [a]	Combined	Total
Primary Efficacy Analysis Set	319	320	322	642	961
UC disease duration (yrs)					
N	319	320	322	642	961
Mean (SD)	8.01 (7.190)	8.13 (7.179)	8.17 (7.822)	8.15 (7.502)	8.10 (7.397)
Median	5.97	5.90	6.03	5.97	5.97
IQ range	(2.71; 11.30)	(2.84; 11.41)	(2.68; 11.07)	(2.80; 11.16)	(2.78; 11.20)
Range	(0.3; 36.1)	(0.3; 34.0)	(0.3; 54.1)	(0.3; 54.1)	(0.3; 54.1)
Extent of disease					
N	316	318	320	638	954
Limited to left side of colon	167 (52.8%)	183 (57.5%)	168 (52.5%)	351 (55.0%)	518 (54.3%)
Extensive	149 (47.2%)	135 (42.5%)	152 (47.5%)	287 (45.0%)	436 (45.7%)
Mayo score (0-12)					
N	319	320	321	641	960
Mean (SD)	8.9 (1.62)	8.9 (1.57)	8.9 (1.51)	8.9 (1.54)	8.9 (1.57)
Median	9.0	9.0	9.0	9.0	9.0
IQ range	(8.0; 10.0)	(8.0; 10.0)	(8.0; 10.0)	(8.0; 10.0)	(8.0; 10.0)
Range	(5; 12)	(5; 12)	(6; 12)	(5; 12)	(5; 12)
Severity of UC disease					
N	319	320	321	641	960
Moderate (6≤ Mayo score ≤ 10)	263 (82.4%)	271 (84.7%)	276 (86.0%)	547 (85.3%)	810 (84.4%)
Severe (Mayo score >10)	54 (16.9%)	48 (15.0%)	45 (14.0%)	93 (14.5%)	147 (15.3%)
Extraintestinal manifestations					
N	319	320	322	642	961
Present	84 (26.3%)	90 (28.1%)	97 (30.1%)	187 (29.1%)	271 (28.2%)
Absent	235 (73.7%)	230 (71.9%)	225 (69.9%)	455 (70.9%)	690 (71.8%)
Biologic failure status					
N	319	320	322	642	961
Yes	161 (50.5%)	164 (51.3%)	166 (51.6%)	330 (51.4%)	491 (51.1%)
No	158 (49.5%)	156 (48.8%)	156 (48.4%)	312 (48.6%)	470 (48.9%)

Source: Applicant data from Clinical Study Report CNTO1275UCO3001IND Table TSIDEM02, (p. 712).
Abbreviations: SD = standard deviation; UC = ulcerative colitis

8.1.2.7. Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance

In the induction study, doses of ustekinumab were administered by licensed professionals to the treatment groups and compliance with treatment assignments was controlled by study-site personnel. Site personnel administered the ustekinumab infusion and recorded the total amount of the agent given. In the maintenance study, ustekinumab was administered as an SC injection by qualified staff. The details of each administration were recorded on the eCRF, including date and time of injection.

Blinded site monitors designated by the Applicant verified source documents, performed drug accountability, and ensured overall site compliance. During site monitoring visits, all procedures were evaluated for compliance with the protocol, and missed study visits were recorded on the eCRF. Patient charts were reviewed and compared with data entries on the eCRFs to ensure consistency. Used vials of study agent were to be retained at the site until the study agent accountability forms had been checked by the site monitor.

Concomitant Medications

At baseline, 90.2% of all patients were receiving a concomitant UC medication in similar proportions across all treatment groups. The most frequent concomitant UC medications reported among patients were using the following: 52% corticosteroids; 28% immunomodulatory drugs (i.e., 6-MP, AZA, methotrexate); and 69% aminosalicylates. The proportion of patients receiving each type of concomitant UC medication were generally similar across all treatment groups; however, a slightly greater proportion of patients was receiving aminosalicylates in the 6 mg/kg group compared to the 130 mg and placebo groups. The use of these UC medications in stable dose regimens was allowed in the enrollment criteria as long as an individual was on a stable dose for at least 2 weeks, and in the case of AZA or 6-MP, the stable dose was to be at least for 4 weeks before enrollment. A summary of concomitant medications is included in Table 12.

Dosages of concomitant medical therapy for UC were to be stable from Week 0 of the induction study through Week 0 of the maintenance study unless the therapy had to be discontinued or reduced in dose because of toxicity or medical necessity.

Table 12. Summary of Concomitant Medications at Baseline in Induction Study

		Ustekinumab IV			
	Placebo IV	130 mg	~6 mg/kg [a]	Combined	Total
Primary Efficacy Analysis set	319	320	322	642	961
Any UC medication	283 (88.7%)	290 (90.6%)	294 (91.3%)	584 (91.0%)	867 (90.2%)
Corticosteroid use	157 (49.2%)	173 (54.1%)	168 (52.2%)	341 (53.1%)	498 (51.8%)
Corticosteroid use (excl. budesonide and beclomethasone dipropionate)	133 (41.7%)	149 (46.6%)	145 (45.0%)	294 (45.8%)	427 (44.4%)
Budesonide	26 (8.2%)	19 (5.9%)	24 (7.5%)	43 (6.7%)	69 (7.2%)
Beclomethasone dipropionate	0	6 (1.9%)	1 (0.3%)	7 (1.1%)	7 (0.7%)
Immunomodulatory drugs	89 (27.9%)	93 (29.1%)	89 (27.6%)	182 (28.3%)	271 (28.2%)
6-mercaptopurine/ azathioprine	88 (27.6%)	88 (27.5%)	85 (26.4%)	173 (26.9%)	261 (27.2%)
Methotrexate	1 (0.3%)	5 (1.6%)	4 (1.2%)	9 (1.4%)	10 (1.0%)
Aminosalicylates	207 (64.9%)	215 (67.2%)	238 (73.9%)	453 (70.6%)	660 (68.7%)

[a] Weight-range based ustekinumab doses approximating ~6 mg/kg: 260 mg (weight ≤55 kg), 390 mg (weight > 55 kg and ≤85 kg), 520 mg (weight > 85 kg).
Source: Applicant data from Clinical Study Report CNTO1275UCO3001IND Table 3 (p. 67).
Abbreviations: IV = intravenous; UC = ulcerative colitis

Rescue Medication

Initiating, increasing, or switching UC medical therapy including corticosteroids, 6-MP, AZA, MTX, and the aminosalicylates (oral 5-ASAs) that was required to treat a loss of response during the clinical trial was defined as rescue medication. Patients who used a rescue medication during the clinical trial were considered a treatment failure from the time of the event onward. Study patients were permitted to use short courses of corticosteroids, defined as ≤4 weeks for reasons other than loss of response (e.g., asthma flare).

Any patient who initiated or increased the dose of a concomitant UC medication (e.g., AZA, 6-MP, MTX, oral 5-ASAs) during any period of the induction study, as well as other restricted or prohibited medications during the entire clinical trial, were not eligible to enter the maintenance study.

As expected, of patients who were in clinical response to ustekinumab IV induction, the proportion of patients who met treatment failure criteria and used a rescue medication to treat the clinical flare prior to Week 44 was larger in the placebo arm (26/175 [14.9%]) as compared to the ustekinumab Q12W (16/172 [9.3%]) or Q8W (7/176 [4.0%]) arms. Similarly, the proportion of patients who had a prohibited change in UC medication was larger in the placebo arm (27/175 [15.4%]) as compared to the ustekinumab Q12W (12/172 [7.0%]) or Q8W (10/176 [5.7%]) arms. Overall, the patients who met one or more treatment failure criteria (i.e., had an ostomy or colectomy, discontinued study drug due to lack of therapeutic effect, used a rescue medication, or had a prohibited change in UC mediation) prior to Week

44 was larger in the placebo arm (66 [37.7%]) compared to the ustekinumab Q12W (33/172 [19.2%]) or Q8W (18/176 [10.2%]) arms.

8.1.2.8. Efficacy Results: Primary Endpoint

As described in Section 7.2, Review Strategy, the efficacy analyses in the following sections will be based on our currently recommended endpoint definitions. Clinical remission is defined by a rectal bleeding subscore =0, stool frequency subscore =0 or 1, and an endoscopy subscore =0 or 1 (modified so that 1 does not include friability).

Of note, only a small number of patients achieved an endoscopic subscore of 1 with the presence of friability. There were 19 patients in the induction study at Week 8 and 14 patients in the maintenance study at Week 44 with an endoscopy subscore of 1 that included friability. In the induction study, there was one patient with an endoscopy subscore of 0 that included friability. The majority of patients who were deemed to have a subscore of 1 did not have documented friability which generally supports that friability is not consistent with remission and we continue to recommend that the endoscopy subscore of 1 be modified so that 1 does not include friability.

Additionally, any other endpoint that relied on clinical remission or an endoscopic subscore, the definitions were modified to align with the currently recommended approach. Therefore, for the multiplicity-controlled endpoints for both the induction and maintenance study, our assessment was primarily focused on the evaluation of the versions of the primary and secondary endpoints that are consistent with the currently recommended approach to endpoint definitions for UC trials as reflected in the draft guidance for industry *Ulcerative Colitis: Clinical Trial Endpoints* (August 2016). The results using the currently recommended definitions did not differ greatly overall from the results using the Applicant's definitions. Analyses using the Applicant's prespecified endpoint definitions are located in the Appendix.

The results of the efficacy analyses are shown below for the induction study followed by the maintenance study.

Induction Study

Primary endpoint

Table 13 shows the efficacy results for the primary endpoint, clinical remission at Week 8, in all randomized patients (primary analysis population). The primary endpoint was also analyzed in subpopulations of patients who were biologic naïve and prior biologic failures because prior failure with other biologic therapies has been associated with lower remission/response rates for other drug classes. The Applicant proposed this descriptive subgroup analyses for inclusion in the labeling and we determined that this information is important to be communicated to prescribers and patients.

Based on the primary analysis method, stratified Cochran-Mantel-Haenszel test, significantly greater proportions of patients in the ustekinumab 6 mg/kg and 130 mg groups achieved clinical remission at Week 8 (19.3% and 16.9%, respectively) when compared with patients in the placebo group (6.9%), with p-values <0.001 for both comparisons. Similarly, in both types of subgroups, bio-naive and prior biological failures, the proportion of patients achieving remission was larger in the ustekinumab treatments compared to placebo.

Table 13. Induction Study, Clinical Remission at Week 8 (FDA Recommended)

	Placebo (N=319)	Ustekinumab 130 mg (N=320)	Ustekinumab 6 mg/kg (N=322)
Clinical remission % (n/N)	6.9% (22/319)	16.9% (54/320)	19.3% (62/322)
Treatment difference (97.5% CI); p-value	—	10.0% (4.4%, 15.6%) p<0.001	12.4% (6.6%, 18.2%) p<0.001
Subpopulation: biologic naïve	9.3% (14/151)	22.8% (33/145)	24.4% (36/147)
Subpopulation: prior biologic failure	4.3% (7/161)	11.6% (19/164)	14.4% (24/166)

Source: Clinical Study Report CNTO1275UCO3001 Induction Table TEFCREM23 (pg. 469) and FDA's Results. Applicant's results were confirmed by FDA
An additional 7 patients on placebo, 11 on ustekinumab 130 mg, and 9 patients on ustekinumab 6 mg/kg had been exposed to, but had not failed, biologics.
Abbreviation: CI = confidence interval

The percentage of patients who achieved clinical remission at Week 8 was slightly larger in the ustekinumab 6 mg/kg dose arm. This trend is also observed in the subpopulation of patients who were prior biologic failures and supports labeling of the 6 mg/kg dose for the initial ustekinumab dose. Multiplicity-adjusted hypothesis tests comparing the two ustekinumab dose arms were not planned.

Maintenance Study

Primary endpoint

Clinical remission at Week 44 was the primary endpoint for the maintenance study. The primary efficacy results using a stratified Cochran-Mantel-Haenszel test are presented in Table 14. Both ustekinumab dose arms (90 mg SC Q8W and Q12W) were statistically superior to placebo as measured by proportion of patients achieving remission.

A larger percentage of patients were observed achieving clinical remission at Week 44 in the ustekinumab 90 mg SC Q8W dose arm (44.9%). In addition, among the subgroup of patients who were prior biologic failures, the percentage of patients who achieved clinical remission at Week 44 was larger in the 90 mg Q8W dose arm (40.7%) compared to placebo and the Q12W arm. Multiplicity-adjusted hypothesis tests comparing the two ustekinumab dose arms were not planned.

Table 14. Maintenance Study, Clinical Remission at Week 44 (FDA Recommended)

Outcome/Population	Placebo SC (N=175)	Ustekinumab 90 mg SC Q12W (N=172)	Ustekinumab 90 mg SC Q8W (N=176)
Clinical remission at Week 44, % (n/N)	26.3% (46/175)	38.4% (66/172)	44.9% (79/176)
Treatment difference (95% CI); p-value	—	12.2% (3.0%, 21.5%) p=0.0121	18.5% (8.9%, 28.1%) p<0.001
Subpopulation: biologic naïve	35.7% (30/84)	47.4% (45/95)	49.4% (39/79)
Subpopulation: prior biologic failure	18.2% (16/88)	22.9% (16/70)	40.7% (37/91)

Source: Clinical Study Report Clinical Study Report CNTO1275UCO3001 Maintenance Table TEFCREM05A (pg. 758) and FDA's Results. Applicant's results were confirmed by FDA
An additional 3 patients on placebo, 7 patients on Q12W, 6 patients on Q8W had been exposed to, but had not failed, biologics.
Abbreviations: CI = confidence interval; Q8/12W = every 8/12 weeks; SC = subcutaneous

Although the primary analysis was based on achievement of clinical remission at Week 44 in all randomized patients (i.e., who achieved clinical response at Week 8), the Applicant

included a secondary analysis of remission at Week 44 in the subpopulation of patients who were in remission at the start of the maintenance study. This analyses is shown in the forthcoming secondary endpoint section of this document.

Data Quality and Integrity

There were no major issues identified with the quality and integrity of the submitted data.

8.1.2.9. Efficacy Results: Secondary and Other Relevant Endpoints

Induction Study

Secondary endpoints

There were three multiplicity-controlled secondary endpoints evaluated at Week 8: endoscopic improvement, clinical response, and histologic-endoscopic mucosal improvement ("mucosal healing"). In the analyses presented below, the endoscopic subscore of 1 used in the endoscopic improvement and histologic-endoscopic mucosal improvement endpoints was modified to exclude the presence of friability. Additional analyses using our currently recommended endpoint definitions were provided by the Applicant in response to an Information Request, received July 25, 2019. Table 15 shows efficacy results in all randomized patients based on stratified Cochran-Mantel-Haenszel tests and includes a summary of remission rates in two subpopulations: bio-naive and prior biological failure.

In the analyses presented below, clinical response is based on the currently recommended definition (a decrease in the Mayo score, without the PGA, of ≥2 points and ≥30%, and either a decrease in rectal bleeding of ≥1 or a rectal bleeding score of 0 or 1), and the endoscopic improvement did not allow presence of friability. As mentioned above in Section 8.1.1.3 Efficacy Endpoint Definitions, the definition of clinical response used to evaluate patients at Week 8 to determine eligibility for randomization into the maintenance study was based on the following: a decrease from induction baseline in the Mayo score by ≥30% and ≥3 points (using the Mayo endoscopy subscore assigned by the local endoscopist), with either a decrease from baseline in the rectal bleeding subscore ≥1 or a rectal bleeding subscore of 0 or 1.

Table 15. Induction Study, Efficacy Results for Multiplicity-Controlled Secondary Endpoints at Week 8 (FDA Recommended)

Efficacy Outcome	Placebo (N=319)	Ustekinumab 130 mg (N=320)	Ustekinumab 6 mg/kg (N=322)
Endoscopic Improvement % (n/N)	12.5% (40/319)	23.4% (75/320)	24.8% (80/322)
Treatment difference (97.5% CI); p-value	—	10.9% (4.3%, 17.4%) p<0.001	12.3% (5.7%, 19.0%) p<0.001
Biologic naïve	18.5% (28/151)	31.0% (45/145)	29.3% (43/147)
Failure in prior biologic use	6.8% (11/161)	16.5% (27/164)	20.5% (34/166)
Clinical response % (n/N)	31.0% (99/319)	48.8% (156/320)	57.8%(186/322)
Treatment difference (97.5% CI); p-value	—	17.7% (9.2%%, 26.1%) p<0.001	26.8% (18.4%%, 35.1%) p<0.001
Biologic naïve	36.4% (55/151)	55.9% (81/145)	64.0% (94/147)
Failure in prior biologic use	26.1% (42/161)	42.1% (69/164)	51.8% (86/166)
Histologic-endoscopic improvement % (n/N)	8.2% (26/319)	18.1% (58/320)	16.8% (54/322)
Treatment difference (97.5% CI); p-value	—	9.9% (4.1%, 15.8%) p<0.001	8.7% (2.9%, 14.4%) p<0.001
Biologic naïve	12.6% (19/151)	23.4% (34/145)	20.4% (30/147)
Failure in prior biologic use	3.7% (6/161)	12.8% (21/164)	12.7% (21/166)

Source: Clinical Study Report CNTO1275UCO3001 Induction TEFENDO01A (pg. 496), TEFMUCO01A (pg.549), and FDA's Results. Applicant's results were confirmed by FDA
An additional 7 patients on placebo, 11 on ustekinumab 130 mg, and 9 patients on ustekinumab 6 mg/kg had been exposed to, but had not failed, biologics.
Abbreviation: CI = confidence interval

Both ustekinumab treatment arms achieved statistically significant improvement in all three secondary endpoints when compared to placebo. In both types of subgroups, the proportion of patients achieving remission was larger in the ustekinumab treatments compared to placebo.

The histologic-endoscopic mucosal improvement endpoint was multiplicity-controlled at Week 8 of the induction but not at Week 44 in the maintenance study. This endpoint is potentially clinically meaningful because improvement in the mucosa has been linked to improvements in steroid use, hospitalizations, etc. The relationship of this histologic-endoscopic mucosal improvement endpoint, as defined in the clinical trials, with long-term clinical outcomes (e.g., reduction in hospitalization, colectomy, malignancy rates) was not evaluated. At Week 44, histologic-endoscopic mucosal improvement (modified so that patients with friability are considered as nonresponders) was also observed in a larger proportion of ustekinumab-treated patients compared to placebo (75/172 [43.6%] in Q8W, 62/170 [36.5%] in Q12W, 40/172 [23.3%) in placebo). This observation is supportive of the benefit of ustekinumab treatment during the maintenance study; however, one of our main review issues related to this endpoint was the appropriateness of the histologic improvement ("healing") component of this endpoint definition.

Appropriateness of histologic-endoscopic improvement "mucosal healing" definition

(b) (4)

. At this time, there is no consensus on which histologic scoring system is most appropriate. The Applicant included additional data in the sBLA submission to support the proposed definition of histologic improvement ("healing"), included as part of the "mucosal healing" endpoint definition. We evaluated the Applicant's "Histologic and Mucosal Healing Position Paper" to assess whether (1) available data are adequate to support that the Geboes scoring system (Geboes et al. 2000) can reliably define histologic remission and (2) the definition of histologic remission reflects a clinically meaningful change in the relevant patient population (b) (4)

This endpoint is potentially clinically meaningful because improvement in the mucosa has been linked to improvements in steroid use, hospitalizations, etc. However, correlation does not necessarily imply causation (Fleming and Powers 2012) so there remains some uncertainty about whether drug effects on histologic endpoints will reliably predict drug effects on long-term clinical outcomes. The evidence from published literature supports that histologic improvement is relevant in achieving reduced steroid use and hospitalizations due to acute, severe UC over 72 months (Bryant et al. 2016), and in predicting relapse or exacerbation at 6 or 12 months (Park et al. 2016). Several histologic scoring systems for UC exist, including the Geboes Score (GS), the Robarts Histology Index (RHI), and the Nancy Histologic Index (NHI); none of which includes a definition for histologic improvement. The Applicant selected the GS score due to its high level of reproducibility and extensive use in prior studies. In addition, the RHI is strongly correlated with the GS (r =0.97 for continuous versions of both scores). All three measures (GS, NHI, and RHI) have similar levels of association with change in Mayo score and endoscopic endpoints. Although further research is needed to explore the relationship of each scoring system with long-term outcomes, to establish clinically meaningful cutoff points, and to explore the feasibility of use in clinical practice, the Applicant provided available data to support the selected cutoff values used in these clinical trials to define histologic improvement.

The Applicant defined "mucosal healing" by the presence of both endoscopic improvement (endoscopy subscore of 0 or 1) and histologic improvement based on Grades 3, 4, and 5 of the Geboes Score (which is shown in the Appendix): <5% neutrophils in epithelium (Grades 3.0 and 3.1 component; subscore 0 or 1); no crypt destruction (Grade 4 component; subscore 0); and no erosions, ulcerations, or granulation tissue (Grade 5; subscore 0). The Applicant did not include Grades 0, 1, 2A, and 2B in the definition of histologic "healing" since these components of the GS score are more reflective of chronic inflammation, rather than acute active inflammation. The selection of Grades 3.0, 3.1, 4, and 5 appear reasonable to evaluate active acute inflammation.

Based on our review of the submitted information, we determined that communicating the findings observed from the histologic analyses in the context of endoscopic and histologic improvement (i.e., Applicant's term, "mucosal healing") may provide useful information for physicians. (b) (4)

See Appendix, Section 15.5 for additional details and discussion.

Maintenance Study

Secondary endpoints

There were four multiplicity-controlled secondary endpoints evaluated at the end of the double-blind maintenance period: maintenance of clinical response at Week 44, endoscopic improvement at Week 44, corticosteroid-free clinical remission at Week 44, and maintenance of clinical remission at Week 44 among patients who had achieved clinical remission at maintenance baseline. In the analyses presented below, clinical remission and clinical response were based on FDA recommended definition, and the endoscopic improvement did not allow presence of friability. The results of these additional analyses using the FDA recommended definitions were provided by the Applicant in response to an Information Request, received July 25, 2019.

Both treatment arms showed statistically significant improvement in all secondary endpoints when compared to placebo using a stratified Cochran-Mantel-Haenszel test. Table 16 presents these efficacy results in all randomized patients and summarizes remission rates in two subpopulations: bio-naive and prior biological failure. In both subgroups, the proportion of patients achieving remission was larger in the ustekinumab treatments compared to placebo.

Table 16. Maintenance Study, Efficacy Results for Multiplicity-Controlled Secondary Endpoints at Week 44 (FDA Recommended Endpoints)

Efficacy Result	Placebo SC (N=175)	ustekinumab 90 mg SC Q12W (N=172)	ustekinumab 90 mg SC Q8W (N=176)
Clinical response % (n/N)	48.0% (84/175)	69.8% (120/172)	73.9% (130/176)
Treatment difference (95% CI); p-value	—	21.9%(12.1%, 31.6%) p<0.001	25.8% (16.1%, 35.5%) p<0.001
Biologic naïve	58.3% (49/84)	81.1% (77/95)	78.5% (62/79)
Failure in prior biologic use	39.8% (35/88)	54.3% (38/70)	70.3% (64/91)
Endoscopic Improvement % (n/N)	26.9% (47/175)	41.3% (71/172)	47.2% (83/176)
Treatment difference (95% CI); p-value	—	14.6% (5.2%, 23.9%); p=0.003	20.2% (10.6%, 29.9%) p<0.001
Biologic naïve	34.5%(29/84)	51.6% (49/95)	53.2%(42/79)
Failure in prior biologic use	20.5% (18/88)	24.3%(17/70)	41.8%(38/91)
Corticosteroid-free clinical remission % (n/N)	25.7% (45/175)	37.8% (65/172)	43.2% (76/176)
Treatment difference (95% CI); p-value	—	12.2% (3.0%, 21.4%) p=0.012	17.4% (7.9%, 26.9%) p<0.001
Biologic naïve	35.7% (30/84)	46.3% (44/95)	48.1% (38/79)
Failure in prior biologic use	17.1% (15/88)	22.9% (16/70)	38.5% (35/91)
Maintenance of clinical remission at Week 44 among patients who had achieved clinical remission 8 weeks after induction (at maintenance baseline) % (n/N)	36.0% (18/50)	61.1% (33/54)	65.9% (27/41)
Treatment difference (95% CI); p-value	—	26.5% (8.1%, 44.9%) p=0.009	31% (11.9%, 50.2%) p=0.004
Biologic naïve	44.4% (12/27)	68.4% (26/38)	70.0% (14/20)
Failure in prior biologic use	26.1% (6/23)	35.7% (5/14)	66.7% (12/18)

Source: Clinical Study Report CNTO1275UCO3001 Maintenance Table 8 (pg. 106), Table TEFENDO01A (pg. 842), Table 11 (pg. 112), Table 13 (pg. 116), Applicant's response to FDA's information request, received July 25, 2019, Applicant's submission in response to labeling, received October 16, 2019, and FDA's Results. Applicant's results were confirmed by FDA.
Abbreviations: CI = confidence interval; Q8/12W = every 8/12 weeks; SC = subcutaneous

A larger proportion of patients in the ustekinumab 90 mg SC Q8W dose arm achieved success in each of the secondary endpoints compared to the Q12W dose arm. This supports labeling of the Q8W dose for maintenance treatment; multiplicity-adjusted hypothesis tests comparing the two ustekinumab dose arms were not planned.

In addition to evaluating endoscopic improvement at Week 44, the Applicant also performed an exploratory analysis of endoscopic improvement at Week 44 in patients who met the criteria for endoscopic improvement at maintenance baseline. Patients with friability were considered not to have achieved endoscopic improvement (Mayo endoscopy subscore of 0 or 1). In response to an information request, received July 25, 2019, this analysis was performed in which an endoscopic subscore of 1 did not include friability. In these patients, a larger proportion of patients in the ustekinumab Q8W and Q12W groups continued to meet the criteria endoscopic improvement at Week 44 (33/53 [62%] and 38/65 [58%], respectively) compared with patients in the placebo group (20/61 [33%]).

The corticosteroid-free remission endpoint only considered patients who were in clinical remission and not taking corticosteroids at the Week 44 timepoint. Therefore, the Applicant

also evaluated corticosteroid-free remission in patients on corticosteroids at maintenance baseline and not receiving concomitant corticosteroids at least 90 days prior and 30 days prior to Week 44. In response to an information request, received July 27, 2019, these analyses were performed using FDA's recommended definition of clinical remission. The proportion of patients on corticosteroids at maintenance baseline and achieving corticosteroid-free remission at least 90 days prior to Week 44 was 36/92 (39%) in the ustekinumab Q8W and 24/82 (29%) in the Q12W, compared with 17/91 (19%) in the placebo group. Similar results were observed for discontinuation of corticosteroids for at least 30 days prior to Week 44.

Although the trial was not powered for the endpoint of maintenance of clinical remission through Week 44 among patients who achieved remission at maintenance baseline, the subgroup analyses support that more patients are able to stay in remission when treated with ustekinumab 90 mg SC as compared to placebo. A slightly larger percentage of patients were noted to have achieved success on this endpoint in the Q8W regimen.

8.1.2.10. Other Relevant Efficacy Endpoints

Symptomatic Remission

Symptomatic remission was defined by achieving a Mayo stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0.

At Week 8, 144/322 (44.7%) patients in the 6 mg/kg and 132/320 (41.3%) in the 130 mg dose arms achieved symptomatic remission compared to 72/319 (22.6%) in the placebo arm.

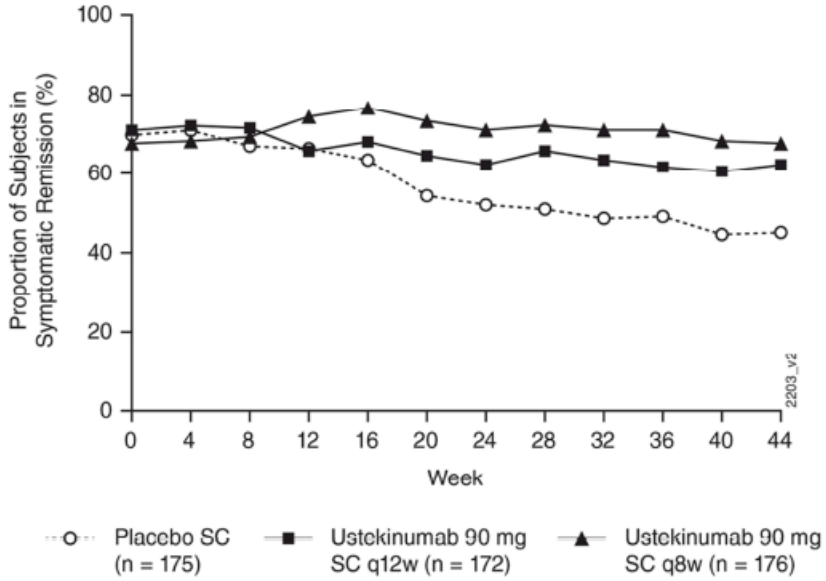
Improvements in the rectal bleeding and stool frequency Mayo subscores were observed as early as Week 2.

- At baseline, 3/322 (0.9%) patients in the 6 mg/kg IV dose arm, 1/320 (0.3%) in the 130 mg IV dose arm, and 2/319 (0.6%) patients in the placebo arm reported a normal number of stools. The majority of patients reported at least three stools more than normal at baseline, and approximately 50% of the patients in each dose arm reported at least five or more stools than normal at baseline. At Week 2, the proportion of patients reporting a normal number of stools increased to 26/322 (8.1%) patients in the 6 mg/kg IV dose arm, 32/320 (10.0%) in the 130 mg IV dose arm, and 16/319 (5.0%) in placebo.
- At baseline, 39/322 (12.2%) patients in the 6 mg/kg IV dose arm, 35/320 (10.9%) in the 130 mg IV dose arm, and 42/319 (13.5%) in placebo reported no blood in their stools. At Week 2, the proportion of patients reporting no blood in their stools increased to 120/322 (37.3%) in the 6 mg/kg IV dose arm, 104/320 (32.5%) in the 130 mg IV dose arm, and 83/319 (26.0%) in placebo.

At maintenance baseline, the proportions of patients in symptomatic remission were similar across the dose arms with 119/176 (67.6%) of patients in the Q8W, 122/172 (70.9%) in the Q12W, and 122/175 (69.7%) in the placebo arm. At Week 44, the proportions of patients who achieved symptomatic remission were greater in the Q8W and Q12W groups (119/176 [67.6%] and 107/172 [62.2%], respectively) compared to the placebo group (79/175 [45.1%]). The Q8W and Q12W dose arms showed separation around Week 12 and the proportion of patients in symptomatic remission was generally greater in the Q8W dose arm compared to the Q12W during the trial period. The figure below shows a graphical representation of the

trends in this endpoint, and suggests that more patients were able to stay in remission (based on noninvasive measurements) during the 44 weeks of maintenance therapy with ustekinumab as compared to placebo.

Figure 11. Proportion of Patients in Symptomatic Remission Over Time Through Week 44 (Primary Efficacy Analysis Set)



Source: Applicant sBLA submission, dated 12/20/18, module 5.3.5.1, clinical study report CNTO1275UC3001 Maintenance, Figure 11, page 120/1560
Abbreviations: Q8/12W = every 8/12 weeks; SC = subcutaneous

Endoscopic Normalization

Normal/inactive mucosal disease was defined by a Mayo endoscopy subscore of 0. Patients who had a prohibited change in UC medication or an ostomy or colectomy prior to Week 8 were considered not to have normal or inactive mucosal disease.

At Week 8, 25/322 (7.8%) patients in the 6 mg/kg arm and 33/320 (10.3%) in the 130 mg arm achieved an endoscopic subscore of 0 compared with 12/319 (3.8%) in the placebo arm.

At Week 44, an endoscopy subscore of 0 was achieved in 51/176 (29%) of patients in the Q8W arm, 41/172 (23.8%) in the Q12W arm, and 32/175 (18.3%) in the placebo arm.

Histologic Improvement ("Healing per Applicant)"

"Histologic healing" was defined as neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue. In the analysis, patients with an unevaluable biopsy at Week 8 were excluded from the analysis. A post hoc sensitivity analysis was conducted by considering patients with an unevaluable biopsy (i.e., a biopsy that was collected, but could not be assessed due to sample preparation or technical errors) at Week 8 as not having met the endpoint; the results were consistent with the original analyses.

At Week 8, greater proportions of patients in the 6 mg/kg and 130 mg dose arms achieved histologic improvement (105/295 [35.6%] and 113/298 [37.9%], respectively) compared with

65/297 (21.9%) patients in the placebo arm. At Week 44, greater proportions of patients in the Q8W and Q12W groups achieved histologic improvement (99/167 [59.3%] and 88/163 [54.0%], respectively) compared with patients in the placebo group (55/167 [32.9%]).

Delayed-Responders to Ustekinumab Induction

At Week 8 of the induction study, ustekinumab-treated patients who were not in clinical response received a dose of ustekinumab 90 mg subcutaneously. Eight weeks later at Week 16, 55/101 (54%) patients achieved clinical response and then entered the maintenance study during which they received ustekinumab 90 mg SC Q8W. At Week 44, 97/157 (62%) of all delayed (Week 16) responders maintained clinical response and 51/157 (32%) achieved clinical remission. This observation is important because not all patients will achieve clinical remission or response at the same timepoint (by Week 8) after an initial IV induction. In light of the limited available therapies for the treatment of UC, we recommend that this information be communicated in the labeling to inform prescribers and patients of the possibility of achieving remission or response beyond Week 8 with continued therapy.

Induction-Maintenance Dosing Regimen

Patients who received either induction dose of 6 mg/kg or 130 mg IV and achieved at least clinical response were rerandomized into the maintenance study. Therefore, we considered whether the 6 mg/kg IV induction and 90 mg SC Q8W maintenance regimen was supported by the available data. The subgroup analyses by induction dose was limited by the relatively small size of the subgroups (45 to 70 patients per group); however, overall the totality of the evidence supports the Q8W-week dose over the Q12W dose, including consideration for dropouts due to worsening UC and lack of efficacy. Overall, the clinical benefit for both the primary and secondary endpoints for 6 mg/kg IV induction group and Q8W dosing group were similar or slightly better than the other ustekinumab dose arm in the induction and maintenance studies.

Durability of Response

Data were available through 52 weeks of treatment total (induction and maintenance) and support the durability of response through Week 52 (one IV induction dose followed by a SC dose 8 weeks later and continued dosing every 8 weeks for 44 weeks).

The maintenance study began at Week 44 and included an LTE that is planned to continue through Week 220. In the LTE, all patients will receive the same treatment regimen that they were receiving at the end of the maintenance study (either placebo or ustekinumab 90 mg SC Q8W or Q12W), with the first dose of the LTE administered at Week 48. Additional data on longer term outcomes will be available in the future from this LTE study.

Persistence of Effect

Available data did not permit a robust analysis of persistence of effect (i.e., treatment benefit after the drug was stopped); however, the maintenance study was a randomized-withdrawal design and the proportion of patients meeting the criteria for symptomatic remission declined in the placebo group over time compared to the ustekinumab-treated patients (see Figure 11 above). Since UC is a chronic condition that requires long-term therapy, stopping the drug in

patients who are responding would not provide useful information and we would expect the inflammation to return in the majority of patients if left untreated.

8.1.2.11. Integrated Review of Effectiveness

The Applicant conducted a single induction study and a single maintenance study as one large clinical trial for submission for review. Therefore, an integrated assessment of effectiveness was not performed.

8.1.3. Assessment of Efficacy Across Trials

8.1.3.1. Subpopulations

Analyses by Demographic Subgroup

Induction study

Subgroup analyses for the induction study are presented in Table 17 and Table 18. Clinical remission rates at Week 8 (FDA recommended definition) were summarized for region, sex, race, and age subgroups. Generally, for almost all investigated subgroups, the results were in favor of the ustekinumab 130 mg and 6 mg/kg doses in comparison to placebo.

Table 17. Induction Study, Clinical Remission at Week 8 by Region

Region (n)	Placebo	Ustekinumab 130 mg	Ustekinumab 6 mg/ kg
Asia (133)	0% (0/44)	15.9% (7/44)	11.1% (5/45)
Eastern Europe (368)	9.0% (11/122)	21.1% (26/123)	26.0% (32/123)
Rest of the world, including United States (460)	7.2% (11/153)	13.7% (21/153)	16.2% (25/154)
United States/non-United States (n)			
United States (179)	8.3% (5/60)	12.7% (8/63)	21.4% (12/56)
Outside of United States (782)	6.6% (17/259)	17.9% (46/257)	18.8% (50/266)

Source: FDA results

Table 18. Induction Study, Clinical Remission at Week 8 by Sex, Age, and Race

Subgroup	Placebo	Ustekinumab 130 mg	Ustekinumab 6 mg/ kg
Sex (n)			
Female (379)	9.0% (11/122)	18.5% (24/130)	21.3% (27/127)
Male (582)	5.6% (11/197)	15.8% (30/190)	17.9% (35/195)
Age category (n)			
<65 (910)	6.3% (19/303)	16.9% (51/302)	19.7% (60/305)
≥65 (51)	18.8% (3/16)	16.7% (3/18)	11.8% (2/17)
Race (n)			
Asian (143)	0.0% (0/48)	17.4% (8/46)	10.2% (5/49)
White (730)	8.5% (21/248)	18.4% (44/239)	21.4% (52/243)
Not reported (46)	0.0% (0/12)	5.6% (1/18)	12.5% (2/16)
Other (42)	9.1% (1/11)	5.9% (1/17)	21.4% (3/14)

Source: FDA results

Maintenance study

Table 19 and Table 20 summarize clinical remission rates at Week 44 (FDA recommended definition) in the maintenance study for region, sex, age and race subgroups. For almost all

subgroups the observed proportion of patients achieving remission was larger in the ustekinumab treatment arms as compared to placebo.

Table 19. Maintenance Study, Clinical Remission at Week 44 by Geographic Region

Region (n)	Placebo	Ustekinumab 90 mg Q12W	Ustekinumab 90 mg Q8W
Asia (78)	22.6% (7/31)	42.9% (9/21)	26.9% (7/26)
Eastern Europe (215)	32.4% (22/68)	41.3% (33/80)	58.2% (39/67)
Rest of the world, including United States (230)	22.4% (17/76)	33.8% (24/71)	39.8% (33/83)
United States/non-United States (n)			
United States (91)	18.5% (5/27)	32.3% (10/31)	48.5% (16/33)
Outside of United States (432)	27.7% (41/148)	39.7% (56/141)	44.1% (63/143)

Source: FDA Results

Table 20. Maintenance Study, Clinical Remission at Week 44 by Sex, Age Category, and Race

Subgroup	Placebo	Ustekinumab 90 mg Q12W	Ustekinumab 90 mg Q8W
Sex (n)			
Female (226)	26.5% (18/68)	43.4% (33/76)	45.1% (37/82)
Male (297)	26.2% (28/107)	34.4% (33/96)	44.7% (42/94)
Age category (n)			
<65 (497)	26.8% (44/164)	39.0% (64/164)	46.2% (78/169)
≥65 (466)	18.2% (2/11)	25.0% (2/8)	14.3% (1/7)
Race (n)			
Asian (87)	23.5% (8/34)	41.7% (10/24)	24.1% (7/29)
White (387)	28.8% (36/125)	37.8% (51/135)	52.8% (67/127)
Other (49)	12.5% (2/16)	38.5% (5/13)	25/0% (5/20)

Source: FDA Results

8.1.4. Assessment of Overall Effectiveness

In the two phase 3 studies, induction and maintenance, ustekinumab demonstrated statistically significant improvement compared to placebo in achieving remission at Week 8 (induction) and Week 44 (maintenance) based on FDA recommended definitions.

Overall, in both studies ustekinumab demonstrated efficacy results which were consistent across multiplicity controlled secondary endpoints as well as relevant exploratory efficacy endpoints.

8.2. Review of Safety

8.2.1. Safety Review Approach

Safety Review Strategy

The safety assessment focused on the data from the induction and maintenance trials of adult patients with moderately to severely active UC. Because the trial design and the duration of treatment differed between the two phase 3 studies, analyses were conducted for each trial separately. Safety data on the longer-term exposure to ustekinumab was also obtained by following patients in the open-label LTE study; available data were submitted in the 120-day safety update.

As was the strategy with the approach for efficacy, the safety analyses for the induction and maintenance trials were conducted separately, and none of the respective data were pooled for safety analyses. Similar to the efficacy analyses, only the randomized population in the maintenance study was included in our primary assessment of safety. Safety data in the nonrandomized population were assessed separately.

Adverse events of special interest (AESIs) included atypical infections associated with the immunocompromised host, nonmelanoma skin cancers, non–skin cancer malignancies, hypersensitivity reactions of ustekinumab infusion or subcutaneous injections, and the incidence of major adverse cardiovascular events (MACEs). Initially, MACE cases were observed in the psoriasis and psoriatic arthritis trials, but subsequent assessments have failed to establish a causal link for ustekinumab in IBD clinical trials for MACE. In addition, the Warnings and Precautions of the current ustekinumab label includes reversible posterior leukoencephalopathy syndrome (RPLS), a potentially fatal, rare neurological disorder. Our safety review assessed whether any patient developed RPLS.

UC was recorded by the Applicant as an AE; however, since UC was the disease of interest, UC was excluded from the tables presented in the subsequent safety assessment and the proportion of patients who reported UC as an AE are described in text.

The nonrandomized population included patients who were induction delayed-responders (responded at Week 16) and were followed in the maintenance trial but were not included in the randomized population (the primary analysis population). In this population, patients who were induction delayed-responders to ustekinumab received treatment with 90 mg Q8W and placebo responders continued on placebo. See Section 8.1.1.1 above for details on the analysis populations. An overview of the safety findings in this nonrandomized population is provided after each subsection describing specific safety results in the randomized population.

Recoding Adverse Event Dictionary Terms Reported by Applicant in ADAE Files

During the conduct of the safety analysis several terms were recoded. The table below describes the terms and number of events that were recoded in the safety analyses described in the following sections of this document.

Table 21. Recoded Terms for Safety Analyses From ADAE Files

Applicant's Adverse Event Code (Number of Events Recoded)	Reviewer's Recoded Term
Abdominal pain lower	Abdominal pain
Abdominal pain upper	Abdominal pain
Bacterial pneumonia	Pneumonia
Body temperature increased	Pyrexia
Blood phosphorus decreased	Hypophosphatemia
Ear infection viral	Ear infection
Gastrointestinal viral infection	Gastroenteritis
Gastroenteritis viral	Gastroenteritis
Respiratory tract infection bacterial	Respiratory tract infection
Upper respiratory tract infection	Nasopharyngitis
Viral upper respiratory tract infection	Nasopharyngitis

8.2.2. Review of Safety Database

Overall Exposure

The safety database included 641 patients who received a single IV ustekinumab induction dose (randomized population): 320 patients received the weight-tiered 6 mg/kg dose and 321 patients received 130 mg (319 patients received placebo). Three-hundred forty-eight patients received subcutaneous ustekinumab for 44 weeks (52 weeks of treatment total). There were 157 patients in the nonrandomized population (delayed-responders to IV induction who achieved clinical response by Week 16 and continued on 90 mg SC Q8W during the maintenance study). Following Week 44 of the maintenance study patients were eligible to continue in an LTE study. As reported in the 120-day safety update, a total of 361 patients from the randomized population and an additional 131 patients from the nonrandomized population (492 total patients) have received ustekinumab 90 mg SC ustekinumab Q8W through November 30, 2018.

Of the patients treated with ustekinumab in the UC maintenance study, 348 patients were randomized to SC ustekinumab (172 patients were randomized to 90 mg every 12 weeks and 176 patients were randomized to 90 mg every 8 weeks) in the maintenance study. Of these 348 patients, 334 (96.0%) patients were exposed to ustekinumab (IV and SC) for at least 6 months and 305 (87.6%) patients were exposed to ustekinumab (IV and SC) for at least 1 year.

Table 22 below shows the overall exposure for patients with UC who were randomized to ustekinumab in the phase 3 trials (induction and maintenance). The table shows the number of patients, and duration of IV and SC exposure, for patients who continued into the maintenance trial. The exposure in patients with IBD (both UC and CD) is shown to provide context for the Applicant's overall development program in IBD.

Table 22. Summary of Exposure to Ustekinumab During Induction and Maintenance Phase 3 Trials: Overall IBD Experience

	Ulcerative Colitis Ustekinumab			Crohn's Disease Ustekinumab		
	90 mg SC q12w	90 mg SC q8w	Combined	90 mg SC q12w[d]	90 mg SC q8w	Combined[e]
Subjects treated	172	176	348	132	131	263
Duration of IV and SC ustekinumab exposure						
At least 6 months[b]	162 (94.2%)	172 (97.7%)	334 (96.0%)	110 (83.3%)	125 (95.4%)	251 (95.4%)
At least 1 year[c]	146 (84.9%)	159 (90.3%)	305 (87.6%)	86 (65.2%)	106 (80.9%)	212 (80.6%)
Avg duration of treatment (weeks)	40.70	45.43	43.09	34.64	42.51	41.42

[a] Ulcerative Colitis: CNTO1275UCO3001; Crohn's disease: CNTO1275CRD3001, CNTO1275CRD3002 and CNTO1275CRD3003.
[b] The duration between the first IV and last SC ustekinumab administration was at least 14 weeks.
[c] The duration between the first IV and last SC ustekinumab administration was at least 38 weeks.
[d] Includes data up to the time of meeting loss of response criteria for subjects who had a dose adjustment in Crohn's disease.
[e] From the first ustekinumab dose onward, including data after the time of meeting loss of response criteria for subjects who had a dose adjustment in Crohn's disease.

Source: Applicant's submission, dated December 20, 2018, sBLA 761044, module 2.7.4 Summary of Clinical Safety, Table 10, page 61/132
Abbreviations: IBD = inflammatory bowel disease; Q8/12W = every 8/12 weeks; SC = subcutaneous

Adequacy of Safety Database

Overall, the number of patients and duration of exposure appear adequate to characterize the safety of ustekinumab in patients with UC.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Categorization of Adverse Events

The following categories were used to assess the safety of patients in these trials:

- The incidence and type of treatment-emergent adverse events (TEAEs), serious AEs (SAEs), and severe adverse events.
- TEAE demographic analysis included:
  - Age (<65 and ≥65)
  - Sex (male/female)
  - Race/Ethnicity (white/Asian/other)
- The incidence and type of adverse events of special interest were also assessed:
  - Infections and serious infections
  - Malignancies and nonmelanoma skin malignancies
  - RPLS
  - MACE (defined as nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death)
  - Hypersensitivity reactions

Routine Clinical Tests

The time and events for clinical laboratory data to assess safety were reasonable and adequate for the intended patient population. For the induction trial, clinical lab tests were measured at Weeks 0, 3, 6, and 8. For the maintenance trial, the lab studies were measured at Weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40 and 44. All laboratory tests were processed by a central laboratory. No laboratory data were available for the 120-day safety report submitted on April 17, 2019.

Normal clinical laboratory data were defined as follows:

- Hemoglobin ≥8.5 g/dL
- White blood cell count (WBC) ≥3.5X $10^3/\mu L$
- Platelets >100X $10^3/\mu L$
- Creatinine <1.7 mg/dL
- Aspartate aminotransferase (AST) ≤2X upper limit of normal (ULN) for the laboratory measuring the enzyme
- Alanine aminotransferase (ALT) ≤2X ULN for the laboratory measuring the enzyme
- Total bilirubin/direct bilirubin <1.0 mg/dL
- Alkaline phosphatase ≤1.5X ULN
- Albumin ≥3.0 g/dL

8.2.4. Safety Results

8.2.4.1. Deaths

Induction Trial

There was one death reported through the final safety visit in a 47-year-old white male (patient (b) (6)) who received one dose of 6 mg/kg ustekinumab IV who died on Day 42 of the induction trial secondary to bleeding from esophageal varices and hemorrhagic shock. This SAE was considered to be unrelated to ustekinumab exposure because the underlying cause of hemorrhage was likely nonalcoholic steatohepatitis-related cirrhosis and portal hypertension.

Maintenance Trial

One patient in the nonrandomized population died prior to Week 44. Patient (b) (6) was a 54-year-old white male who received ustekinumab 6 mg/kg IV induction and was a delayed-responder to IV induction. He achieved clinical response by Week 16 and continued on 90 mg SC Q8W in the maintenance study. The death (maintenance Day 85) was attributed to acute respiratory failure that occurred during thyroid surgery for a multinodular goiter. During the procedure, the patient experienced hypoxemia and remained hypoxic after the surgery with development of acute respiratory distress syndrome (ARDS) which prevented extubation. The patient's early postoperative course was also complicated by an anterior wall myocardial infarction. This SAE was considered to be unrelated to ustekinumab. Total ustekinumab exposure included an induction dose of 520 mg IV (6 mg/kg) ustekinumab, followed by 90 mg SC ustekinumab at Week 8. The patient received only one dose of ustekinumab 90 mg SC in the maintenance study. The cumulative dose exposure of ustekinumab was 800 mg.

One additional death was reported during the LTE after Week 44. The patient was a 71-year-old white male with a history of severe UC requiring long-term use of corticosteroids with biological failure to adalimumab, assigned to the placebo cohort during the induction trial, and received a dose of ustekinumab 6 mg/kg IV at Week 8. He was also randomized to placebo in the maintenance study. He continued in the LTE and received only one dose during the LTE (573 days post-administration of the first ustekinumab dose). Approximately 10 days after receiving the first dose of ustekinumab in the LTE, the patient was hospitalized for diarrhea secondary to UC complicated by cytomegalovirus (CMV) colitis. Ustekinumab was discontinued but the patient ultimately was transferred to a rehabilitation facility where he died.

8.2.4.2. Treatment-Emergent Adverse Events (TEAEs)

Induction Study

Of the 960 patients treated in the induction study, 160/320 (50.0%) of the ustekinumab-treated patients in the 6 mg/kg IV arm, 133/321 (41.4%) patients in the 130 mg IV arm, and 153/319 (48.0%) patients in the placebo group reported at least one TEAE. UC was reported as a TEAE in 2/321 (0.6%) patients in the ustekinumab 130 mg treatment arm and in 2/319

(0.6%) in the placebo arm. UC was not reported as a TEAE in the ustekinumab 6 mg/kg treatment arm.

The most frequent treatment-emergent adverse events that occurred in at least 3% of patients and greater in either ustekinumab arm compared to placebo during the 8-week induction study in the randomized population were nasopharyngitis, headache, fatigue, oropharyngeal pain, nausea, abdominal pain, and pruritus. All of these TEAEs have been previously described in the approved label for other indications for ustekinumab including Crohn's Disease.

Table 23. Treatment-Emergent Adverse Events Reported in at Least 3% of Patients and Greater in Either Ustekinumab Arm Over Placebo Through Week 8 of Induction Study (Randomized Population)

MedDRA Preferred Term for Adverse Event	Placebo N=319 (%n/N)	Ustekinumab 130 mg IV N=321 (%n/N)	Ustekinumab 6 mg/kg IV N=320 (%n/N)
Number of patients (n) with at least 1 TEAE	153 (48.0%)	133 (41.4%)	160 (50.0%)
Nasopharyngitis*	13 (4.1%)	20 (6.2%)	22 (6.9%)
Headache	14 (4.4%)	22 (6.9%)	13 (4.1%)
Fatigue	5 (1.6%)	6 (1.9%)	8 (2.5%)
Oropharyngeal pain	1 (0.3%)	1 (0.3%)	8 (2.5%)
Nausea	6 (1.9%)	9 (2.5%)	7 (2.2%)
Abdominal pain	8 (2.5%)	13 (4.0%)	7 (2.2%)
Pruritus	4 (1.3%)	8 (2.5%)	3 (0.9%)

Source: Reviewer analysis using Applicant's data BLA 761044, UC induction dataset ADAE module 5.3.5.1.
* Nasopharyngitis includes viral upper respiratory tract infection and upper respiratory tract infection.
Anemia occurred in 11 (3.4%) patients in the placebo cohort, in 7 (2.2%) patients in the ustekinumab 130 mg IV cohort, and in 8 (2.5%) patients of the ustekinumab 6 mg/kg IV cohort.
Abbreviations: AE = adverse event; IV = intravenous; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event

Nasopharyngitis will be described in the label because it was reported with a frequency in patients of at least 3% or more in the ustekinumab 6 mg/kg IV dose arm and were greater in frequency in the placebo arm. (b) (4) (b) (4) since these events were often reported in patients with nasopharyngitis/upper respiratory tract infections and there is insufficient evidence to support that the term (b) (4) is meaningful to physicians and patients.

Maintenance Study

Of the 523 patients enrolled in the maintenance study, 136/176 (77.3%) of patients in the 90 mg Q8W arm, 119/172 (69.2%) patients in the ustekinumab 90 mg Q12W arm, and 138/175 (78.9%) of patients in the placebo arm experienced at least one TEAE. The most common TEAEs in at least 3% of ustekinumab-treated patients and greater than in placebo included nasopharyngitis, headache, abdominal pain, influenza, pyrexia (fever), diarrhea, fatigue, oropharyngeal pain, sinusitis, and nausea. The majority of these adverse events have been reported previously in the approved label for other indications for ustekinumab.

UC was reported as a TEAE in 18/176 (10.2%) patients in the ustekinumab 90 mg SC Q8W arm, 19/172 (11.0%) patients in the ustekinumab 90 mg SC Q12W arm, and 50/175 (28.6%) patients in the placebo arm.

Table 24. Treatment-Emergent Adverse Events Reported in at Least 3% of Patients and Greater in Either Ustekinumab Arm Over Placebo Through Week 44 in the Maintenance Study (Randomized Population)

Adverse Event	Placebo SC N=175 (%n/N) n(%)	Ustekinumab 90 mg SC Q12W N=172 (%n/N) n(%)	Ustekinumab 90 mg SC Q8W N=176 (%n/N) n(%)
Number of patients with at least 1 TEAE	138 (78.9)	119 (69.2)	136 (77.3)
Nasopharyngitis*	35 (20.0)	36 (20.9)	42 (23.9)
Headache	7 (4.0)	11 (6.4)	18 (10.0)
Abdominal pain	6 (3.4)	6 (3.5)	12 (6.8)
Influenza	8 (4.6)	6 (3.5)	10 (5.7)
Pyrexia	7 (4.0)	1 (0.6)	9 (5.1)
Diarrhea	2 (1.1)	5 (2.9)	7 (4.0)
Fatigue	4 (2.2)	4 (2.3)	7 (4.0)
Oropharyngeal pain	5 (2.9)	4 (2.3)	7 (4.0)
Sinusitis	2 (1.1)	2 (1.2)	7 (4.0)
Nausea	4 (2.2)	4 (2.3)	6 (3.4)

Source: Reviewer analysis of Applicant data, ADAE dataset module 5.3.5.1.
* Nasopharyngitis also includes upper respiratory tract infection and viral upper respiratory tract infection.
Abbreviations: Q8/12W = every 8/12 weeks; SC = subcutaneous; TEAE = treatment-emergent adverse event

Adverse events that were reported in least 3% of patients and greater in the ustekinumab 90 mg Q8W dose arm and greater than in the placebo arm will be described in the label, (b) (4) (b) (4)

Nonrandomized Population: TEAEs

Overall, the proportion of patients reporting TEAEs in the nonrandomized population was 38/157 (24.2%) in the 90 mg Q8W arm, which was similar to the proportion of patients in the randomized population receiving ustekinumab 90 mg SC Q8W (46/176 (26.1%)); the proportion of patients reporting TEAEs in the placebo groups were also similar. The most frequent class of TEAEs affecting the delayed responder population was infections and infestations, which was also the most frequent class of TEAES affecting the randomized population receiving ustekinumab. In the nonrandomized population, UC was reported as a TEAE in 26/157 (16.6%) patients in the induction delayed-responder group.

8.2.4.3. Serious Adverse Events

Induction Study

The proportion of patients who reported at least one SAE through Week 8 of the induction study included 10/320 patients (3.1%) in the 6 mg/kg IV arm, 12/321 (3.7%) patients in the 130 mg IV arm, and 21/319 (6.6%) patients in the placebo arm. The most frequent SAE reported was UC. The proportion of patients reporting an SAE of UC in the induction trial was 3/320 (0.9%) in the ustekinumab 6 mg/kg arm, 4/321 (1.2%) patients in the 130 mg ustekinumab arm, and 11/319 (3.4%) in the placebo arm. The only other SAEs that occurred in more than one patient were deep venous thrombosis and hyperventilation, occurring in two patients (0.6%) each.

Other SAEs that occurred in one patient each are as follows:

- Ustekinumab 6 mg/kg mg IV arm: abdominal pain and hemorrhagic diarrhea (same patient), esophageal varices hemorrhage, pulmonary embolism (patient also had deep venous thrombosis (DVT) and an SAE of UC), migraine, ureterolithiasis, pyoderma gangrenosum, and ankle fracture.
- Ustekinumab 130 mg IV arm: gastroenteritis, pneumonia, aphasia/cognitive disorder/motor dysfunction (each in the same patient), nephrolithiasis, rash, and autoimmune hemolytic anemia.
- Placebo arm: anal fissure and anal abscess (same patient), large intestine perforation, pleurisy, anal abscess, C. diff infection, hepatitis C infection, epilepsy, ischemic stroke, pyoderma gangrenosum (patient also had an SAE of UC), limb injury, procedural intestinal perforation, and anaphylactic reaction.

In general the frequency of these SAEs was comparable to the proportion of patients who had one or more SAEs in the induction studies conducted for ustekinumab IV for the indication of Crohn's Disease (Lee 2016b).

The only event reported that was suggestive of an anaphylactic reaction at induction occurred in a placebo patient. The patient did not have documented antibodies to ustekinumab and had never been exposed to ustekinumab. Two patients in the 130 mg IV induction cohort suffered from hyperventilation which in both cases resolved and were not serious (see Section 8.2.5.2 on hypersensitivity reactions).

There were several SAEs that are most likely to be related to UC rather than ustekinumab infusions and are discussed below.

- Pyoderma gangrenosum reported in one placebo patient and one patient in the 6 mg/kg induction cohort is a well-known complication of UC. Another patient in the placebo group experienced a large intestine perforation which could have been a consequence of severe, uncontrolled UC. Anal abscess and anal fissure, each reported in a placebo-treated patient could also be attributed to uncontrolled UC.
- Two patients in the 6 mg/kg IV induction arm reported a DVT and of these two patients, one experienced a DVT and pulmonary embolism.
- One patient with a DVT reported the event 4 days after the initial ustekinumab infusion, was hospitalized and underwent placement of an inferior vena cava filter placement and blood transfusion. Approximately 2 months later, he had a second clot in the same extremity requiring hospitalization and was discharged on anticoagulation. This patient did not respond to the initial infusion at Week 8 and did not respond to the dose of 90 mg SC at Week 8, thus he discontinued the trial.
- The other patient with a bilateral pulmonary embolism and left sided DVT received a single induction dose 5 weeks before she developed the thromboembolism. She was also hospitalized for worsening UC at the same time. Her baseline Mayo score was 12 (severe) at entry into the trial and her duration of disease was approximately 36 years; she did not enter the maintenance trial. Her disease history suggests that uncontrolled disease along with other comorbidities were likely associated with these SAEs. Her medical history was very complex including, congestive heart failure, heart palpitations,

chest pain at rest, transient hypertension, syncope, collapse, dyspnea, mild aortic insufficiency, orthostatic hypotension, pericarditis, acute pyelonephritis, nephrolithiasis, kidney stone removal, lymphedema, cervical cancer, removal of cervix, ovarian cancer, hysterectomy, fibromyalgia, neuropathy, headache, insomnia, lumbar/cervical degenerative disc disease, hypermobility syndrome, thrombocytopenia, lymph node dissection, and ocular migraine; family history included heart failure and heart attack (father), stroke (maternal grandmother), and aortic aneurysm (mother). The multiple confounding factors make it difficult to attribute this event to a single dose of ustekinumab.

Patients with inflammatory bowel disease are at an increased risk of thromboembolic complications which can affect patients' morbidity and mortality (Giannotta et al. 2015). The most common thromboembolic events, including DVT and pulmonary embolism, are estimated to occur three times more than a patient who is healthy without IBD. However, the pathogenesis to explain the increased risk association between IBD and thromboembolism is not fully understood.

Maintenance Study

The frequency of SAEs reported in the maintenance study was generally similar between the ustekinumab and placebo arms. A total of 45 patients reported at least one SAE in the maintenance trial: 17/176 (8.5%) of patients in the 90 mg SC Q8W arm, 13/172 (7.6%) patients in the 90 mg SC Q12W arm, and 15/175 (9.7%) in the placebo arm. Ulcerative colitis was reported in the largest number of patients, occurring in more patients in the placebo arm. The proportion of patients who experienced an SAE of UC included 2/176 (1.1%) in the 90 mg SC Q8W arm, 1/172 (0.6%) in the 90 mg SC Q12W, and 8/175 (4.6%) in the placebo arm. Two other SAEs were reported in more than one patient, including spontaneous abortion (two patients in the Q8W arm), and CMV colitis (two patients in Q12W arm).

Other SAEs occurring in one patient each are as follows:

- Ustekinumab Q8W arm: diverticulitis and enterovesical fistula (same patient), gastroenteritis, periorbital cellulitis (discussed in detail under serious infections), salpingitis, enterovesical fistula, vomiting, colon cancer and dermatitis (same patient), rectal adenoma, hip fracture, lumbar vertebral fracture, pericarditis, and pyrexia.
- Ustekinumab Q12W arm: diverticulitis, influenza, enteritis, mesenteric fibrosis, lumbar hernia, skin papilloma and pyelonephritis (same patient), intraductal breast papilloma, anemia, and pulmonary embolism.
- Placebo arm: appendicitis, pharyngeal abscess, anal abscess, abdominal pain, upper abdominal pain, colon dysplasia, ovarian adenoma, cardiac arrest (patient also had SAE of UC), liver disorder (patient also had SAE of UC), neurosensory deafness and diabetic decompensation (same patient), gastroenteritis and tonic-clonic seizure (same patient), kidney injury and anorectal disorder (same patient; also had an SAE of UC), and hemorrhage.

Of the types of SAEs reported for the maintenance study, many of them were likely associated UC, including pyrexia (fever), anemia, and abdominal pain, anal abscess, diverticulitis, enterovesical fistula, gastroenteritis, and anorectal disorder. There were several neoplasms reported, including rectal adenoma, colon cancer, and colonic dysplasia, which

could also be associated with the underlying disease. Patients with UC are at risk for developing these types of neoplasms, since any one of these can occur with increased frequency in patients who have longstanding active UC (Gordillo et al. 2018). While most clinicians associate anorectal disorders with Crohn's disease since the disease is transmural and frequently results in fistulae. However, perianal diseases and anorectal disorders have been documented in higher prevalence in patients with UC with frequencies that are under-appreciated by providers (Hamzaoglu and Hodin 2005). Although no details are provided for the SAE of anorectal disorder it is conceivable this SAE was related to UC.

Two patients in the ustekinumab 90 mg Q12W arm reported CMV colitis, which occurs in patients with UC who are immunosuppressed. However, CMV is not only associated with immunosuppressant agents in patients with UC. A recent observational study demonstrated that older age, higher disease activity, deeper ulcerations, as well as more frequent use of immunosuppressant drugs are all independently associated with increased CMV colitis (Oh et al. 2019).

Finally, while not directly associated with UC, patients with severe osteoporosis may have vitamin D deficiency and also suffer from osteoporosis. In the ustekinumab Q8W arm one hip fracture and one vertebral fracture were each reported as an SAE. Both of these fractures are frequently associated with bone loss associated with osteoporosis. There are some data suggesting that mesenteric fibrosis may be associated with the fibrogenesis aimed at tissue repair in IBD, although the preponderance of evidence suggests that this association is much stronger with Crohn's disease than UC. In general, the totality of evidence suggests ustekinumab for UC did not result in the development of SAEs in the randomized populations.

Nonrandomized Population: SAEs

Overall, the number of patients experiencing an SAE in the maintenance trial among the nonrandomized population was similar to the randomized population. SAEs were reported in 11/157 (7.0%) patients in the 90 mg Q8W ustekinumab arm and 8/103 (7.8%) patients in the placebo arm. Gastrointestinal disorders were the most frequently reported SAE and UC was reported in 7/157 (4.5%) patients in the ustekinumab arm and in 3/103 (2.9%) of the placebo arm.

8.2.4.4. Dropouts and/or Discontinuations Due to Adverse Effects

Induction Study

The induction trial was an 8-week trial and patients were followed through a Week 20 safety evaluation. Therefore, the safety assessment for the induction trial also includes patients who discontinued before Week 8 and those who did not complete the final 20-week safety evaluation.

In the induction trial, no patients in either ustekinumab induction arm discontinued before/at Week 8 because of an AE and 3/319 (0.9%) patients in the placebo arm discontinued before or at Week 8 because of an AE. Through the final Week 20 safety visit, one patient in the ustekinumab 6 mg/kg IV arm discontinued because of death due to unrelated causes secondary to portal hypertension (see Section 8.2.4.1, Deaths, above). Another patient in the 6 mg/kg IV induction arm, a non-responder at Week 8 who was treated with 90 mg SC at

Week 8 and did not enter the maintenance phase, discontinued between Weeks 8 and 16 due to a DVT (details discussed in Section 8.2.4.3; Patient 1).

None of the discontinuations in the induction study appear to be related to adverse events related to ustekinumab.

Maintenance Study

In the maintenance study, the proportion of patients who discontinued due to an AE, excluding UC, was 5/176 (2.8%) patients in the ustekinumab Q8W treatment arm, 5/172 (2.9%) of patients in the ustekinumab Q12W treatment arm, and 5/175 (2.9%) of patients in the placebo group. UC accounted for the most frequently cited reason for discontinuation. In the randomized population, patients who left the study due to UC disease progression included 0/176 in the ustekinumab Q8W group, 4/172 (2.3%) in the ustekinumab Q12W group, and 15/175 (8.6%) in the placebo group.

Other than UC, the AEs leading to discontinuation in the randomized population receiving ustekinumab 90 mg Q8W treatment arm occurring in one patient each included: colonic dysplasia, colon cancer, spontaneous abortion, abnormal histology, and rash. In the ustekinumab 90 mg Q12W in one patient each: mesenteric fibrosis, papillary renal cell carcinoma, unintended pregnancy, rectal polyp, and vertigo.

Nonrandomized Population: Discontinuations

Among the nonrandomized population, 3/103 (2.9%) patients in the placebo arm and 4/157 (2.5%) patients in the ustekinumab arm discontinued because of an AE. Eight out of 157 (5.1%) patients in the ustekinumab Q8W arm and 10/103 (9.7%) patients in the placebo arm discontinued due to worsening UC. These data support the benefit observed with ustekinumab treatment, compared to placebo, in reducing the frequency of worsening UC in both the nonrandomized and the randomized populations. The AEs leading to discontinuation included one (0.6%) patient each: squamous cell carcinoma (skin cancer), decreased weight, ankylosing spondylitis, and acute respiratory failure.

8.2.4.5. Severe Adverse Events

Induction Study

In the induction study, AEs of severe intensity were reported through Week 8 in 12/320 (3.8%) patients in the 6 mg/kg IV ustekinumab arm, 9/321 (2.8%) patients in the 130 mg IV ustekinumab arm, and 15/319 (4.7%) patients in the placebo arm. The proportion of patients with severe UC was 2/320 (0.6%) in the 6 mg/kg ustekinumab arm, 3/321 (0.9%) in the 130 mg ustekinumab arm, and 8/319 (2.5%) in the placebo arm. A larger percentage of patients reported severe UC in the placebo arm compared to either drug arm, which supports the clinical benefit of the drug observed in the efficacy analyses.

The following were recorded as adverse events of severe intensity in one patient (0.3%) each (except as noted):

- Ustekinumab 6 mg/kg IV: abdominal pain, esophageal variceal hemorrhage, toothache, thrombocytopenia, hypophosphatemia, hyperkalemia, pulmonary

embolism, ureterolithiasis, hepatic steatosis, ankle fracture, migraine, pregnancy, and pyoderma gangrenosum.

- Ustekinumab 130 mg IV: anemia, autoimmune hemolytic anemia, thrombocytopenia, vomiting, hypoglycemia, hypophosphatemia in two patients (0.6%), hyponatremia, and hyperventilation.
- Placebo arm: large intestine perforation, anemia, epilepsy, ischemic stroke, pyoderma gangrenosum, anaphylactic reaction, *C. difficile* infection, and vaginal hemorrhage.

Maintenance Study

Through Week 44 of the maintenance study, 15/176 (8.5%) patients in the ustekinumab 90 mg SC Q8W treatment arm, 6/172 (3.5%) patients in the 90 mg Q12W arm, and 22/175 (12.6%) patients in the placebo arm experienced at least one AE of severe intensity. UC occurred as an AE of severe intensity in 1/176 (0.6%) patient in the ustekinumab 90 mg Q8W arm, 2/172 (1.2%) patients in the ustekinumab 90 mg Q12W arm, and 8/175 (4.6%) in the placebo arm.

The proportion of GI AEs of severe intensity in the placebo group are higher when compared to the ustekinumab Q8W treatment arm, which had no GI AEs of severe intensity observed. Infections, including occurrences of *C. difficile* colitis, are discussed separately as AEs of special interest.

AEs of severe intensity other than UC reported in the ustekinumab 90 mc SC Q8W treatment arm included influenza in two patients (1.1%), and one patient each (0.6%) experienced salpingitis, urinary tract infection, retinal detachment, hypokalemia, hypophosphatemia, acute kidney injury, fever (pyrexia), lumbar vertebral facture, ALT and AST increase resulting in lab inquiry, back pain, colon cancer, and spontaneous abortion.

Nonrandomized Population: Severe AEs

Of the nonrandomized patients who were followed in the maintenance trial, 16/157 (10.2%) patients in the 90 mg Q8W arm and 6/103 (5.8%) in the placebo arm reported an AE of severe intensity. Severe UC was reported in 8/157 (5.1%) patients in the ustekinumab 90 mg Q8W arm and 3/103 (2.9%) patients in the placebo arm.

In the nonrandomized population, one patient experienced pulmonary eosinophilia that was reported as an AE of severe intensity (also reported as a serious TEAE). This patient was a 45-year-old male who received ustekinumab 130 mg IV induction and did not respond at Week 8, thus received another dose of ustekinumab 90 mg Q8W SC at Week 8. The AE was reported around the same time he received the Week 8 SC dose. The patient required hospitalization for the AE, recovered, and did not enter the maintenance trial. Noninfectious pneumonia, including eosinophilic pneumonia, is already described in the product label.

8.2.4.6. 120-Day Safety Update Report and Adverse Events

In the 120-Day Safety Update Report, the Applicant provided follow-up data from the ongoing 220-week, open-label, LTE study and from patients in the maintenance study who did not enter the LTE. The data reported in the 120-day safety update include events reported after Week 44 of the maintenance trial through November 30, 2018. All patients after Week 44

who were eligible, regardless of their Week 0 assignment in the maintenance study, began receiving ustekinumab 90 mg SC Q8W treatment in the LTE. Data presented in the 120-day report for all treated patients who were also treated in the maintenance trial were categorized in the 120-day safety report by their randomization status in the maintenance trial. Therefore, a patient who received ustekinumab 90 mg SC Q12W during the 44-week maintenance trial is categorized in the report under this dose heading even though the patient had a dose adjustment to 90 mg SC Q8W in the LTE. The Applicant used the same approach to categorize patients who received placebo SC in the maintenance trial and subsequently received ustekinumab 90 mg SC Q8W treatment in the LTE.

The Applicant included updates for patients from Week 0 of the maintenance trial through November 30, 2018, of the LTE. In addition, the Applicant reported data for patients who were receiving ustekinumab 90 mg SC Q8W after Week 44 of the maintenance trial through November 30, 2018, in the LTE. In this section, a review of the patients with one or more serious AEs is included, as well as a review of patients who discontinued ustekinumab because of one or more AE.

One death was reported in the 120-day safety report; this case is described in this review in the Section 8.2.4.1, Deaths. The Applicant also included an update on neoplasms that arose in patients (described in Section 8.2.5.3, Malignancy), and additional details regarding serious infections (described in the Section 8.2.5.1, Infections).

No SAE was reported in more than one patient except for worsening UC in three patients who were treated with 90 mg SC Q12W in the maintenance trial. In the absence of a comparator and given the small number of patients (n=3) who reported an SAE of UC during the LTE, this information does not change the overall benefit-risk of ustekinumab. Other new SAEs reported during the LTE included two new cases of intervertebral disc protrusion, which are unlikely related to treatment with the study drug, and one additional case of pulmonary embolism in a patient who had only received placebo in the maintenance study.

Fifteen patients discontinued due to an AE during the LTE; UC was the most commonly reported AE that led to discontinuation in five patients (two SAEs, three nonserious AEs). Other reasons for discontinuation included pregnancy in three patients, failure to thrive and cytomegalovirus infection both in one patient (SAE described under deaths), and AESIs that are described further in Section 8.2.5, Analysis of Submission-Specific Safety Issues: listeriosis in one patient, optic neuritis, basal cell carcinoma, malignant melanoma, tonsillitis, and colon adenoma.

No cases of hypersensitivity reactions, including anaphylaxis, were reported from the LTE.

The ustekinumab label was updated recently to include a Warning and Precaution of non-infectious pneumonia, including interstitial pneumonia, eosinophilic pneumonia and cryptogenic organizing pneumonia. No reports of interstitial lung disease were reported in the LTE through November 30, 2018. One patient reported a suicide attempt during the LTE. This patient was treated with 90 mg SC Q8W in the maintenance trial and reported suicidal ideation on Day 646, 28 days after the last dose of ustekinumab. The patient had a history of depression, anxiety, obsessive compulsive disorder, and mood disorder. The patient had no prior history of self-harm or inpatient psychiatric care, and was not being treated with antidepressants or other psychiatric medication at the time of the event. There were no reports of serious depression reported after Week 44 through November 30, 2018.

Overall, there were no new or unexpected findings during the LTE that change the overall safety profile of ustekinumab. AESIs that are not currently described in the label, such as listeriosis, will be included in labeling.

8.2.4.7. Laboratory Findings

Induction Study

Hematology parameters

Serum hemoglobin, hematocrit, white blood count (WBC) absolute lymphocytes, monocytes, neutrophils, eosinophils, and platelets were measured at Weeks 0, 2, 4, 8, and 16 (patients who received IV induction were followed for a total of 20 weeks for safety) of the induction study. No clinically meaningful trends were identified between the ustekinumab dosing arms and the placebo arm with regard to these hematology measurements. Changes in hematology parameters at Week 8 demonstrated a greater proportion of patients in the 6 mg/kg and 130 mg groups with normal hemoglobin levels compared to the placebo group. The WBC, neutrophils, and platelets in the treatment groups showed a trend toward normalization through Week 8 when compared to the placebo group.

Serum chemistry parameters

Serum chemistries including total protein, albumin, electrolytes, blood urea nitrogen, creatinine, calcium, phosphorus, and liver biochemistries were measured at Weeks 0, 2, 4, 8, and 16 (patients who received IV induction were followed for a total of 20 weeks for safety) of the induction study. No clinically meaningful trends were identified between the ustekinumab dosing arms and the placebo arm with regard to serum chemistry lab values except for serum albumin, which was increased in both the 130 mg and 6 mg/kg ustekinumab treatment arms compared to the placebo arm.

Analysis of liver biochemical testing, including serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, and total bilirubin, was conducted on samples drawn at baseline, postbaseline, and at Week 8. More than 96% of all patients, regardless of the assigned treatment arm, had baseline liver biochemistry and postbaseline liver biochemistry values less than 2X the upper limit of normal (ULN) as determined by shift analysis. The frequency of patients that had an ALT ≥ 2X ULN among the ustekinumab-treated arms was 3.3%, while the frequency among patients in the placebo group was 7%. These trends were similar for AST, ALP, and total bilirubin, and these trends continued through Week 8 of the induction trial. There was no evidence that any patient in either of the two ustekinumab arms, or in the placebo group, had evidence of hyperbilirubinemia or showed any evidence of Hy's Law. Therefore, ustekinumab did not appear to induce a pattern of drug-induced liver injury when compared to placebo administration.

Maintenance Study

Hematology parameters

Serum hematology studies were drawn at Weeks 4, 8, 12, 16, 20, 24, 36, 40, and 44 in the maintenance study. Changes in major hematology parameters through Week 44 demonstrated improvements in hemoglobin and decreases in median WBC and neutrophil

counts in both the ustekinumab Q8W and Q12W treatment groups compared to the placebo group. These changes are expected as the disease improves. The decrease in both the median WBC and neutrophil counts did not appear to be a result of a dose-related effect.

Serum chemistry parameters

Serum chemistries in the induction study were drawn at Weeks 4, 8, 12, 16, 20, 24, 36, 40, 44 in the maintenance study. There were no meaningful differences identified between the mean serum chemistry values of ustekinumab-treated patients versus the placebo-treated patients at baseline or through Week 44.

Analysis of liver biochemical testing including serum AST, ALT, alkaline phosphatase, and total bilirubin, were conducted at maintenance baseline, every 4 weeks post-baseline during the trial, and at Week 44 of the maintenance trial, and shift analysis was performed. At maintenance baseline, 92% of placebo patients had a mean serum ALT ≤2X ULN, 95% of patients treated with ustekinumab 90 mg SC Q12W had a mean serum ALT ≤2X ULN, and 92% of the ustekinumab 90 mg SC Q8W patients had a mean serum ALT ≤2X ULN. Post-baseline, shift analysis revealed that in the placebo cohort, 93% of patients had a mean serum ALT ≤2X ULN, while 95% of the 90 mg Q12W cohort continued to have a mean serum ALT ≤2X ULN. Finally, 98% of the 90 mg Q8W cohort post-baseline continued to have a mean serum ALT ≤2X ULN. Data reporting for total bilirubin and serum alkaline phosphatase for either treatment groups at baseline, postbaseline, or at Week 44, were nearly 96 to 99% of 1.5 to 2.0X ULN. Through Week 44 there was no evidence that ustekinumab was associated with any Hy's Law drug-induced liver injury in the randomized population.

In both treatment arms of the maintenance trial, no patients had post-baseline ALT elevations at 5X, 10X, or 20X ULN, while in the placebo arm the percentage of patients with an ALT 5X ULN was 2% and with an ALT 10X ULN was 1%. Results were similar for AST, ALP, and total bilirubin. In general, there is no evidence to suggest that the low level frequency of these enzyme abnormalities could be associated with ustekinumab since the frequencies were at least as high, if not higher in the placebo-treated group.

Taken together, the laboratory data analyzed during the ustekinumab trials for UC did not reveal any clinically meaningful differences from the data summarized for trials of ustekinumab for psoriasis, psoriatic arthritis, and Crohn's disease.

Vital Signs

Induction study

Overall, there were no meaningful differences in vital signs in patients who received ustekinumab versus patients who received placebo.

Maintenance study

Overall, there were no meaningful differences in vital signs in patients who received ustekinumab versus patients who received placebo.

Electrocardiograms

Electrocardiogram monitoring was only performed during studies at screening. Ustekinumab is currently approved for the treatment of psoriasis, psoriatic arthritis, and Crohn's Disease, and is not known to have anti-arrhythmic or arrhythmogenic properties.

QT

EKGs/QT were assessed in earlier completed phase 1 studies, and no warnings or precautions are described in the currently approved label.

Immunogenicity

Please also refer to Section 6, Clinical Pharmacology, for complete details.

Induction study

Through Week 8, four patients (0.6%) developed antidrug antibodies (ADA) to ustekinumab: two patients each in the 130 mg IV and 6 mg/kg dose arms. Through the final safety visit, 18 patients (2.2%) had positive antibody titers for ADA. None of the patients who were positive for antibodies to ustekinumab through the final safety visit had an adverse event within 1 hour of ustekinumab infusion or thereafter. Of note, one patient in the placebo arm experienced anaphylaxis during the placebo infusion and recovered after appropriate intervention. The patient was tested and found not to have ADA against ustekinumab (also see Section 8.2.5.2Hypersensitivity Reactions, below)

Maintenance study

In the maintenance trial through Week 44, patients who developed antibodies to ustekinumab included 6 patients (3.4%) in the 90 mg SC Q8W arm, 6 patients (3.5%) in the 90 mg SC Q12W arm, and 16 patients (9.1%) in the placebo arm. In the nonrandomized population through Week 44, 11 patients (7.0%) had developed ADA.

None of the patients who developed ADA to ustekinumab through Week 44 reported an injection-site reaction after an ustekinumab SC injection.

Because there were a limited number of patients who developed ADA for ustekinumab, it is difficult to draw conclusions about the relationship between ADA development for ustekinumab in the maintenance trial and the injection-site reactions identified in this trial. Refer to clinical pharmacology assessment in Section 6.3.2.

8.2.5. Analysis of Submission-Specific Safety Issues

Drug specific safety issues discussed below include: infections, hypersensitivity reactions, malignancy, reversible posterior leukoencephalopathy syndrome, and MACE.

8.2.5.1. Infections

Induction Study

In the induction trial, the proportion of patients who had at least one infection was similar across each of the arms of the study: 49/320 (15.3%) patients in the 6 mg/kg IV arm, 51/321

(15.9%) patients in the 130 mg IV arm, and 48/319 (15.0%) patients in placebo. Nasopharyngitis was the most common infection observed in the induction study with 22/320 (6.9%) patients in the ustekinumab 6 mg/kg arm, 20/321 (6.2%) patients in the 130 mg arm, and 13/319 (4.1%) patients in the placebo arm. Through Week 8, the proportion of patients with infection requiring antibiotics were similar across treatment groups; 10/320 (3.1%) of patients in the 6 mg/kg arm, 17/321 (5.3%) of patients in the 130 mg arm, and 16/319 (5.0%) of patients in the placebo arm. Sinusitis and urinary tract infection in the ustekinumab-treated groups were the most frequently reported infections that required either oral or parenteral antimicrobial therapy.

Maintenance Study

In the maintenance trial, patients who experienced at least one infection included: 86/176 (48.9%) in the ustekinumab 90 mg SC Q8W arm, 58/172 (33.7%) in the 90 mg SC Q12W arm, and 81/175 (46.3%) in the placebo arm. The two most commonly reported infections were nasopharyngitis. Nasopharyngitis was reported in 42/176(23.9%), 36/172 (20.9%), and 35/175 (20.0%) of patients in the ustekinumab Q8W, ustekinumab Q12W, and placebo groups, respectively.

The proportion of randomized patients who required antimicrobial treatment were 40/176 (23.0%) in the ustekinumab Q8W group, 28/172 (16.0%) in the ustekinumab Q12W group, and 34/175 (19.4%) in the placebo group. The most frequently treated infections with antibiotics included bronchitis, nasopharyngitis (including upper respiratory tract infection), and sinusitis. There was one patient in the ustekinumab Q8W dose arm that experienced concurrent oral and ophthalmic herpes simplex that required treatment with oral therapy; the infection resolved, and the patient recovered.

Nonrandomized Population: Infections

Among the nonrandomized population, 58/157 (37.0%) ustekinumab-treated patients had one or more infections vs 44/103 (43.0%) patients in the placebo group. Nasopharyngitis was the most frequently reported infection with 17/157 (10.8%) of ustekinumab-treated patients and 13/103 (12.6%) patients in the placebo arm.

The most frequent infection requiring antibiotics in the non-randomized patient population was urinary tract infection in 4/157 (2.5%), followed by bronchitis 3/157 (1.9%). In general, the infection profile was comparable between the randomized and the nonrandomized population during the maintenance study.

Serious Infections

Induction study

In the induction study through Week 8, serious infections were reported in 1/320 (0.3%) patients in the 6 mg/kg ustekinumab arm (pyoderma gangrenosum); 2/321 (0.6%) patients in the 130 mg ustekinumab group (pneumonia and gastroenteritis), and 4/319 (1.3%) patients in the placebo arm (anal abscess, pleurisy, hepatitis C virus, and *C. difficile* infection).

No opportunistic infections were reported during the induction study through the final safety visit at Week 20, as were no cases of active tuberculosis (TB). However, one patient in the

6 mg/kg ustekinumab arm developed bilateral legionella pneumonia at Day 84, 27 days following ustekinumab infusion. The patient was also receiving methylprednisolone (8 mg daily) at the time of this adverse event, and was subsequently treated and ultimately recovered. This adverse event was considered related to the study agent by the investigator according to the clinical study report.

While no active cases of TB were identified, latent TB was identified in 4/320 (1.3%) patients in the ustekinumab 6 mg/kg arm and 5/321 (1.6%) patients in the ustekinumab 130 mg arm. There were no TB events reported in patients in the placebo group.

Maintenance study

Serious infections were reported in 3/176 (1.7%), 6/172 (3.5%), and 4/175 (2.3%) patients in the ustekinumab Q8W, ustekinumab Q12W, and the placebo cohorts, respectively. The proportions of patients with serious infection are similar to those observed in the maintenance trial conducted for Crohn's disease. The only serious opportunistic infection that was reported in more than one randomized patient was CMV colitis, which was reported in two patients in the ustekinumab Q12W group. Other serious infections reported in one patient each in the ustekinumab arms included: diverticulitis, influenza, periorbital cellulitis, pyelonephritis, skin papilloma, enteritis, and ulcerative colitis (although we do not consider this as a serious infection since UC is the underlying disease of interest). Pyrexia was also listed as a serious infection; however, we consider pyrexia to be a manifestation of the underlying disease or a clinical sign of an infection rather than an infection itself. In the placebo group serious infections included: anal abscess, appendicitis, gastroenteritis, and pharyngeal abscess.

In the nonrandomized population, serious infections were reported in 2/103 (1.9%) placebo patients (appendicitis, ulcerative colitis) and 2/157 (1.3%) ustekinumab-treated patients (pneumonia, respiratory failure).

Details of serious infections presented in 120-day safety report

The 120-day safety update report included additional information on the patients with serious infections reported during the maintenance. In addition to periorbital cellulitis discussed under serious infections during the maintenance trial, the 120-day safety update report included reports of pneumonia, anal abscess, enterococcal bacteremia/sepsis, human herpesvirus 6 infection, listeriosis, pelvic inflammatory disease, and complicated *C. difficile* colitis. Because listeriosis, human herpesvirus 6 infection, and enterococcal bacteremia/sepsis are unlikely related to the underlying disease and are clinically significant infections, brief narratives on these patients are provided below.

- The patient with listeriosis was an 85-year-old patient in the Q8W maintenance group who was diagnosed with a positive blood culture on maintenance Day 668 after presenting with fever and worsening UC. Two months prior the patient had undergone bilateral hip replacement for osteoarthritis. The patient eventually required emergent total colectomy with ileostomy. Postoperatively the patient developed disseminated intravascular coagulation, sepsis, and bacterial meningitis all attributed to listeria infection. The patient did recover without sequelae. This infection should be included in the product label.
- Human herpesvirus-6 (HHV-6) infection was reported in a 30-year-old female in the Q12W maintenance group who was hospitalized for fever and oropharyngeal testing was performed for DNA viruses, including HHV-6. The patient remained hospitalized for 13

days and was treated with parenteral prednisolone, acyclovir, ceftriaxone, and umifenovir (an agent used to treat influenza in Russia and China, but not in the United States). The patient recovered. HHV-6 ordinarily is an infection of children. In an adult reactivation, as with most DNA viruses it occurs in the setting of immunosuppression. Other than fever, the patient had no other systemic symptoms that would raise concern for viral reactivation. This infection will not be included in the product label because the diagnosis was uncertain given that the oropharyngeal smear was positive for HHV-6 but the blood PCR testing was negative. Oropharyngeal PCR has been found to be positive in asymptomatic patients and lacks specificity.

- While enterococcal bacteremia is a serious infection that can be associated with gastrointestinal diseases and surgical complications of the gastrointestinal and hepatobiliary tree, the case report of the patient who experienced the enterococcal bacteremia had numerous medical problems including cirrhosis. For this reason, enterococcal bacteremia was not recommended for inclusion as a serious infection in the product label.

8.2.5.2. Hypersensitivity Reactions

Induction Study

In the randomized population, no serious hypersensitivity reactions were reported that resulted in any patient being discontinued from the induction study. One out of 319 (0.3%) patients in the placebo group experienced an anaphylactic reaction (as reported by the investigator) and fully recovered and was discontinued from the study.

Sixteen patients experienced an adverse event within 1 hour of the IV induction infusion: 3/320 (0.9%) patients in the ustekinumab 6 mg/kg IV arm, 7/321 (2.2%) patients in the ustekinumab 130 mg IV induction arm, and 6/319 (1.9%) patients in the placebo arm. Of the AEs that occurred within 1 hour of infusion among the patients exposed to ustekinumab, three were SAEs (migraine headache in one patient in the 6 mg/kg group, hyperventilation in another patient in the 130 mg group, and anaphylactic reaction in one patient in the placebo group, as described above). Only the AE of rash was reported in more than one ustekinumab-treated patient, one patient in the 6 mg/kg group and one patient in the 130 mg group. There were no cases of delayed hypersensitivity or serum sickness-like reaction through Week 20, the final safety visit of the induction study.

Patients who were non-responders at Week 8 in the induction trial received either ustekinumab 6 mg/kg IV (if received placebo during induction) or 90 mg SC (if received ustekinumab during induction) and also received placebo SC and placebo IV, respectively, to maintain the blind. Of these patients, 5/184 (2.7%) patients reported an AE within 1 hour of infusion of ustekinumab 6 mg/kg plus placebo SC, and 6/233 (2.6%) experienced an AE within 1 hour of receiving ustekinumab 90 mg SC plus placebo IV.

Maintenance Study

Injection site reactions were defined as any adverse reaction at the SC injection site. A total of 5/176 patients (2.8%) in the ustekinumab Q8W group, 1/172 (0.6%) patient in the ustekinumab Q12W group, and 4/175 (2.3%) patients in the placebo arm reported injection-site reactions through Week 44. The most common reaction was erythema, reported in four

patients. Injection site reactions were all localized reactions and included erythema as the most frequent site reaction occurring in four patients receiving ustekinumab; as well as bruising, induration, pain, rash, and urticaria. None of these reactions were considered to be serious or severe and no cases of anaphylaxis or delayed hypersensitivity reactions were reported among randomized patients during the maintenance trial through Week 44. There were no differences in the types of local reactions observed between the Q8W and Q12W dose arms. Similar types of localized reactions were observed in patients who received placebo as well.

Among the nonrandomized population, no patients receiving placebo SC had injection-site reactions, while 4/157 (2.5%) patients in the ustekinumab 90 mg SC Q8W arm experienced injection site reactions. The most common reaction was erythema, reported in three patients.

8.2.5.3. Malignancy

Malignancies in Induction Trial

No malignancies were diagnosed or reported through Week 8 of the induction trial; however, a 61-year-old white male patient was diagnosed with prostatic cancer at Week 16 of the induction study (delayed responder). He had received 130 mg IV ustekinumab at Week 0 at induction, failed to respond, and went on to receive 90 mg SC at Week 8. The patient had a radical prostatectomy with extensive pelvic lymphadenectomy. He did not enter the maintenance trial, although his caner was reported as resolved before the 16-week safety visit.

Another patient was a 32-year-old white male in the induction study, who was also randomized to the 130 mg IV induction treatment group. The patient failed to respond, and received 90 mg of ustekinumab SC at Week 8, and was diagnosed at Week 16 with adenocarcinoma of the rectum after having a total colectomy for high-grade dysplasia. This patient underwent chemotherapy and radiation treatment for a total of 6 months according to the clinical study report. The patient did not enter the maintenance study.

No skin cancers were diagnosed during the induction trial. The malignancies reported during the induction trial are unlikely related to treatment with a single IV dose of ustekinumab.

Malignancies in Maintenance Trial

A total of three malignancies were diagnosed during the 44-week maintenance study among the randomized population and three malignancies were diagnosed among the nonrandomized population. A summary of all malignancies that arose during the induction and maintenance trials is included in Table 25.

Solid tumors in randomized population

- (Colon cancer): The patient was a 48-year-old Japanese female who had a duration of disease for 28 years and was diagnosed with colon cancer on maintenance Day 2. She was randomized to ustekinumab 90 mg Q8W. The patient participated in the induction study, and was randomized into the maintenance study. Since the patient underwent total colectomy prior to receiving any SC ustekinumab, the patient was withdrawn from the study and was not included in the primary analysis in the maintenance trial.

- (Papillary renal cell carcinoma): The patient was a 70-year-old male randomized to the Q12W cohort and diagnosed on maintenance Day 37 incidentally. The patient was discontinued from the study and underwent a right partial nephrectomy.

Solid tumors in nonrandomized population

- (Testicular Cancer): Occurred on maintenance Day 245 in a patient who was receiving placebo SC only and was in the placebo cohort throughout both induction and maintenance studies.

Skin cancers in randomized population

- (Squamous cell carcinoma): A 46-year-old white male in the ustekinumab Q12W cohort was diagnosed with two squamous cell carcinomas of the skin on maintenance Day 83. The patient had a history of azathioprine use for more than 2 years and was receiving concomitant azathioprine during the study. The patient continued through the end of Week 44 but did not enter the LTE. The patient did meet criteria to leave the maintenance trial at the time of diagnosis but was not withdrawn.

Skin cancers in nonrandomized population

- (Squamous cell carcinoma): A 72-year-old white male in the induction delayed-responder cohort received 90 mg Q8W in the maintenance trial was diagnosed with squamous cell carcinoma of the skin on maintenance Day 154 in a location of a previously excised squamous cell lesion. This patient also had a history of 6-mercaptopurine use for more than 2 years, had a strong history of sun exposure as a farmer, and a past history of skin cancer.
- (Basal cell carcinoma): A 77-year-old white male was diagnosed with two basal cell carcinomas on maintenance Day 245. He also had a history of longstanding azathioprine use and was receiving azathioprine during the clinical trial. The patient had a long history of chronic sun exposure.

Table 25. Summary of Malignancies Occurring in Induction and Maintenance Studies of Ustekinumab for Moderately Active to Severely Active Ulcerative Colitis

	Induction Trial Randomized Population Through Week 8 N=960 2/960 (0.21%)			Maintenance Trial Randomized Population Through Week 44 N=523 3/523 (0.57%)			Non-Randomized Population	120-Day Safety Report (Through 11/3018)
Tumor Type	Placebo IV N=319	130 mg IV N=321	6 mg/kg IV N=320	Placebo SC N=175	Ustekinumab 90 mg SC Q12W N=172	Ustekinumab 90 mg SC Q8W N=176	Ustekinumab 90 mg SC Q8W N=157	
Basal cell carcinoma	0	0	0	0	0	0	1	3
Squamous cell carcinoma	0	0	0	0	1	0	1	
Melanoma	0	0	0	0	0	0	0	2^
Lymphoma/ leukemia	0	0	0	0	0	0	0	
Solid organ	0	2	0	0	1	1	0/1^	

Source: Table abstracted from Applicant submission of clinical study report for induction and maintenance trials for CNTO1275UCO3001 5.3.5.1. and individual case reports as well as 120-day safety report through November 30, 2018 also in 5.3.5.1.
^ One patient in the placebo arm of the non-randomized population had testicular cancer and had a second malignancy melanoma *in* situ N=103 (2/103, 1.9%).
Abbreviations: IV = intravenous; Q8/12W = every 8/12 weeks; SC = subcutaneous

Malignancies reported in 120-day safety report through November 30, 2018

In the 120-day safety update, skin malignancies were diagnosed in four additional patients. Three patients had basal cell carcinomas: one patient was a 77-year-old male in the delayed-responder cohort; the second was a 38-year-old male in the randomized population who received 90 mg Q12W; and a third patient was a 65-year-old female who received 6 mg/kg IV ustekinumab induction at Week 0 of the induction trial but was randomized to the maintenance trial placebo group. All three patients had a history of azathioprine use. Only the 77-year-old man was discontinued from the study, the other two patients continued.

A fourth patient from the 90 mg Q8W randomized population was diagnosed with malignant melanoma on maintenance Day 327, 40 days after the last administration of ustekinumab on maintenance Day 287. The patient was a 41-year-old female who had a history of tanning bed use, excess sun exposure, blistering sunburn, and a history of a skin lesion that started showing color changes 2 years prior to diagnosis of melanoma. This patient also had a brief history of use of both 6-mercaptopurine and azathioprine (<1 year). The patient underwent wide-local excision and was discontinued from the study.

Summary and Conclusion Regarding Malignancies in UC Trials

The frequencies of solid organ and nonmelanoma skin cancers are similar to those observed in the clinical trials which studied the efficacy of ustekinumab for the treatment of Crohn's disease. In review of the data for the UC trial to date, two of four solid tumors are associated with colorectal cancer, which is likely due to inherent risk association with UC. One of the patients had UC for more than 2 decades. The renal cell carcinoma and prostate cancer events observed are not likely to be associated with ustekinumab given the individual patient's limited exposure, and the association of these two malignancies with age (and sex in prostate cancer) as significant risk factors.

In the UC trials, there were no reports of lymphomas or leukemias. This differs from the Crohn's clinical trials. At the close of Crohn's disease trials for ustekinumab, one 50-year-old patient was reported to have developed chronic myelogenous leukemia, who had never been exposed to an immunosuppressant before exposure to ustekinumab. Another patient in one of the two induction studies in the 6 mg/kg cohort, and who carried a diagnosis of monoclonal gammopathy of unknown significance, developed multiple myeloma during the safety follow-up period, and was withdrawn from the study.

Although malignancies occurred in a small proportion of patients during the UC trials, it is difficult to fully ascertain risk of malignancy during relatively short duration of clinical trials, and for this reason collecting additional long-term data in the postmarketing setting to assess risk of malignancy in ustekinumab-treated patients with UC long-term is likely to yield more data on the risk of malignancy. A postmarketing study evaluating the long-term risk of malignancy is ongoing for patients with Crohn's disease who are being treated with ustekinumab. A postmarketing study with the same goals will be required for patients with UC; the study in UC may be combined with the ongoing study in Crohn's disease.

8.2.5.4. Reversible Posterior Leukoencephalopathy Syndrome and Other Neurological Events

No cases of RPLS were reported during the phase 3 clinical trials in patients with UC nor in the 120-day safety report through November 30, 2018.

An assessment of the safety data for other neurologic events revealed one report of optic neuritis. A 33-year-old female nonresponder at Week 8 who was rerandomized to the placebo group in the maintenance study was diagnosed with optic neuritis 738 days following administration of a single IV infusion of ustekinumab 6 mg/kg during the induction study at Week 8. This patient was treated with corticosteroids and improved. She was permanently discontinued from the study. Given that the patient received a single dose of study drug it is highly unlikely there is any relationship between ustekinumab and the patient's optic neuritis.

8.2.5.5. Major Adverse Cardiac Events

The Applicant defined MACE as (1) nonfatal myocardial infarction; (2) nonfatal stroke; or (3) cardiovascular death. This is the same definition the Applicant used in the previous BLAs and efficacy supplements.

During the review of BLA 125261 to support the initial approval of ustekinumab for psoriasis, the review team noted an imbalance in serious cardiovascular (CV) events in a psoriasis clinical trial. As a consequence of these findings, the review division (Division of Dermatology and Dental Products, or DDDP) requested that the Applicant perform an extensive review of MACEs, defined as CV death, nonfatal MI, and nonfatal stroke, as well as other nonfatal thrombotic evens, defined as unstable angina pectoris, venous thromboembolic disease (DVT, pulmonary embolism, and other peripheral venous thrombosis), and peripheral arterial thrombosis. Other nonfatal CV events, defined as heart failure and arrhythmia requiring intervention, were also examined. DDDP reviewed the Applicant's analysis and agreed that there was no consistent evidence of increased CV risk with ustekinumab and that no labeling changes were warranted. Refer to clinical review by Dr. Brenda Carr, dated September 13, 2014, for details.

Upon review of BLA 761044 to support approval of ustekinumab for the treatment of CD, the potential for MACE was again assessed. There was no substantial evidence to justify inclusion of additional information to the product label; nor, were further postmarketing studies dedicated to monitoring MACE required apart from typical postmarketing surveillance (Lee 2016a).

During the induction trial for ustekinumab with the indication for treatment of UC, no cases of MACE were reported for ustekinumab-treated patients through the final 20-week safety visit. Through Week 8, there was one patient in the placebo group that had an ischemic stroke.

In the maintenance trial, along with review of the 120-day safety report, a total of four patients experienced a MACE: three ustekinumab-treated patients experienced a nonfatal myocardial infarction, while one patient in the maintenance randomized placebo group, who received a single dose of ustekinumab during the induction study, had a nonfatal cardiac arrest on maintenance Day 143 (199 days *after* receiving the last dose of ustekinumab). Brief narratives of each event are described below in relationship to the patient's status in the maintenance trial.

Patients Who Experienced a MACE

Patient 1: Randomized placebo patient in maintenance trial

The patient was a 45-year-old white male in the placebo group, and the nonfatal arrest occurred in a perioperative setting. The patient had a history of hypertension and ischemic heart disease and underwent a total proctocolectomy with ileostomy for severe ulcerative colitis, refractory to treatment. Postoperatively on the same day the patient suffered a nonfatal cardiac arrest and then developed acute renal failure and altered consciousness. The patient was successfully resuscitated, recovered, and discharged. Given the patient's overall medical history, it is unlikely that this cardiovascular event was related to ustekinumab exposure. He had a single exposure at day 57 of the induction trial to 520 mg ustekinumab IV. The cardiac event occurred on Day 225 (Week 16 maintenance).

Patient 2: Nonrandomized patient in delayed-responder treatment arm of maintenance trial

A 54-year-old white male experienced acute respiratory failure on Day 179 of the maintenance study in which the patient had undergone removal of a goiter from the thyroid. The patient was in the nonrandomized population of the maintenance trial (delayed induction responder who received ustekinumab 90 mg SC Q8W in the maintenance trial). There is no date specific for when the actual anterior wall MI occurred with respect to the MI, however. The surgical procedure was complicated by acute respiratory failure with prolonged hypoxemia which prevented extubation. The patient had a complicated past medical history including multinodular goiter, hypothyroidism, hyperparathyroidism, morbid obesity, sleep apnea and UC. The patient ultimately died (see Section 8.2.4.1, Deaths) from complications of ARDS. Given the medical history of this patient, and the circumstances in which the MI occurred, it is unlikely that ustekinumab contributed to the patient's MACE.

Patient 3: Randomized patient to placebo in maintenance trial

A 48-year-old white male sustained a nonfatal myocardial infarction on maintenance Day 588, 25 days after the first dose of ustekinumab SC in the LTE. The patient was randomized to placebo IV in the induction trial, did not achieve clinical response and received a dose of

ustekinumab 6 mg/kg IV at Week 8. The patient achieved clinical response at Week 16 and was randomized into the placebo maintenance trial but continued into the LTE and started ustekinumab 90 mg Q8W on Day 563 in the LTE. The patient had a past medical history significant as a former cigarette smoker, but no prior cardiac history and no family history of cardiovascular disease. The patient's last dose of placebo was on Day 644 of the maintenance study, or 56 days prior to the MACE. The first dose of 90 mg SC ustekinumab was Day 675 or 25 days prior to the MACE.

The patient's past medical history was unremarkable, and he was taking no other medications at the time of this event. In this patient's case, there is a temporal relationship of ustekinumab exposure to the patient's acute MI. However, in the absence of other known historical or precipitating events, determining causality as to why the patient sustained a MACE, although the patient was male, is more difficult than the other cases in which a MACE occurred. The date/timing of when the patient stopped smoking, or the pack-year smoking history was unknown.

Patient 4: Nonrandomized patient in delayed-responder treatment group

A 67-year-old male sustained a nonfatal acute myocardial infarction on maintenance Day 497, 40 days after receiving his last dose of ustekinumab 90 mg Q8W on maintenance Day 457. The patient was in the ustekinumab induction delayed-responder cohort. This patient had numerous past medical history issues that likely put him at high risk for MACE. These include medical renal disease, hypertension, dyslipidemia, former tobacco smoking, history of aortic stenosis, male sex, and age >65. Therefore, the patient's numerous medical issues and age were much more likely to have been associated risk factors for his acute myocardial infarction.

Summary of MACE Assessment for Ustekinumab in UC Clinical Trials

In the current trials for UC, the number of MACE was small, and two of the four MACEs were unlikely to have been associated with ustekinumab exposure. Although a temporal relationship exists between ustekinumab exposure and the event in a 48-year-old male, there is limited evidence to suggest that a causal relationship exists between ustekinumab and the event. Therefore, the totality of evidence of this review supports the conclusions drawn from prior reviews of ustekinumab for psoriasis, psoriatic arthritis, and Crohn's disease; that no labeling changes or additional postmarketing requirements are needed for the indication of ustekinumab for moderately to severely active UC with regard to further evaluating MACE as a safety signal.

8.3. Safety Analyses by Demographic Subgroups for Ustekinumab Controlled Trials for UC

Overall, in both the induction trial and the maintenance trial, no clinically meaningful trends were observed between drug arms and placebo when safety was assessed by demographic subgroup (sex, race, age).

TEAEs by Age

In the induction trial, 607/641 (94%) patients in the ustekinumab IV induction dose arms (130 mg and 6 mg/kg) and 303/319 (95%) patients in the placebo arm were <65 years of age. Thirty-four out of 641 (5.5%) patients in the ustekinumab IV induction treatment arms (130 mg and 6 mg/kg) and 16/319 (5%) patients in the placebo arm were ≥65 years of age. Of the patients <65 years of age, 297/607 (49%) patients in the ustekinumab IV dose arms and 156/303 (51%) patients in the placebo arm reported a TEAE during the induction trial. The most common TEAEs in ≥ 3% of patients either ustekinumab arm and greater than placebo in patients < 65 years of age were generally similar to the types of TEAEs reported in the overall patient population of the induction trial, including nasopharyngitis, headache, fatigue, and oropharyngeal pain. The most common TEAEs in patients ≥ 65 years of age in either ustekinumab arm and greater than in placebo were reported in small numbers of patients and included anemia (2 patients in 6 mg/kg IV, no patients in 130 mg IV or placebo), ulcerative colitis (2 patients in 6 mg/kg IV, 1 patient in 130 mg IV, and none in placebo), and nasopharyngitis (2 patients in 6 mg/kg IV, 4 patients in 130 mg IV, and none in placebo. Other TEAEs in patients ≥ 65 years of age occurred in one patient each and did not raise concerns for any new or unexpected TEAEs. Overall, there were no trends in the types of TEAEs that raise concerns for the safety of ustekinumab in geriatric patients; however, the number of patients in the randomized population ≥65 years of age is too small to provide meaningful comparisons.

In the maintenance trial 15/348 patients in the ustekinumab treated groups were age 65 or older, while 333/348 of the treated patients were younger than age 65. This represents a disproportionate fraction of the randomized population younger than age 65 (89%) compared to 11% who were age 65 or older. The TEAEs that occurred in patients age less than 65 years of age in the ustekinumab 90 mg Q8W cohort are similar to the entire cohort that received this dose in the maintenance trial and is comparable to the placebo population of that respective age group. The most common TEAEs in either ustekinumab arm and greater than in placebo in patients < 65 years of age were generally similar to the types of TEAEs reported in the overall patient population of the maintenance trial, and included nasopharyngitis, ulcerative colitis, headache, abdominal pain, influenza, and pyrexia. The most common TEAEs in either ustekinumab arm and greater than in placebo in patients ≥ 65 years of age that occurred in more than 1 patient included headache and arthralgia (2 patients each and both in the Q12W arm). Since the data for the geriatric population for the maintenance trial is quite small, more meaningful comparisons cannot be assessed.

TEAEs by Sex

In the induction trial, 385/641 (60%) patients in the ustekinumab IV induction treatment arms (130 mg and 6 mg/kg) and 197/319 (62%) patients in the placebo arm were male. TEAEs were reported in 165/385 (43%) male patients in the ustekinumab IV arms and 92/197 (47%) male patients in the placebo arm. TEAEs were reported in 128/256 (50%) female patients in the ustekinumab IV arms and 64/122 (53%) female patients in the placebo arm. The most common TEAEs occurring in male and female patients in either ustekinumab arm when compared to males and females on placebo, respectively, were generally similar to the types of TEAEs observed in the overall patient population for the induction trial. No clinically

meaningful trends were identified in the types of AEs reported between males and females treated with ustekinumab compared to respective sex-matched placebo cohorts.

In the maintenance trial, the TEAEs in males in the ustekinumab treatment groups were comparable to the placebo-treated males, and TEAEs in females in the ustekinumab treatment groups were also comparable to placebo-treated females. The most common TEAEs occurring in male and female patients in either ustekinumab arm when compared to males and females on placebo, respectively, were generally similar to the types of TEAEs observed in the overall patient population for the maintenance trial. No obvious trends were observed, except that nasopharyngitis was not a TEAE observed at a greater frequency among males in either the ustekinumab 90 mg Q12W or 90 mg Q8W arms when compared to the placebo cohort for this demographic.

TEAEs by Race/Ethnicity

In the induction trial, 481/641 (75%) patients in the ustekinumab IV induction dose arms (130 mg and 6 mg/kg) and 248/319 (78%) patients in the placebo arm were white. Six patients in the ustekinumab IV arms and three patients in the placebo arm were black/African American, 95 patients in the ustekinumab IV arms and 48 patients in the placebo arm were Asian. The proportion of patients reporting TEAEs was generally similar between patients treated with ustekinumab who were white and Asian compared to respective placebo. Although the majority of patients were white, there did not appear to be trends in the types of TEAEs that raise concerns for the safety of ustekinumab. The number of black/African American and Hispanic patients was too small to provide meaningful data to make comparisons.

White patients in the randomized population of the maintenance trial represented 74% of all patients and 75% of the ustekinumab-treated population. The TEAEs of white patients treated in either ustekinumab arm were comparable to the race-matched placebo cohort. As would be expected, the types of TEAEs are also similar to the overall TEAE frequency of the treatment trials given the large proportion of patients who were white.

Both the induction and maintenance trials included participation of Asian patients in all dose arms. The overall TEAE profile in the induction study in the Asian population treated with ustekinumab at either the 130 mg IV dose or the 6 mg/kg dose revealed no meaningful trends compared to Asian patients in the placebo group. There were no obvious trends in TEAEs in Asian patients compared to those observed in the overall population for either the induction trial or the maintenance trial.

In the induction trial a total of nine (0.9%) patients were African-American. No Hawaiian or Pacific Islanders were reported to have participated, and one (0.1%) Native American or Alaskan Native participated. There were a total of 17 (1.8%) Hispanic-Americans participated in the induction trial and 15 (2.3%) were exposed to ustekinumab. Since the numbers of the patients were quite small, and more patients were reported as ‘other’ or otherwise ‘not reported’, the most common TEAEs for both the induction trial and the maintenance trials were analyzed by collecting TEAE data for all of the populations as designated by the Applicant.

There were no meaningful trends that can be discerned from review of these data. The analyses of TEAES in these demographic subgroups did not reveal any new or unexpected

TEAEs that were not previously reported in the TEAE analyses for the overall patient population of either the induction trial or the maintenance trial.

8.4. Specific Safety Studies/Clinical Trials

No specific safety studies were conducted for this application.

8.5. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

See Section 8.2.5.3 on Malignancy.

Human Reproduction and Pregnancy

Cumulatively, eight females became pregnant from the time the induction trial began through December 31, 2018. Two pregnancies were continuing at the time of this submission; 4/8 pregnancies progressed to live births, with 1/4 having an AE (classified as 'other'); 2/8 underwent spontaneous abortion. The two spontaneous abortions occurred in females in the maintenance study on ustekinumab 90 mg SC Q8W.

Five pregnancies occurred where paternal exposure to ustekinumab occurred over the same time frame. Three pregnancies progressed to live births without any AEs, while 2/5 were continuing at the time the 120-day report was submitted.

The current label states that limited data on the use of ustekinumab in pregnant women are insufficient to inform a drug associated risk. In animal reproductive and development toxicity studies, no adverse developmental effects were observed after administration of ustekinumab to pregnant monkeys.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated population(s) are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage of clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

No further changes to the pregnancy information in the current label are recommended at this time.

Pediatrics and Assessment of Effects on Growth

The clinical trials induced in this submission were conducted in adults and therefore pediatric assessment of effects on growth were not conducted in these clinical trials.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

These categories are not applicable to this application.

8.6. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Postmarketing safety events are described in the current label and in periodic safety update reports for the indications of psoriasis, psoriatic arthritis, and Crohn's disease. These events include safety concerns discussed in this review including cutaneous squamous cell carcinomas, hypersensitivity reactions, anaphylaxis, reversible posterior leukoencephalopathy syndrome (RPLS), and interstitial lung disease.

Including data from the 120-day safety update through November 30, 2018, there were additional data that identified new patients in the UC trials exposed to ustekinumab who experienced hypersensitivity reactions that were not previously identified and reported in either the clinical study reports for the induction trial or maintenance trial. The current label describes the potential for serious hypersensitivity reactions (including anaphylaxis and angioedema).

RPLS is a rare neurological disorder that can present with headache, seizures, confusion, and visual disturbances. RPLS can be fatal. RPLS was noted in clinical trial safety database for psoriasis in a patient who had received approximately 12 doses of ustekinumab over approximately 2 years. Ustekinumab was discontinued and the patient recovered. No cases of RPLS were reported during the clinical trials for Crohn's disease or ulcerative colitis. To date, two cases of RPLS have been reported in patients exposed to ustekinumab. Both cases were reported in patients who were treated for psoriasis and psoriatic arthritis.

Expectations on Safety in Postmarket Setting

Specific safety concerns for malignancy and serious opportunistic infection are discussed in Section 13, Postmarketing Requirements and Commitments.

8.7. Integrated Assessment of Safety

Not applicable to review of this application since one induction study and one maintenance study were submitted, and they were assessed separately.

8.8. Conclusions and Recommendations

Based on a review of the submitted safety datasets and clinical study reports, ustekinumab has a safety profile that supports a favorable benefit/risk for the treatment of patients with moderately to severely active ulcerative colitis.

No new or unexpected adverse events of special interest were identified. Serious or otherwise clinically significant infections included gastroenteritis, ophthalmic herpes zoster, pneumonia, and listeriosis. These serious infections are also described for the Crohn's indication except listeriosis (note that listeria meningitis is reported in the labeling under the Crohn's indication). The adverse events of special interest are similar to those reported in the past for previously approved indications including plaque psoriasis, psoriatic arthritis, and Crohn's disease. As with the indication of ustekinumab for Crohn's disease, a postmarketing

study will be required to assess the long-term risk of malignancy and serious and opportunistic infections.

9. Advisory Committee Meeting and Other External Consultations

No advisory committee was held for this application.

10. Pediatrics

On February 22, 2017 the Applicant received an Orphan Designation Status for pediatric UC (#16-5375). Therefore, the Applicant is exempt from Pediatric Research Equity Act requirements and will be issued PMCs for pediatric studies.

11. Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing Information

Refer to the approved label for the final language. The key changes to the label are summarized below.

Section 1 Indications and Usage

- The indication statements for both Crohn's disease and UC were simplified (b) (4) (b) (4) The revised indications are as follows:
  - Crohn's Disease (CD): STELARA is indicated for the treatment of adult patients with moderately to severely active Crohn's disease.
  - Ulcerative Colitis: STELARA is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis.

Section 5: Warnings and Precautions

- Updated to include information on infections included (b) (4), gastroenteritis, ophthalmic herpes zoster, pneumonia, and listeriosis that were observed during the phase 3 clinical trials in patients with UC.

Section 6: Adverse Events

- Revised to include adverse reactions that occurring during the phase 3 clinical trials in patients with UC to provide more detailed information to prescribers.
  - Induction (UC-1): nasopharyngitis (7% vs 4%).
  - Maintenance (UC-2): nasopharyngitis (24% vs 20%), headache (10% vs 4%), abdominal pain (7% vs 3%), influenza (6% vs 5%), fever (5% vs. 4%), diarrhea (4% vs 1%), sinusitis (4% vs 1%), fatigue (4% vs 2%), and nausea (3% vs 2%).

  Rationale: Although we acknowledge that abdominal pain could be related to the underlying disease, an imbalance was observed between ustekinumab and placebo, with abdominal pain being reported in a larger proportion of patients than placebo. We also acknowledge that upper abdominal pain is a different localization of pain from generalized abdominal pain, but we are not aware of evidence to support that patients in the trial were instructed on how to report abdominal pain based on its location. For example, some patients may have reported abdominal pain even if they were experiencing upper abdominal pain. Similarly, for influenza and fever, both met the criteria for occurring in at least 3% of patients and greater in ustekinumab than placebo. Ustekinumab has the ability to suppress the immune system and a small imbalance was observed between ustekinumab and placebo with a larger proportion of ustekinumab-treated patients experiencing these events compared to placebo.

- Although the specific types of nonmelanoma skin cancers are listed in the label under the psoriasis indication, the proportion of patients with nonmelanoma skin cancers in the UC (and CD) population was smaller compared to the proportion of patients in the psoriasis population with nonmelanoma skin cancers (1.5% of Stelara-treated patients with psoriasis versus 0.2% of patients with CD and 0.5% of patients with UC). Other malignancies reported during the phase 3 trials in patients with UC, including one patient with malignant melanoma, were associated with other confounding factors that made it difficult to establish causality to treatment with Stelara. Therefore, the specific types of malignancies that were reported during the UC trials are not described in the label.

Section 12.2: Pharmacodynamics

- Added language as per 21 CFR 201.571(12)(i)(B) which requires 'Exposure-response relationships (e.g., concentration-response, dose-response) and time course of pharmacodynamic response (including short-term clinical response) must be included if known. If this information is unknown, this subsection must contain a statement about the lack of information.' The following language was added:
  - In both study UC-1 (induction) and study UC-2 (maintenance), a positive relationship was observed between exposure and rates of clinical remission, clinical response, and endoscopic improvement. The response rate reached a plateau at the ustekinumab exposures associated with the recommended dosing regimen for maintenance treatment [*see Clinical Studies (14.5)*].

Section 12.3: Pharmacokinetics

- Updated the Population PK analysis to evaluate each concomitant medication as a time-dependent covariate on ustekinumab clearance, rather than the current analysis which appeared to pool them into one time-dependent covariate. The section was revised as follows:
  - In patients with Crohn's disease and ulcerative colitis, population pharmacokinetic analyses did not indicate changes in ustekinumab clearance with concomitant use of corticosteroids or immunomodulators (AZA, 6-MP, or MTX); and serum ustekinumab concentrations were not impacted by concomitant use of these medications.

Section 14: Clinical Studies

- Revised throughout Section 14 to reflect the results of efficacy analyses from the induction and maintenance trials using the FDA recommended endpoint definitions. Two tables, one for the induction and one for the maintenance trial, will describe the results of the primary and secondary endpoints:
  - Induction trial: clinical remission, endoscopic improvement, clinical response, and histologic-endoscopic mucosal improvement.
  - Maintenance trial: clinical remission, maintenance of clinical response at Week 44, endoscopic improvement, corticosteroid-free clinical remission, and maintenance of

clinical remission at Week 44 among patients who achieved clinical remission 8 weeks after induction.

– Rationale: We revised this section to reflect current FDA recommended endpoint definitions and the results of those analyses. We acknowledge that in previous communications we did not object to the endpoint definitions selected for these trials. We note that the trials were designed and initiated (June 2015) prior to the publication of the draft UC Guidance (August 2016) and our thinking was evolving. Since that time and in response to the comments we received on the 2016 draft Guidance, we have had additional internal discussions regarding endpoint selection. We recommended in several communications, including the pre-BLA meeting, that the Applicant also conduct additional analyses using the currently recommended endpoints for clinical trials evaluating therapies intended to treat UC, noting that any differences between the analyses using the pre-specified definitions and the currently recommended definitions would be a review issue.

Since the time these trials were designed, we have developed a clearer path forward for endpoint selection in clinical trials evaluating therapies for UC. The (b) (4) (b) (4) In this case, the label describes the results of endpoints that are recommended by the Division and being used/recommended for use across clinical trials for UC.

- The tables will also show subgroup analyses in patients who were biologic-naïve and those who had failed prior biologic therapy. The results of these subgroup analyses are clinically relevant to patients and prescribers.
- The results of other exploratory endpoints will be described in text under “other endpoints” including efficacy in the nonrandomized analysis population (week 16 responders to ustekinumab induction), histologic-endoscopic mucosal improvement at Week 44, and endoscopic normalization.
- The following statement will be included for the Week 8 and Week 44 endpoint of histologic-endoscopic improvement: The relationship of histologic-endoscopic mucosal improvement, as defined in UC-2, at Week 44 to progression of disease or long-term outcomes was not evaluated in UC-2.
  – Rationale: This is one of the first products for UC that will describe an endpoint that combines endoscopic and histologic data in the labeling. Because the scientific and regulatory knowledge is evolving regarding the endpoint definition for histologic outcomes and the long-term clinical relevance remains uncertain at this time, we recommend including this statement.

- Rationale: We considered the Applicant's rationale (b) (4) (b) (4) However, we recommended using the term "histologic-endoscopic mucosal improvement" for the following reasons.
  - (b) (4) . A description of the definition used for these analyses is included in the label (b) (4)
  - (b) (4) The degree of histologic inflammation may vary by location of the biopsies. (b) (4)

In addition to the review team and consultants, the labeling was also reviewed by the Division of Medication Error Prevention and Analysis, and the Office of Prescription Drug Promotion (OPDP). Their comments and recommendations have been incorporated into final labeling.

Other Prescription Drug Labeling

No revisions were proposed to the Instructions for Use and Medication Guide. The Medication Guide was revised to align with the revisions in Section 6 to the common adverse reactions.

12. Risk Evaluation and Mitigation Strategies

A risk evaluation and mitigation strategy is not recommended.

13. Postmarketing Requirements and Commitments

Refer to the Approval Letter for the final postmarketing requirement/commitment (PMR/PMC) language. The following PMR/PMCs are proposed.

Postmarketing Requirement

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 ulcerative colitis. The study's primary outcome is malignancy. Secondary outcomes include, but are not limited to, opportunistic infections (e.g., 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 prespecified 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.

The existing observational study in patients with Crohn's disease with the same objectives, may be amended to also enroll patients with ulcerative colitis.

Active Risk Identification and Analysis Sufficiency

The Division of Epidemiology I (DEPI) evaluated the sufficiency of Active Risk Identification and Analysis (ARIA) to track the risks of serious infection and malignancy in the UC population treated with ustekinumab. DEPI deemed ARIA not sufficient for identifying malignancy and is in agreement with issuing the PMR described above. For serious infections, DEPI determined ARIA to be sufficient and plans to conduct ARIA-directed analysis of serious infections in UC patients on ustekinumab. See DEPI memo, dated September 20, 2019 for full details.

Postmarketing Commitment—Pediatric Assessments

A one-year, randomized, controlled, blinded trial to evaluate the safety, efficacy, and pharmacokinetics of Stelara (ustekinumab) in pediatric patients 2 to 17 years of age with moderately severely active ulcerative colitis.

A multicenter, open-label extension study to evaluate the long-term safety of Stelara (ustekinumab) in pediatric patients 2 to 17 years of age with moderately severely active ulcerative colitis who participated in the one-year, randomized controlled efficacy and safety trial (PMC above).

Postmarketing Commitment—Clinical Pharmacology

Conduct a clinical trial to assess whether ustekinumab alters the metabolism or pharmacokinetics of cytochrome P450 (CYP) substrates in patients with UC treated with ustekinumab (e.g., using a cocktail of relevant CYP probe drugs). The ongoing trial in patients with Crohn's disease with the same objectives, may be amended to also enroll patients with ulcerative colitis.

14. Associate Division Director (DGIEP) Comments

I concur with the recommendation of the review team to approve supplemental BLA 761044/S-003 for Stelara (ustekinumab) for the treatment of adult patients with moderately to severely active ulcerative colitis (UC). Ustekinumab is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that is directed against the p40 subunit of interleukin (IL)-12 and IL-23 cytokines, which have been implicated as important contributors to the chronic inflammation in inflammatory bowel disease. Ustekinumab was approved in 2016 for the treatment of adult patients with moderately to severely active Crohn's disease, and it will be the first product in this class to be approved for use in patients with UC. The recommended dosage is a single intravenous infusion using weight-tiered induction dosing (~6 mg/kg), followed by a subcutaneous 90 mg dose (regardless of body weight) 8 weeks after the initial intravenous dose, then every 8 weeks thereafter. Data submitted in the sBLA support the conclusion that the benefits of treatment with ustekinumab in the intended population outweigh the identified risks.

I agree with the review team that data submitted in this sBLA are adequate to support a conclusion that the effectiveness of ustekinumab has been established in the intended adult population. The submission included two adequate and well-controlled trials (an 8-week 'induction' trial and a 44-week 'maintenance' trial), and both trials achieved statistical significance on the primary endpoint of clinical remission. Secondary endpoints also supported the primary efficacy analysis in both trials.

The risks associated with ustekinumab treatment in UC are generally comparable to those reported for approved indications, including Crohn's disease. The most common adverse reactions reported in clinical trials of patients with UC include nasopharyngitis, headache, abdominal pain, influenza, fever, diarrhea, sinusitis, fatigue, and nausea. Serious infections reported during clinical trials include gastroenteritis, ophthalmic herpes zoster, pneumonia, and listeriosis; these will be added to the Warnings and Precautions section of labeling. The known risk of serious infection with the use of ustekinumab will be monitored proactively in the Sentinel's Active Risk Identification and Analysis (ARIA) System. Because neither an analysis of spontaneous postmarketing adverse events nor the ARIA System will be sufficient to assess the known serious risks of malignancy and opportunistic infections, the Applicant will be required to conduct a long-term, postmarketing, observational study to assess these serious risks.

Ustekinumab has an orphan drug designation for UC and, therefore, the Applicant is exempt from Pediatric Research Equity Act (PREA) requirements. However, the Applicant agreed to conduct postmarketing commitment studies to assess 1) the safety, efficacy and pharmacokinetics of ustekinumab in pediatric patients 2 to 17 years of age with moderately to severely active UC, and 2) the long-term safety of ustekinumab in these pediatric patients. In addition, a clinical drug interaction study will be conducted to assess whether ustekinumab alters the metabolism or pharmacokinetics of cytochrome P450 substrates in patients with UC treated with ustekinumab.

15. Appendices

15.1. References

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15.2. Financial Disclosure

Table 26. Financial Interest Form for Covered Clinical Study: 3001

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 265		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 7		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the 7 could be influenced by the outcome of the study: _____ Significant payments of other sorts: 6 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator: 1 Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

In Table 26 above, seven investigators disclosed financial arrangements with the Applicant. Included in this table are financial arrangements for both the induction and maintenance studies of this single clinical trial (CNTO1275UC3001). Six of these arrangements were either payments attributed to research and educational support or speaking/consulting fees. The highest enrolling of these sites was Drs. (b) (6) and (b) (6), who each enrolled (b) (6) patients. Dr. (b) (6) received a research grant exceeding $25,000 to support patient care–related activities and did not directly receive payment from the Applicant. Dr. (b) (6) received $26,194 for participation in both an Advisory Board and as a Data Safety and Monitoring Board member, presumably being paid directly by the Applicant for his services. In conclusion, given the randomized, double-blind, placebo-controlled, multisite, parallel-dosing regimen, and the clinical trial design which enrolled patients from multiple sites resulting in pooled data, this reviewer does not conclude that the financial disclosures represent a significant effect on the outcome of the clinical trial.

Table 27. Investigators With Financial Disclosure Forms 3454 and 3455 for CNTO1275UCO3001

Investigator	Site	Number of Patients Enrolled	Category of Disclosure (From Form 3455)	Description of Disclosure (e.g., Speaker Fees)	Rationale or Steps Taken to Minimize Bias
(b) (6)	A96 (b) (6)	(b)	Significant payment of other sorts, such as a research grant, honoraria for speaking, etc.	This principal investigator received $98,428 primarily for advisory boards, training, and promotional speaker programs	Stelara for Ulcerative Colitis (CNTO1275UCO3001) was a randomized, double-blind, placebo-controlled, parallel-group clinical trial which consisted of multiple international sites. Dr. (b) (6) at a site in (b) (6) enrolled (b) (6) patients out of 931 patients in the induction study and 783 patients in the maintenance study.
(b) (6)	A96- (b) (6)	(b) (6)	Significant payment of other sorts, such as a research grant, honoraria for speaking, etc.	This was a subinvestigator who received $73,680 mainly for promotional speaker programs, advisory board participation, and miscellaneous payments	Stelara for Ulcerative Colitis (CNTO1275UCO3001) was a randomized, double-blind, placebo-controlled, parallel-group clinical trial which consisted of multiple international sites. Dr. (b) (6) at a site in (b) (6) enrolled (b) (6) patients out of 931 patients in the induction study and 783 patients in the maintenance study.
(b) (6)	A96- (b) (6)	(b)	Significant payment (as above)	This investigator was a principal investigator who received in excess of $25,000 as grant support for activities related to patient care	Stelara for Ulcerative Colitis (CNTO1275UCO3001) was a randomized, double-blind, placebo-controlled, parallel-group clinical trial which consisted of multiple international sites. Dr (b) (6) at a site in (b) (4) enrolled (b) (6) patients out of 931 patients in the induction study and 783 patients in the maintenance study.

Investigator	Site Number	Number of Patients Enrolled	Category of Disclosure (From Form 3455)	Description of Disclosure (e.g., Speaker Fees)	Rationale or Steps Taken to Minimize Bias
(b) (6)	A96- (b) (6)	(b) (6)	Significant payment (as above)	Dr. (b) (6) received $132,232 for his activities on an Applicant Advisory Board, promotional speaker programs, general consulting payments and other payments	Stelara for Ulcerative Colitis (CNTO1275UCO3001) was a randomized, double-blind, placebo-controlled, parallel-group clinical trial which consisted of multiple international sites. Dr. (b) (6) at a site in (b) (6) enrolled (b) (6) patient out of 931 patients in the induction study and 783 patients in the maintenance study.
(b) (6)	A96- (b) (6)	(b) (6)	Equity	Dr. (b) (6) owned an undisclosed amount of stock	(b) (6) enrolled (b) (6) patients in Stelara for Ulcerative Colitis (CNTO1275UCO3001)
(b) (6)	A96 (b) (6)	(b) (6)	Significant payment (as above)	Dr. (b) (6) was a principal investigator who received $205,619 for a research grant, consulting fees, and for speaker fees.	Stelara for Ulcerative Colitis (CNTO1275UCO3001) was a randomized, double-blind, placebo-controlled, parallel-group clinical trial which consisted of multiple international sites. Dr. (b) (6) at a site in in the (b) (6) (b) (6) enrolled (b) (6) patient out of 931 patients in the induction study and 783 patients in the maintenance study.

Investigator	Site Number	Number of Patients Enrolled	Category of Disclosure (From Form 3455)	Description of Disclosure (e.g., Speaker Fees)	Rationale or Steps Taken to Minimize Bias
(b) (6)	A96-(b) (6)	(b) (6)	Significant payment (as above)	Dr. (b) (6) received $26,194 for serving as an Advisory Board member and as a Data Safety and Monitoring Board member	Stelara for Ulcerative Colitis (CNTO1275UCO3001) was a randomized, double-blind, placebo-controlled, parallel-group clinical trial which consisted of multiple international sites. Dr. (b) (6) at a site in the (b) (6) (b) (6) enrolled (b) (6) patients out of 931 patients in the induction study and 783 patients in the maintenance study.

15.3. OCP Appendices (Technical documents supporting OCP recommendations)

15.3.1. Pharmacometric Review

15.3.1.1. Results of Applicant's Analysis

15.3.1.1.1. Population PK

Development of Final Population PK Model

The Applicant utilized 823 patients from study 3001 for their population PK assessment in patients with ulcerative colitis. Study 3001 and these data and sampling times are summarized in Table 28. Table 29 and Table 30 summarize the continuous and categorical patient characteristics of the patients evaluated in the population PK analysis.

Table 28. Overview of Trial and Data Included for Population PK Analysis

Study ID, Title, and Design	Brief Description of Analysis Data
CNTO1275UCO3001 A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study of Ustekinumab Induction Therapy in Subjects with Moderately to Severely Active Ulcerative Colitis **Induction Study** Population: Subjects with moderately to severely active UC who had an inadequate response to or were intolerant of either conventional or biologic therapy. Design: Induction Study (Week 0), randomized 1:1:1 as follows: • Placebo IV • Ustekinumab 130 mg IV • Weight-range-based ustekinumab doses approximating ustekinumab 6 mg/kg IV (~6 mg/kg) – 260 mg (weight ≤55 kg) – 390 mg (weight >55 kg but ≤85 kg) – 520 mg (weight >85 kg) Subjects who were in clinical response at Week 8 were eligible to enter the maintenance study. Subjects who were not in clinical response at Week 8 received ustekinumab as follows: (1) Subjects who were randomized to placebo at Week 0 received 1 dose of ustekinumab ~6 mg/kg IV plus placebo SC at Week 8.	Population PK analysis included data from 823 subjects who received at least one dose of ustekinumab and had at least one measurable serum ustekinumab concentration through maintenance Week 44 Enrollment: 961 subjects PK sampling For induction study, PK sampling at induction Weeks 0, 2, 4, 8, 16 and safety follow-up visit. Antibodies to ustekinumab sampling at induction Weeks 0, 4, 8 and 16 and safety follow-up visit. At study agent administration visits (ie, at induction Week 0 for all subjects and induction Week 8 for non-responders), blood samples for PK analysis were collected before the start of and approximately 60 minutes after completion of the infusion.

Study ID, Title, and Design	Brief Description of Analysis Data
(2) Subjects who were randomized to ustekinumab at Week 0 received 1 dose of ustekinumab 90 mg SC plus placebo IV at Week 8. At Week 16, subjects who were not in clinical response at Week 8 were re-evaluated for clinical response: (1) Subjects who achieved clinical response at Week 16 were eligible to enter the maintenance study. (2) Subjects who did not achieve clinical response at Week 16 would not enter the maintenance study and would have a safety follow-up visit approximately 20 weeks after their last administration of study agent	
Maintenance Study Population: Subjects with moderately to severely active UC who demonstrated a clinical response to induction treatment with IV ustekinumab	Enrollment: 523 subjects who achieved clinical response following IV induction were randomized to the maintenance therapy in a 1:1:1 ratio as the primary population. Additional 157 subjects (delayed responders) entered the maintenance study but were not randomized into the primary population
Design: Maintenance Study (Maintenance Week 0, ie, Induction Week 8 or Week 16) IV Induction responders to ustekinumab were to be randomized to receive: • Placebo SC • Ustekinumab 90 mg SC every 12 weeks (q12w) • Ustekinumab 90 mg SC every 8 weeks (q8w) Additional subjects entering the maintenance study included: (1) Subjects who were in clinical response to placebo IV induction received placebo SC (2) Subjects who were delayed responder to ustekinumab induction received ustekinumab 90 mg SC q8w.	PK sampling For maintenance study, PK sampling at maintenance Weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and early termination visit (and safety follow-up visit if available). Antibodies to ustekinumab sampling at maintenance Weeks 0, 4, 12, 24, 36, 44, and early termination visit (and safety follow-up visit if available). For maintenance Week 0, data from the study procedure performed at induction Week 8 or induction Week 16 visit were used.

Key: IV=intravenous; PK=pharmacokinetics; q8w=every 8 weeks; q12w=every 12 weeks; SC=subcutaneous; UC=ulcerative colitis.

Source: Applicant's Population PK Report, Table 1

Table 29. Characteristics of Patients Included in Population PK Analysis of Ustekinumab in Ulcerative Colitis; Continuous Covariates (n=823)

Characteristic	Value[a]
Age (years)	
Mean (SD)	41.5 (13.6)
Median	41
IQ	30-51
Range	18-84
Body Weight (kg)	
Mean (SD)	73.2 (17.7)
Median	71.2
IQ	60.4-83.6
Range	36.5-177.2
Baseline Creatinine Clearance (mL/min)	
Mean (SD)	115.5 (34.3)
Median	112.3
IQ	93.5- 131.8
Range	36.0- 425.2
Baseline Serum Albumin (g/dL)	
Mean (SD)	4.1 (0.4)
Median	4.1
IQ	3.9- 4.4
Range	2.3- 5.5
Baseline C-reactive Protein (mg/dL)	
Mean (SD)	10.7 (17.9)
Median	4.7
IQ	1.6-12.3
Range	0.1- 183
Baseline Alkaline Phosphatase (U/L)	
Mean (SD)	73.7 (32.9)
Median	67
IQ	56- 82
Range	9- 392
Baseline Platelets ($\times 10^3/uL$)	
Mean (SD)	345.8 (125.8)
Median	317
IQ	266-406
Range	71-1128

Baseline Fecal Lactoferrin (µg/g)	
Mean (SD)	291.0 (289.0)
Median	186.7
IQ	74.3- 417.8
Range	0.41- 1000
Baseline Fecal Calprotectin (mg/kg)	
Mean (SD)	2679.8 (4278.5)
Median	1392
IQ	659-2685
Range	15-36000
Baseline Mayo Score	
Mean (SD)	8.9 (1.6)
Median	9
IQ	8- 10
Range	5- 12
Disease Duration (year)	
Mean (SD)	8.0 (7.2)
Median	6.0
IQ	2.8- 11.1
Range	0.3- 54.1

Key: IQ=interquartile range; n=number of subjects; SD=standard deviation.
[a]Summary statistics were calculated after the imputation of missing values
Source: Applicant's Population PK Report, Table 2

Table 30. Characteristics of Patients Included in Population PK Analysis of Ustekinumab in Ulcerative Colitis; Categorical Covariates (n=823)

Characteristic	n (%)[a]
Age Category	
< 65 years old	780 (94.8%)
≥ 65 years old	43 (5.2%)
≥ 70 years old	20 (2.4%)
≥ 75 years old	6 (0.7%)
≥ 85 years old	0
Weight Category	
≥100kg	55 (6.7%)
<100kg	768 (93.3%)
Sex	
Male	499 (60.6%)
Female	324 (39.4%)
Race	
Caucasian	620 (75.3%)
Black	8 (1.0%)
Asian	127 (15.4%)
Other	68 (8.3%)
Japanese in Japan	
Japanese	97 (11.8%)
Non-Japanese	726 (88.2%)
Region	
Eastern Europe	312 (37.9%)
Asian	117 (14.2%)
Rest of the world	394 (47.9%)
Renal Function	
Normal (CRCL≥ 90 ml/min)	658 (80.0%)
Mild renal impairment (CRCL≥ 60, <90 ml/min)	141(17.1%)
Moderate renal impairment (CRCL≥ 30, <60 ml/min)	24 (2.9%)
Severe/end renal impairment (CRCL<30 ml/min)	0
Baseline extent of disease	
Extensive	378 (45.9%)
Limited	445 (54.1%)
Baseline endoscopic sub score	
Endoscopic sub score =2	241 (29.3%)
Endoscopic sub score =3	582 (70.7%)
Current Smoker	
Yes	44 (5.3%)
No	779 (94.7%)

Biologic-failure status	
Failed Biologics	431 (52.4%)
Not Failed Biologics	392 (47.6%)
Baseline Corticosteroids	
Receiving	365 (44.4%)
Not receiving	458 (55.6%)
Baseline Immunomodulator use	
Receiving Azathioprine, 6-mercaptopurine, or methotrexate at baseline	230 (28.0%)
Not receiving	593 (72.1%)
Antibodies to Ustekinumab	
Negative	778 (94.5%)
Positive	45 (5.5%)

Key: CRCL=creatinine clearance; n=number of subjects.
[a] Summary statistics were calculated after the imputation of missing values

Source: Applicant's Population PK Report, Table 3

The final structure model was determined to be a two-compartment linear PK model with first-order absorption and first-order elimination, parameterized in terms of CL, volume of distribution of the central compartment (V2), intercompartmental clearance (Q), volume of distribution of the peripheral compartment (V3), absorption rate constant (Ka), and F1.

For covariate selection, the Applicant used a full-model approach with backward elimination at the nominal 0.1% significance level. A full covariate model was initially developed using all statistically significant covariate of interest, as shown in Figure 4. Body weight on CL and V and Baseline Serum albumin had the most notable effects on ustekinumab clearance.

The Applicant's final population PK model is shown in Table 31. Shrinkage for eta(CL) is 4%. Relative standard errors of the structural estimates were also generally good with only one value exceeding 20% (body weight on Q). The goodness-of-fit plots for the model are shown in Figure 12 and indicate that for the majority of the concentration range the model captures the central tendency of the data.

Table 31. Parameter Estimates in Final Population PK Model for Ustekinumab in Patients With Ulcerative Colitis

Parameters[a]	Estimate[b]	95% CI[g]	Magnitude of Change[h]
CL (L/day) [c]	0.186 (1.68)	(0.179, 0.192)	--
BWT on CL	0.641 (7.52)	(0.553, 0.737)	-10.0% to +10.8%
BALB on CL	-1.64 (7.78)	(-1.91, -1.39)	+8.5% to -10.9%
SEX on CL	1.08 (2.12)	(1.04, 1.13)	+8.0%
IRPD on CL	1.14 (3.31)	(1.08, 1.21)	+14 %
Q (L/day)[d]	0.157 (10.2)	(0.121, 0.188)	--
BWT on Q	0.631 (41.2)	(0.154, 1.19)	-9.9% to +10.6%
V2 (L) [e]	3.01 (0.815)	(2.96, 3.07)	--
BWT on V2	0.592 (4.74)	(0.537, 0.651)	-9.3% to +9.9%
V3 (L)[f]	1.43 (3.39)	(1.31, 1.51)	--
BWT on V3	0.667 (16.4)	(0.473, 0.896)	-10.4% to +11.3%
K_a (1/day)	0.142 (3.88)	(0.127, 0.155)	--
F1	0.872 (1.46)	(0.845, 0.899)	--
IIV of V2 (CV%)	5.45% (40.3) [17.2][b]	(4.17%, 8.67%)	--
Covar (V2, CL)	0.0112 (21.2)	(0.00646, 0.0166)	--
IIV of CL (CV%)	27.5% (6.13) [4.03][b]	(25.8%, 29.3%)	--
Covar (V3, V2)	0.0114 (38.1)	(0.00216, 0.0261)	--
Covar (V3, CL)	-0.0186 (39.6)	(-0.0346, -0.00445)	--
IIV of V3 (CV%)	41.2% (20.0) [18.1][b]	(33.5%, 50.1%)	--
IIV of K_a (CV%)	52.2% (12.3) [33.5][b]	(45.6%, 58.4%)	--
Covar (F1, K_a)	-0.419 (13.9)	(-0.588, -0.279)	--
IIV of F1 (CV%)	130% (12.5) [31.6][b]	(114%, 144%)	--
Proportional residual error (CV%)	19.2% (2.62)	(18.2%, 20.0%)	--
Additive residual error (µg/mL)	0.0925 (21.3)	(0.0532, 0.138)	--

[a] BALB=baseline albumin in g/dL; BWT=baseline body weight in kilograms; CI=confidence interval; CL=clearance; F1=subcutaneous bioavailability; IIV=interindividual variability calculated as (variance)$^{1/2}$*100%; IRPD=immune response status over time (1=positive, 0=negative); K_a=first-order absorption rate constant; Q=inter-compartmental clearance; V2=volume of distribution of the central compartment; V3=volume of distribution of the peripheral compartment; SEX=sex (0= female, 1= male).

[b] Mean (RSE%) [Shrinkage %] estimates by NONMEM from the final PK analysis dataset.

[c] $CL\left(\frac{L}{day}\right) = CL\left(\frac{L}{day}\right) = 0.186 \times \left(\frac{BWT}{71.2}\right)^{0.641} \times \left(\frac{BALB}{4.1}\right)^{-1.64} \times 1.08^{SEX} \times 1.14^{IRPD}$

[d] $Q\left(\frac{L}{day}\right) = 0.157 \times \left(\frac{BWT}{71.2}\right)^{0.631}$

[e] $V2(L) = 3.01 \times \left(\frac{BWT}{71.2}\right)^{0.592}$

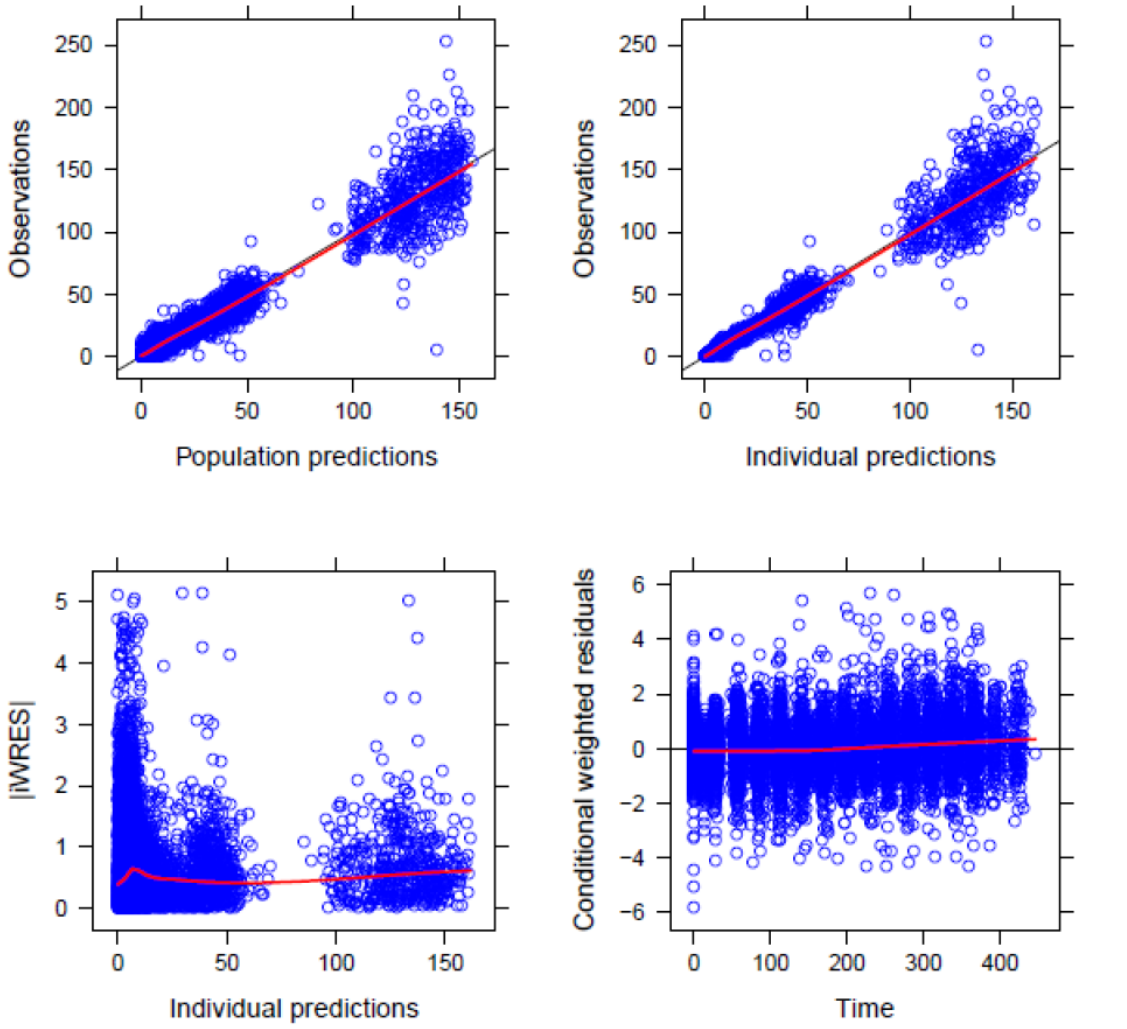
[f] $V3(L) = 1.43 \times \left(\frac{BWT}{71.2}\right)^{0.667}$

[g] 95% CI was obtained from 1000 bootstrap runs implemented in PsN.

[h] The magnitude of change in the parameter estimate caused by a continuous covariate was expressed as a range, ie, % change from the median value when the covariate factor varied from 25th percentile to 75th percentile of the population.

Source: Applicant's Population PK Report, Table 5

Figure 12. Basic Goodness-of-Fit Plots for Final Population PK Model



The black solid line is the line of identity or the zero line, and the red solid line is the trend line. The blue circles are the observations.
Units: Observations or predictions=µg/ml; Time=day.
Key: |iWRES|=absolute individual weighted residuals.
Source: Applicant's Population PK Report, Figure 2

Applicant's Simulation of Exposures for Proposed Dosing Regimens

The Applicant applied the final population model PK to simulate concentration time profiles for the studied body weight-based dosing regimen (proposed) and 130 mg fixed dose regimen.

Figure 13 shows the simulated median ustekinumab serum concentration-time profile following IV ustekinumab induction treatment at Week 0 and SC ustekinumab maintenance treatment from Week 8 and beyond. The upper panel displays the profiles by maintenance dose regimens (i.e., 90 mg SC Q8W and Q12W) for the 130 mg IV induction dose and aggregated by the ~6 mg/kg IV induction dose. The lower panel displays the profiles by maintenance dose regimens for the 130 mg IV induction dose and the various weight-range based IV induction dose levels, i.e., 260 mg (weight ≤55 kg), 390 mg (weight >55 kg but ≤85 kg), and 520 mg (weight >85 kg).

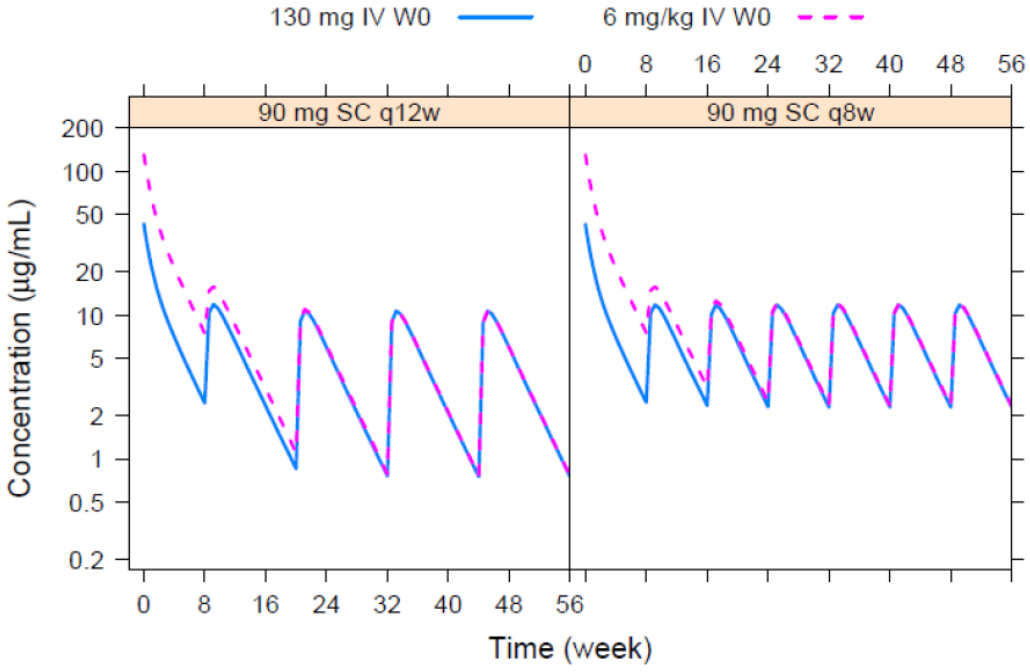
Figure 14 shows the predicted ustekinumab PK metrics during the induction and maintenance studies, respectively, including ustekinumab trough levels at Week 8 ($C_{trough,w8}$), areas under the curve up to Week 8 (AUC_{0-8w}), steady-state trough ($C_{ss,trough}$) and average ($C_{ss,ave}$) concentrations during dosing interval.

As shown in Figure 14, steady-state of serum ustekinumab concentrations for the maintenance study would be achieved by the start of the second maintenance dose following ustekinumab induction and maintenance treatment. The influence of a single IV induction dose on the concentration profile appears to have been washed out by the time of the second maintenance dose. Pharmacokinetic simulations suggest that for the ~6 mg/kg treatment group, ustekinumab exposure during induction ($C_{trough,w8}$ and AUC_{0-8w}) increased slightly as absolute induction doses increased (Figure 5). With respect to maintenance, patients with lower body weights tended to have higher serum steady-state ustekinumab exposures ($C_{ss,trough}$ and $C_{ss,ave}$) (Figure 14).

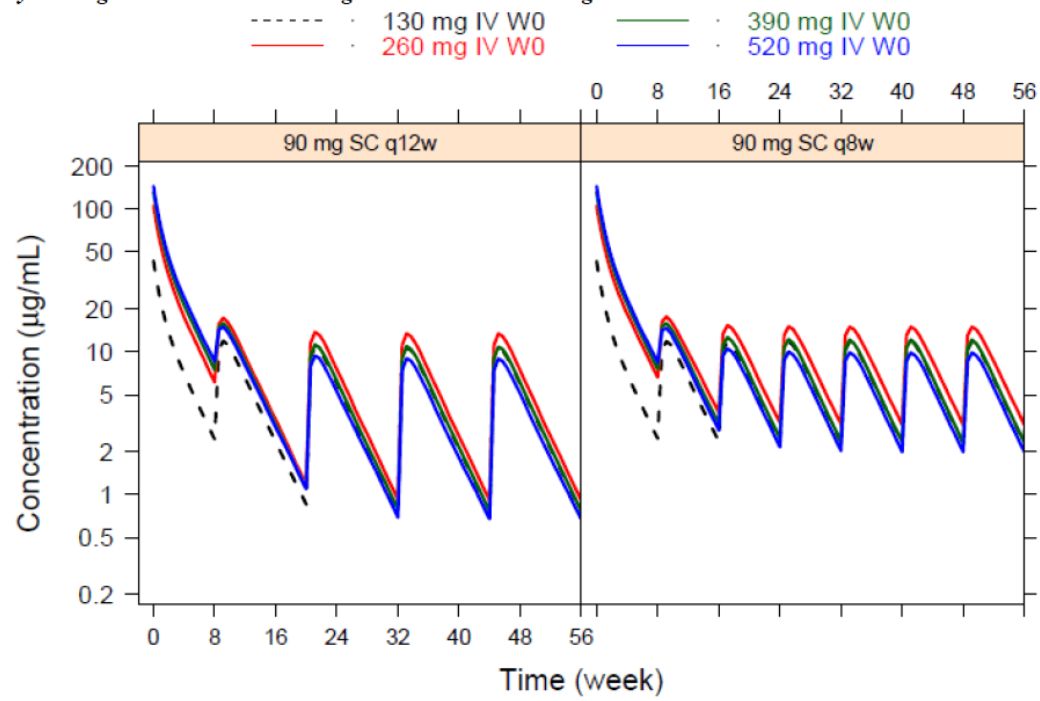
Patients who receive ustekinumab 90 mg SC Q12W are predicted to have 67% lower median steady-state trough concentrations and 33% lower median steady-state average concentrations compared to patients who receive ustekinumab 90 mg SC Q8W.

Figure 13. Predicted Median Concentration-Time Profiles for Induction and Maintenance Treatment of Ustekinumab by Dosing Regimen

By 130 mg IV and ~ 6 mg/kg IV Induction Dose Regimen



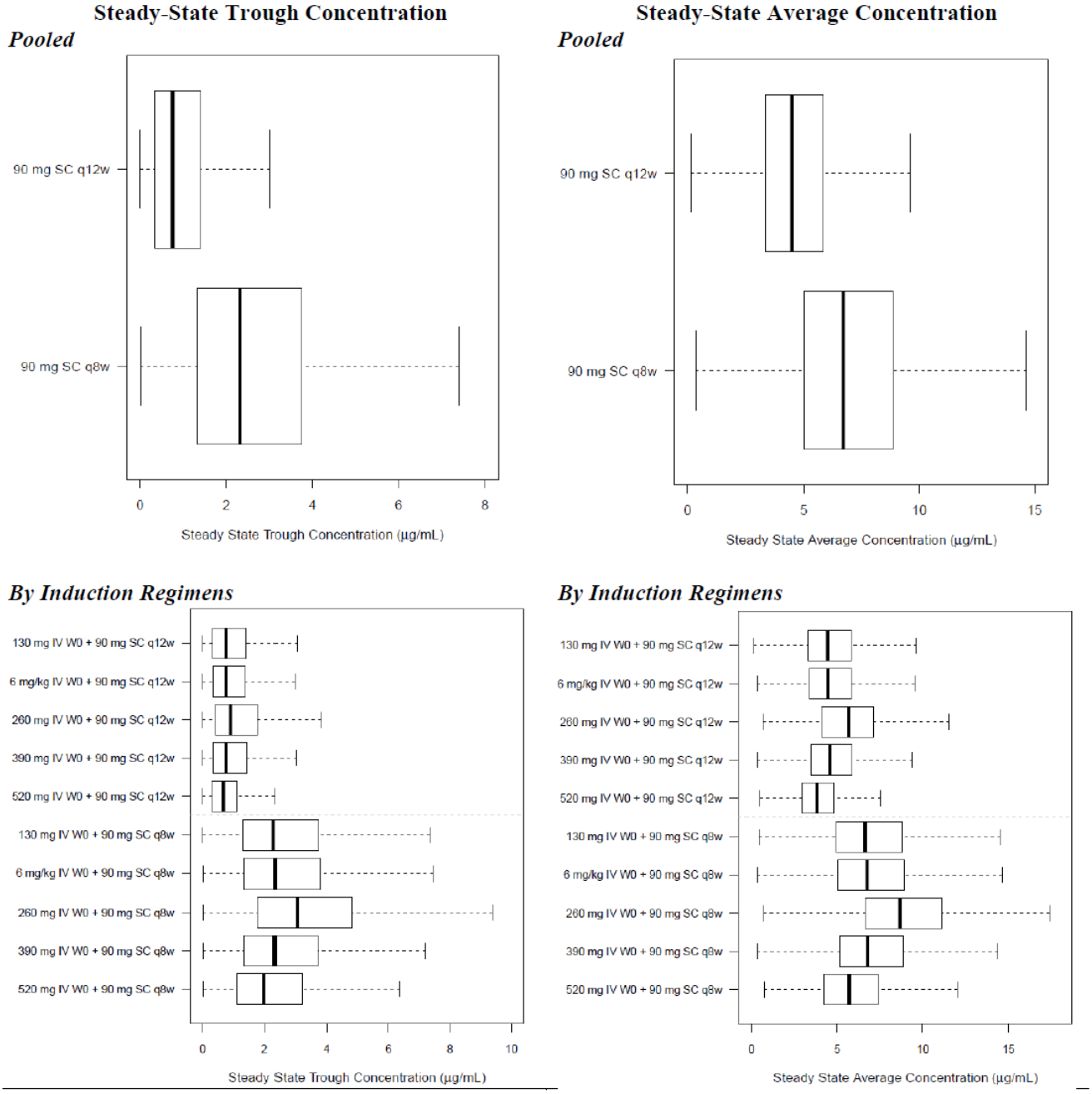
By 130 mg IV and 260/390/520 mg IV Induction Dose Regimen



Simulations were conducted using the final population pharmacokinetic model (n=5,000).
Key: IV=intravenous; q8w=every 8 weeks; q12w=every 12 weeks; SC=subcutaneous.

Source: Applicant's Population PK Report, Figure 5)

Figure 14. Simulated Ustekinumab Concentrations at Steady-State in Maintenance Study



Simulations were conducted using the final population pharmacokinetic model (n= 5,000).
Key: IV=intravenous; q8w=every 8 weeks; q12w=every 12 weeks; SC=subcutaneous.

Source: Applicant's Population Pharmacokinetic-Pharmacodynamic Report, Figure 7

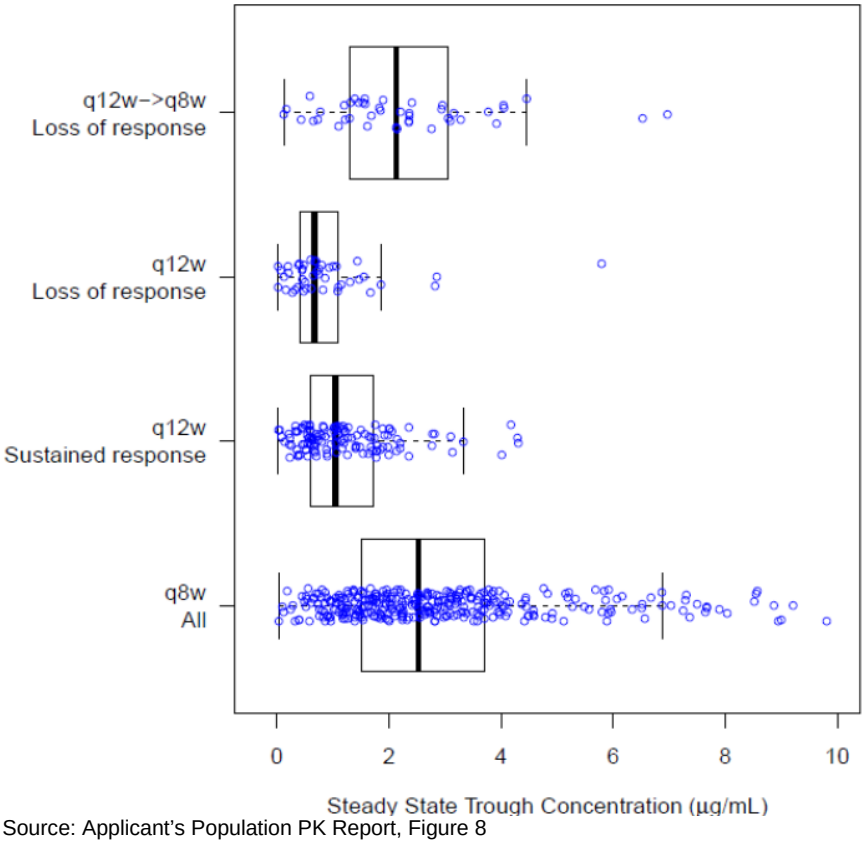
Simulation of Exposures for Patients Who Lost Clinical Response

Figure 15 shows the predicted ustekinumab steady-state trough concentrations for patients who received the 90 mg SC Q12W maintenance regimen and had a loss of clinical response during the maintenance study. For these patients, two dose regimens were used for simulation, 90 mg SC Q12W and 90 mg SC Q8W. Predicted steady-state trough ustekinumab concentrations for patients who had sustained clinical response while receiving

the 90 mg SC Q8W maintenance or 90 mg SC Q12W regimen were also included for comparison purpose.

Among patients who received 90 mg SC Q12W, those who experienced loss of response tended to have a lower median steady-state serum trough concentration compared to those with a sustained clinical response (0.67 µg/mL versus 1.05 µg/mL, respectively; a difference of approximately 36%). If the dose regimen for the patients who experienced loss of response on 90 mg Q12W was adjusted to 90 mg SC Q8W, their model predicted serum trough concentrations would increase about 3-fold from 0.67 µg/mL to 2.1 µg/mL, which is close to the median ustekinumab concentration observed in those receiving 90 mg Q8W initially.

Figure 15. Effects of Decreased in Dosing Interval for Maintenance Treatment on Steady-State Trough Concentrations of Ustekinumab for Patients Who Experienced Loss of Clinical Response



Source: Applicant's Population PK Report, Figure 8

Reviewer's Comments on Population PK

The Applicant 's final population PK model appears to capture the central tendency of the data with reasonable precision. Thus, the model is acceptable for labeling purposes and the generation of individual post hoc exposure estimates for exposure-response analysis. Further the Applicant 's simulations based on the final model are reasonable and support body-weight based dosing during the induction phase. The subgroup analysis for exposure in patients who lost response during the maintenance phase appears to initially support the 90 mg SC Q8W regimen.

The Applicant revised their population PK analysis for DDIs with concomitant immunomodulators per the Agency's request to use a time-dependent covariate for each concomitant immunomodulator. Their updated results indicate no significant change in

objective function and less than 10% change in clearance compared to the previous final model. For each concomitant immunomodulator, PK data are available from a sufficient number of subjects to support this evaluation. The updated results were presented in their response to the FDA's label edits dated 10/8/2019. We agree with their conclusions which supports the labeling of no interaction via population PK assessment for these immunomodulators in Section 12.3.

15.3.1.1.2. Exposure-Response for Efficacy

The Applicant performed exposure-efficacy analyses for clinical response, clinical remission, and histologic-endoscopic improvement ("mucosal healing") at Weeks 8, 16, and 44. For clinical remission and clinical response they provided analyses for both the global and U.S. definitions. In this report we focus on the U.S. definitions for Week 8 of induction and Week 44 of maintenance.

A total of 958 patients from study 3001 (both induction and maintenance) are included in the final dataset. Table 32 and Table 33 summarize exposure metrics stratified by dose groups in the induction Week 8 E-R analyses (Table 32), and maintenance Week 44 analyses (Table 33).

Table 32. Descriptive Statistics of Exposure Metrics of Induction Week 8 Analysis

	Week 8 trough concentration			$AUC_{0\text{-}8w}$		
	Placebo	130 mg	~6 mg/kg	Placebo	130 mg	~6 mg/kg
N	319	320	319	319	320	319
Mean (SD)	0 (0)	2.6 (1.59)	8.18 (4.9)	0 (0)	603 (155)	1800 (454)
Median	0	2.44	7.52	0	596	1790
IQ	0 - 0	1.41 - 3.34	4.48 - 10.9	0 - 0	491 - 696	1490 - 2110
Range	0 - 0	0.057 - 9.85	0.0811 - 24.7	0 - 0	205 - 1110	532 - 2980

Key: IQR=inter-quartile range; N= number of observed concentrations; SD=standard deviation

Source: Applicant's Population Pharmacokinetic-Pharmacodynamic Report, Table 4

Table 33. Descriptive Statistics of Exposure Metrics of Maintenance Week 44 Analysis

	Week 44 Steady-state trough concentration		
	Placebo	90 mg SC q12w	90 mg SC q8w
N	175	171	175
Mean (SD)	0 (0)	1.16 (0.917)	3.21 (2)
Median	0	0.906	2.82
IQ	0 - 0	0.529 - 1.6	1.75 - 4.06
Range	0 - 0	0.0164 - 5.76	0.0965 - 9.26

Key: IQR=inter-quartile range; N=number of observed concentrations; SD=standard deviation; SC=subcutaneous.

Source: Applicant's Population Pharmacokinetic-Pharmacodynamic Report, Table 6

For the majority of E-R relationships evaluated a positive relationship was identified for both C_{trough} and AUC. These modes are summarized in Table 34.

A summary of the significant covariates and the affected model parameters, along with the associated decrease in objective function value between the base and final models with the inclusion of covariates, is presented in Table 34. Biologic-failure status, Mayo score, and

remission at randomization status were the only significant covariates in some of the E-R models; in most instances, these covariates typically influenced the intercept parameter.

Table 34. Summary of Base and Final Models for Exposure-Response Analysis

	Analysis	Significant covariates	ΔOBJV
Induction Week8 (N=958)			
	C8 vs RESP8	NA	NA
	$AUC_{0\text{-}8w}$ vs RESP8	NA	NA
	C8 vs RMGL8	β_0~IBMAY, FBIO; E_{max}~FBIO	52.3
	$AUC_{0\text{-}8w}$ vs RMGL8	β_0~IBMAY, FBIO; E_{max}~FBIO	53.4
	C8 vs RMUS8	β_0~IBMAY, FBIO	54.2
	$AUC_{0\text{-}8w}$ vs RMUS8	β_0~IBMAY, FBIO	61.4
	C8 vs MUCO8	β_0~IBMAY, FBIO	74.7
	$AUC_{0\text{-}8w}$ vs MUCO8	β_0~IBMAY, FBIO	82.3
Induction Week16 (N=233)			
	C16 vs RESP16	β_0~FBIO	20.7
	$AUC_{0\text{-}16w}$ vs RESP16	β_0~FBIO	21.6
Maintenance Week44 (N=521)			
	CSS vs RMGL44	β_0~RMRAN	32.7
	CSS vs RMUS44	β_0~RMRAN	34.7
	CSS vs RESP44	β_0~FBIO	13.2
	CSS vs MUCO44	β_0~ RMRAN, FBIO	33.3

Key: RMGL8, RMGL44=clinical remission (global definition) at induction Week 8, or at maintenance Week 44; RMUS8, RMUS44=clinical remission (US definition) at induction Week 8, or at maintenance Week 44; RESP8, RESP16, RESP44=clinical response at induction Week 8, at induction Week 16, or at maintenance Week 44; MUCO8, MUCO44=endoscopic healing at induction Week 8, or at maintenance Week 44; C8, C16, CSS=ustekinumab concentration at induction Week 8, induction Week 16, or steady-state trough ustekinumab concentration prior to maintenance Week 44; $AUC_{0\text{-}8w}$, $AUC_{0\text{-}16w}$,= area under the ustekinumab concentration time curve from Week 0 to Week 8, or from Week 0 to Week 16; IBMAY=Baseline Mayo score; FBIO=Biologics failure status; RMRAN= Remission status at randomization; NA=not available; vs=versus.

Source: Applicant's Population Pharmacokinetic-Pharmacodynamic Report, Table 9

Exposure-Response for Induction Phase

Clinical remission at Week 8

The Applicant 's parameter estimates for the model relating ustekinumab concentrations at Week 8 and clinical remission at Week 8 are shown in Table 35. The exposure-response relationship and observed rates of response for each exposure quartile are shown in Figure 1 stratified by biologics failure status (left and right panels) and baseline mayo score grouping (red and blue symbols and lines).

Table 35. Parameter Estimates of Exposure-Response Model Relating Ustekinumab Concentration at Week 8 and Clinical Remission at Week 8

Remission Definition		Intercept	IBMAY on Intercept	FBIO on Intercept	E_{max}	FBIO* on E_{max}	EC_{50}
Global	Estimate (RSE%)	-4.82 (15%)	-3.05 19%)	2.31 (31%)	3.95 (21%)	-0.692 (17%)	1.71 (60%)
US	Estimate (RSE%)	-3.44 (7%)	-3.21 (17%)	0.728 (28%)	2.27 (21%)	--	3 (60%)

* The biologic failure subgroup was treated as the reference group.
Source: Applicant's Population Pharmacokinetic-Pharmacodynamic Report, Table 12
Abbreviations: EC_{50} = 50% maximal effective concentration; E_{max} = maximum effective concentration; FBIO = biologics failure status; IBMAY = baseline Mayo score; RSE = relative standard error

Clinical response at Week 8

The parameter estimates of the E-R model for the relationship between ustekinumab concentration at Week 8 and clinical response at Week 8 are provided in Table 36, while the goodness-of-fit plot showing a positive E-R relationship between these variables is presented in Figure 16.

No covariate was significantly associated with the E-R relationship for the clinical response endpoint at Week 8 per the objective function value (OFV) criteria suggesting that this E-R relationship is similar between the subgroups evaluated in this induction E-R analyses (e.g., biologic failure and biologic nonfailure subgroups). The proportion of patients achieving clinical response was numerically higher in the biologic nonfailure subgroup compared with the biologic-failure subgroup. The inclusion of biologic-failure status on the intercept parameter resulted in an OFV decrease of 7.6, which is nominally significant but did not reach the preset criteria for covariate inclusion (ΔOFV of 10.83).

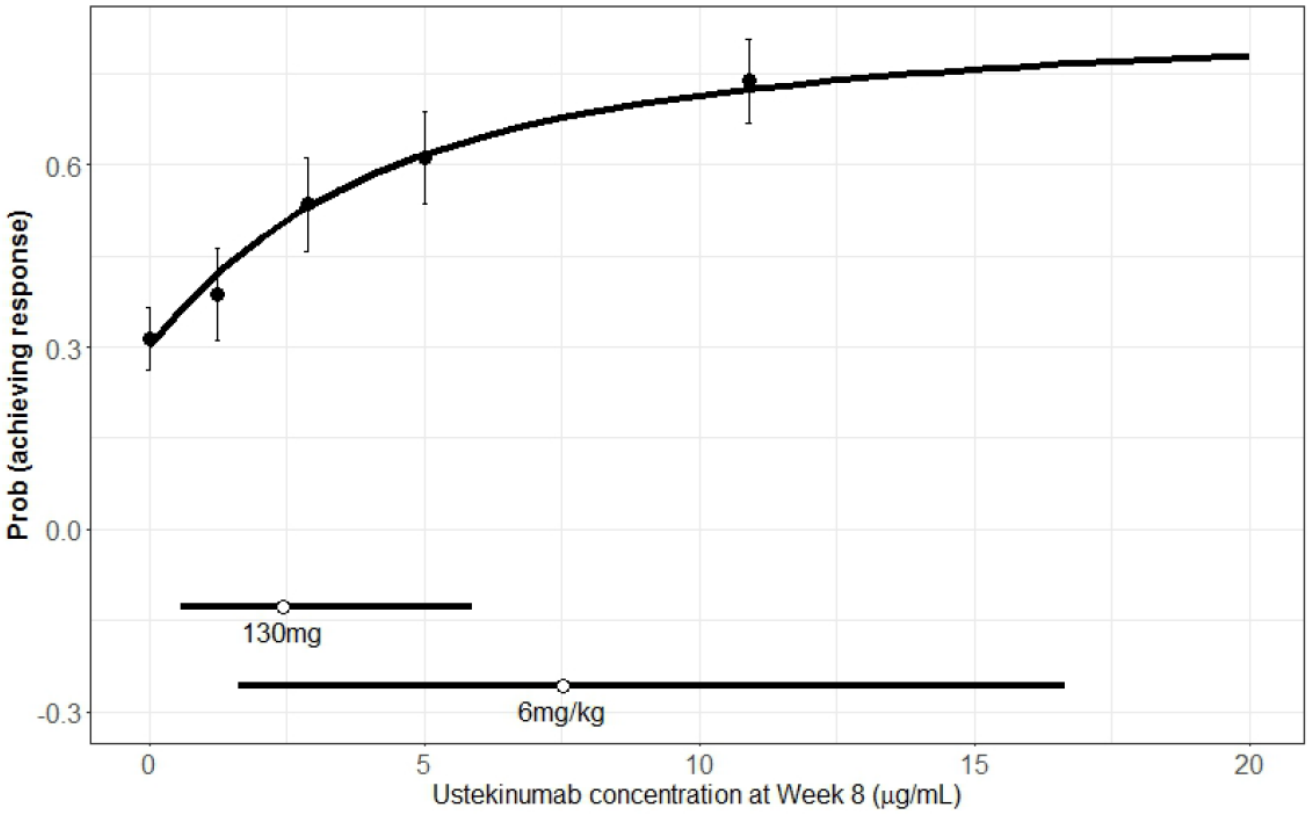
The results of the E-R analyses for the relationship between $AUC_{0\text{-}8w}$ as the exposure metric and clinical response at Week 8 as the efficacy outcome were similar to those reported with concentration at Week 8 as the exposure metric.

Table 36. Parameter Estimates of Exposure-Response Model Relating Ustekinumab Concentration at Week 8 and Clinical Response at Week 8

	Intercept	E_{max}	EC_{50}
Estimate (RSE%)	-0.838 (14%)	2.63 (19%)	5.02 (43%)

Source: Applicant's Population Pharmacokinetic-Pharmacodynamic Report, Table 10
Abbreviations: EC_{50} = 50% maximal effective concentration; E_{max} = maximum effective concentration; RSE = relative standard error

Figure 16. Goodness-of-fit Plot for the Induction Exposure-response Model Relating Ustekinumab Concentration at Week 8 and Clinical Response at Week 8



The solid line curve represents the model-predicted probabilities of achieving clinical response by ustekinumab concentration at Week 8. The dark circle symbols represent observed clinical response rate in the placebo group (corresponding to zero concentration) and in each ustekinumab concentration quartile bin plotted at the median ustekinumab concentration for each bin. The vertical bars on each diamond symbol represent the 95% confidence intervals of the observed rates of clinical response based on the binomial distribution. The solid line segments at the bottom of the chart show the 5th and 95th percentiles of predicted concentrations at Week 8 with the open circles on the line segments plotted at the median values, for the 130 mg IV and ~6 mg/kg IV dose groups, respectively.

(Source: Applicant's Population Pharmacokinetic-Pharmacodynamic Report, Figure 1)

Histologic-endoscopic improvement ("Mucosal healing") at Week 8

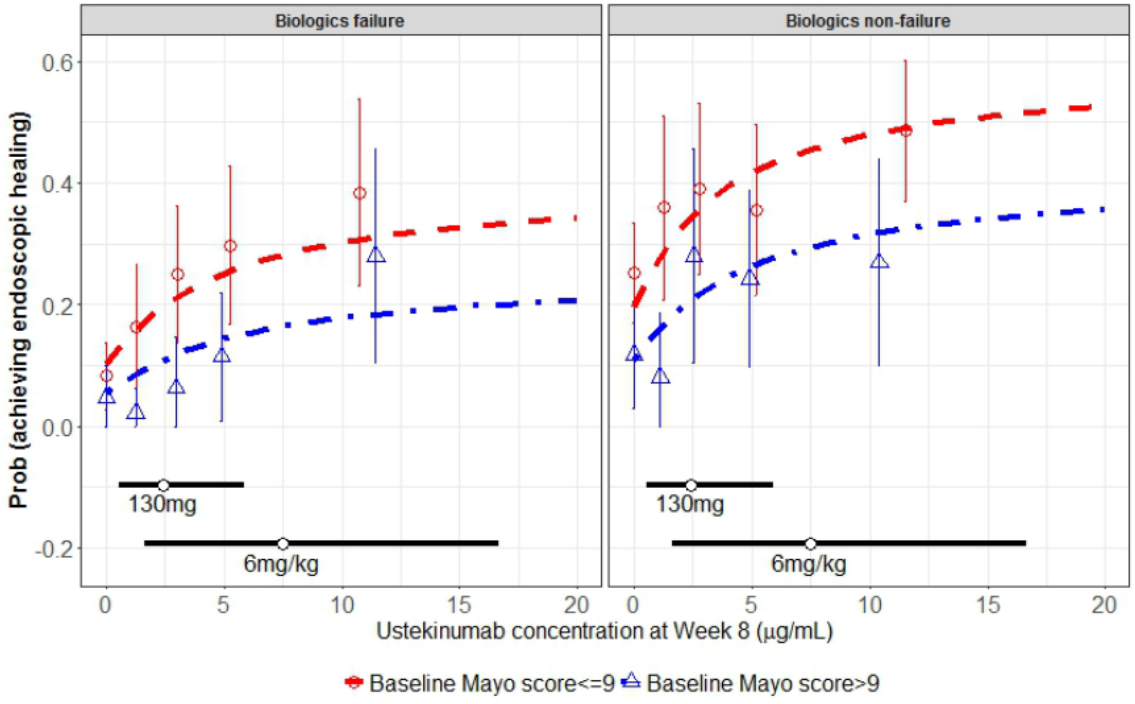
The Applicant 's parameter estimates for the model relating ustekinumab concentrations at Week 8 and "mucosal healing" at Week 8 are shown in Table 37. The exposure-response relationship and observed rates of response for each exposure quartile are shown in Figure 17 stratified by biologics failure status (left and right panels) and baseline mayo score grouping (red and blue symbols and lines).

Table 37. Parameter Estimates of Exposure-Response Model Relating Ustekinumab Concentration at Week 8 and Endoscopic Healing at Week 8

	Intercept	IBMAY on Intercept	FBIO* on Intercept	E_{max}	EC_{50}
Estimate (RSE%)	-2.53 (8%)	-3.11 (14%)	0.756 (22%)	1.75 (27%)	3.19 (84%)

* The biologic-failure subgroup was treated as the reference group.
Source: Applicant's Population Pharmacokinetic-Pharmacodynamic Report, Table 15
Abbreviations: EC_{50} = 50% maximal effective concentration; E_{max} = maximum effective concentration; FBIO = biologics failure status; IBMAY = baseline Mayo score; RSE = relative standard error

Figure 17. Plot for Induction Exposure-Response Relating Ustekinumab Concentration at Week 8 and Endoscopic Healing at Week 8; Stratified by Biologic Failure Status



The curves represent model-predicted probabilities of endoscopic healing at Week 8 by ustekinumab concentration at Week 8 (dashed curve for the subgroup with baseline Mayo score ≤9, and dash-dot curve for the subgroup with baseline Mayo score >9). The symbols represent observed endoscopic healing rate in each quartile bin plotted at the median ustekinumab concentration for each bin (open circle for the subgroup with baseline Mayo score ≤9, and open triangles for the subgroup with baseline Mayo score >9). The vertical bars on each symbol represent the 95% confidence intervals of the observed rates of endoscopic healing based on the binomial distribution. The solid line segments at the bottom of the chart show the 5th and 95th percentiles of predicted concentrations at Week 16 with the open circles on the line segments plotted at the median values, for the 130 mg IV and ~6 mg/kg IV dose groups, respectively.

Source: Applicant's Population Pharmacokinetic-Pharmacodynamic Report, Figure 3

Reviewer's Comments on Week 8 Exposure-Response for Efficacy

There appear to be exposure-efficacy relationships for clinical response, clinical remission and "mucosal healing" at Week 8 while accounting for patient characteristics such as biologics failure status and baseline mayo score. Of importance is the concentration range for the ~6 mg/kg regimen yields exposures that are 2-4 fold higher than the 130 mg regimen and

fall mostly in the plateau of response for these endpoints. This suggests the ~6 mg/kg body weight-tiered based regimen gives more effective exposures compared to the 130-mg dose.

Exposure-Response for Maintenance Phase Endpoints

Clinical remission at Week 44

The parameter estimates for the final E-R model relating ustekinumab concentration at steady-state and clinical remission at Week 44 are provided for the global and U.S. definitions of remission in Table 38. The goodness-of-fit plot showing positive E-R relationships between these variables is presented for the U.S. definition of clinical remission in Figure 2.

Table 38. Parameter Estimates of Exposure-Response Model Relating Steady-State Trough Ustekinumab Concentration and Clinical Remission at Week 44

Remission Definition		Intercept	RMRAN* on Intercept	E_{max}	EC_{50}
Global	Estimate	-1.67	1.19	1.68	0.951
	(RSE%)	(12%)	(18%)	(23%)	(58%)
US	Estimate	-1.63	1.21	1.37	0.589
	(RSE%)	(12%)	(17%)	(22%)	(61%)

*The subgroup of subjects who did not achieve remission at randomization was treated as the reference group.

Source: Applicant's Population Pharmacokinetic-Pharmacodynamic Report, Table 19
Abbreviations: EC_{50} = 50% maximal effective concentration; E_{max} = maximum effective concentration; RSE = relative standard error

Clinical response at Week 44

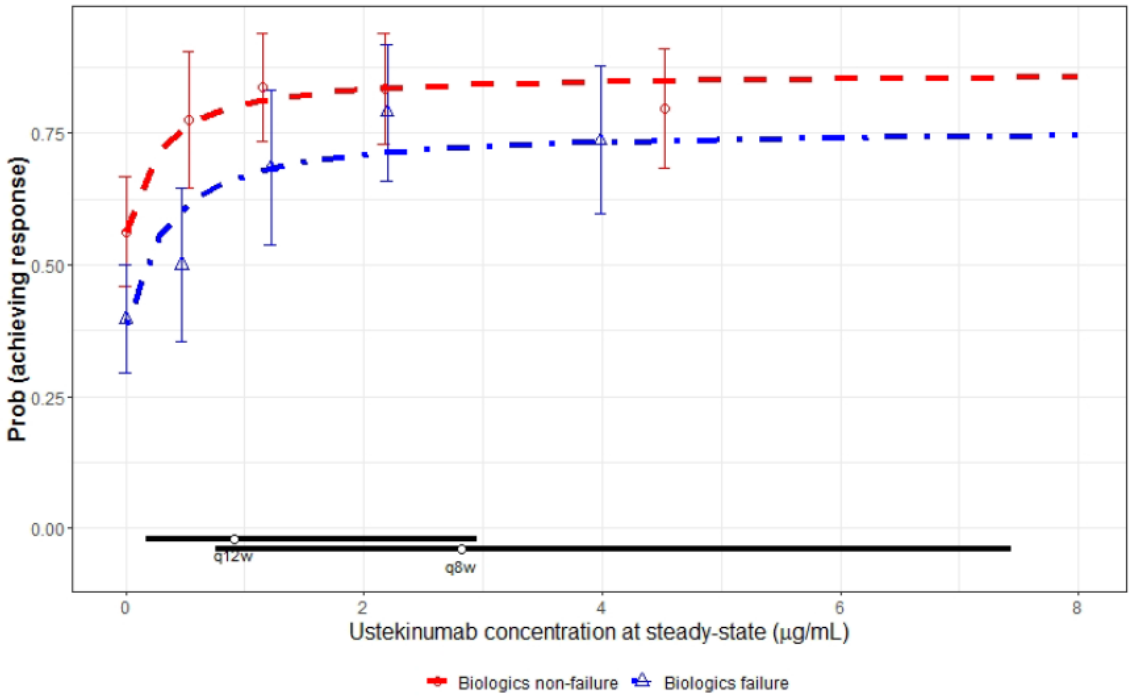
The Applicant 's parameter estimates for the model relating ustekinumab concentrations at steady-state and clinical response at Week 44 are shown in Table 39. The exposure-response relationship and observed rates of response for each exposure quartile are shown in Figure 18 stratified by biologics failure status (left and right panels) and baseline mayo score grouping (red and blue symbols and lines).

Table 39. Parameter Estimates of Exposure-Response Model Relating Steady-State Trough Ustekinumab Concentration and Clinical Response at Week 44

	Intercept	FBIO on Intercept	E_{max}	EC_{50}
Estimate (RSE%)	0.248 (72%)	-0.706 (28%)	1.6 (19%)	0.374 (58%)

*The subgroup of biologic non-failure subjects was treated as the reference group.
Source: Applicant's Population Pharmacokinetic-Pharmacodynamic Report, Table 24
Abbreviations: EC_{50} = 50% maximal effective concentration; E_{max} = maximum effective concentration; FBIO = biologics failure status; RSE = relative standard error

Figure 18. Plot for Maintenance Exposure-Response Model Relating Ustekinumab Concentration at Steady-State and Clinical Response at Week 44; Stratified by Biologic-Failure Status



The curves represent model-predicted probabilities of clinical response at Week 44 by steady-state trough ustekinumab concentration (dashed curve for the biologic non-failure subgroup and dashed-dot curve biologic-failure subgroup). The symbols represent the observed clinical response rate in the placebo group (corresponding to zero concentration) and in each quartile bin plotted at the median ustekinumab concentration for each bin (open circle for the biologics non-failure subgroup and open triangle for the biologic-failure subgroup). The vertical bars on each symbol represent the 95% confidence intervals of the observed rates of clinical response based on the binomial distribution. The solid line segments at the bottom of the chart show the 5th and 95th percentiles of predicted steady-state trough concentrations with the open circle on the line segment plotted at the median value, for the 90 mg 12w dose group and the 90 mg q8w dose group.

Source: Applicant's Population Pharmacokinetic-Pharmacodynamic Report, Figure 7

Histologic-endoscopic improvement ("Mucosal healing") at Week 44

The Applicant 's parameter estimates for the model relating ustekinumab concentrations at steady-state and "mucosal healing" at Week 44 are shown in Table 40. The exposure-response relationship and observed rates of response for each exposure quartile are shown in Figure 19 stratified by biologics failure status (left and right panels) and remission at randomization status (red and blue symbols and lines).

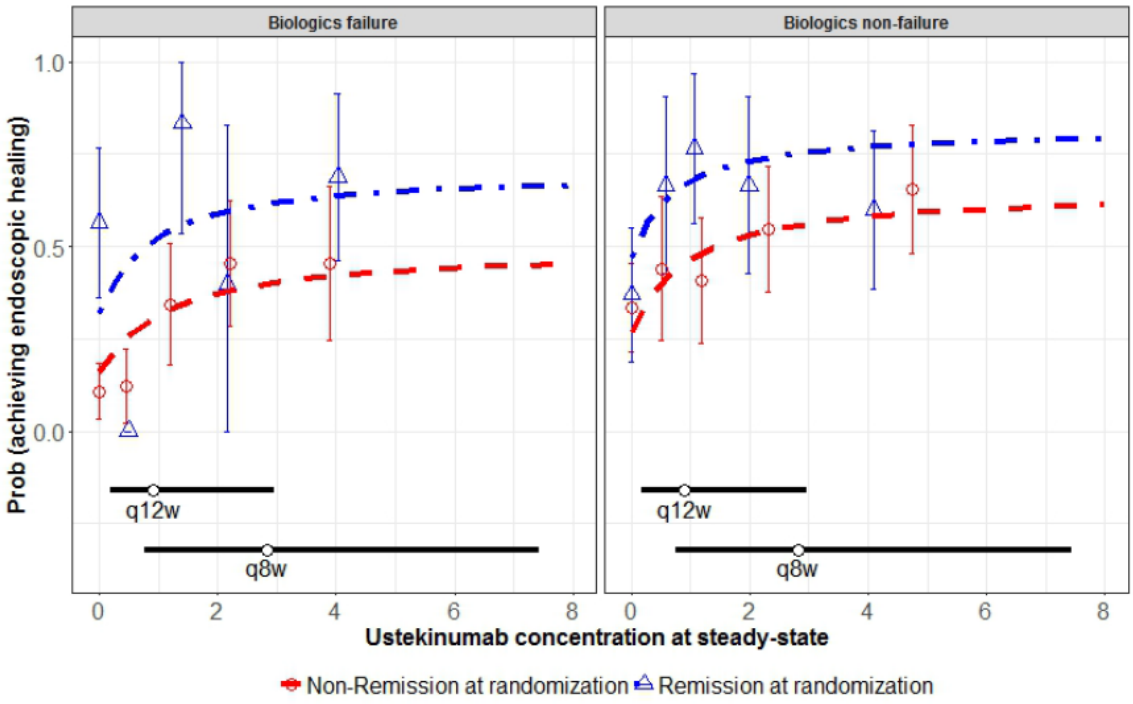
Table 40. Parameter Estimates of Exposure-Response Model Relating Steady-State Trough Ustekinumab Concentration and Endoscopic Healing at Week 44

	Intercept	FBIO* on Intercept	RMRAN* on Intercept	E_{max}	EC_{50}
Estimate (RSE%)	-0.998 (20%)	-0.645 (30%)	-0.88 (24%)	1.61 (22%)	0.875 (58%)

*The biologic non-failure subgroup was treated as the reference group; the subgroup of subjects who did not achieve remission at maintenance randomization was treated as the reference group.

Source: Applicant's Population Pharmacokinetic-Pharmacodynamic Report, Table 22
Abbreviations: EC_{50} = 50% maximal effective concentration; E_{max} = maximum effective concentration; FBIO = biologics failure status; RSE = relative standard error

Figure 19. Plot for Maintenance Exposure-Response Model Relating Ustekinumab Concentration at Steady-State and Endoscopic Healing at Week 44; Stratified by Biologic-Failure Status and Remission Status at Randomization



The curves represent model-predicted probabilities of endoscopic healing at Week 44 by steady-state trough ustekinumab concentration (dashed-dot curve for those in remission at randomization and dashed curve for those not in remission at randomization). The symbols represent the observed clinical remission rate in the placebo group (corresponding to zero concentration) and in each quartile bin plotted at the median ustekinumab concentration for each bin (open triangle for the subgroup of subjects in remission at randomization and open circle for the subgroup of subjects not in remission at randomization). The vertical bars on each symbol represent the 95% confidence intervals of the observed rates of clinical remission based on the binomial distribution. The solid line segments at the bottom of the chart show the 5th and 95th percentiles of predicted steady-state trough concentrations with the open circle on the line segment plotted at the median value, for the 90 mg 12w dose group and the 90 mg q8w dose group.

Source: Applicant's Population Pharmacokinetic-Pharmacodynamic Report, Figure 6

Reviewer's Comments on Week 44 Exposure-Response for Efficacy

There appear to be exposure-efficacy relationships for clinical response, clinical remission and "mucosal healing" at Week 44 while accounting for patient characteristics such as biologics failure status and remission at randomization. Compared to the induction regimens

both the Q12W and Q8W produced a higher proportion of exposures in the plateau of response. Accordingly, the distribution of exposures at Q8W is more contained in the plateau of response for all the evaluated endpoints suggesting the Q8W regimen would offer therapeutic benefit to more patients.

Since the Applicant 's definition for clinical remission differed from the FDA's currently recommended definition, the reviewer conducted independent E-R analysis using the FDA's definition for remission. The results were not substantially different from the Applicant 's analysis and the conclusion on induction and maintenance dosing regimen remains. Refer to Section 15.3.1.2 for details.

15.3.1.2. Reviewer's Analysis

15.3.1.2.1. Introduction

The reviewer's analysis focused on identifying potential confounding factors that may impact the exposure-response analysis as well as updating the Applicant's exposure-response analysis to utilize the FDA's definition for clinical remission to determine if the conclusion regarding the proposed dosing regimen changes.

15.3.1.2.2. Objectives

Analysis Objectives

- Evaluate potential confounders (patient disease characteristics, demographics) that may impact the exposure-response relationship for efficacy.
- Update exposure-response analysis for efficacy with FDA endpoint of clinical remission at Week 44 to determine if the recommendation regarding the maintenance dosing frequency changes.

15.3.1.2.3. Methods

Data Sets

Data sets used are summarized in Table 41.

Table 41. Analysis Data Sets

Study Number	Name	Link to EDR
Pop PK	*.xpt	\\CDSESUB1\evsprod\BLA761044\0074\m5\datasets\uc-pop-pk\analysis\legacy\datasets
PK-PD	*.xpt	\\CDSESUB1\evsprod\BLA761044\0074\m5\datasets\uc-pop-pk-pd\analysis\legacy\datasets
Updated efficacy with FDA endpoint, study 3001	Adeff2.xpt	\\CDSESUB1\evsprod\BLA761044\0094\m5\datasets\cnto1275uco3001main\analysis\adam\datasets\ir01jul2019

Abbreviations: EDR = electronic document room; PD = pharmacodynamic; PK = pharmacokinetic

Software

NONMEM (version 7.3) was utilized to evaluate the Applicant 's final model and variations of that model. The statistical software R was utilized to generate the summary of potential confounders by exposure group.

15.3.1.2.4. Results

Potential Confounders by Dose Group

The major covariates identified in the Applicant 's covariate selection process for the induction part of study 3001 were summarized by dosing group. The aim was to determine if imbalances in potential confounders may be correlated with body weight. Table 42 indicates the distribution of patient characteristics across each dose group is reasonably balanced. There appears to be a correlation between exposure (C_{trough}) at Week 8 and biological failure status (Table 43), which may limit interpretation of exposure-response for the induction phase. However, for the maintenance phase this trend was not readily apparent (Table 44).

Table 42. Summary of Patient Baseline Disease Characteristics by Treatment Group in Induction Phase of Study 3001

			~6 mg/kg IV		
Covariate	**Placebo**	**130 mg**	**260 mg**	**390 mg**	**520 mg**
Baseline Mayo Score	8.87	8.85	8.69	9.06	8.80
Fraction in Remission at Randomization	17%	26%	34%	21%	20%
Biological Failure Status	50%	51%	41%	56%	49%
Body Weight (not significant)	72.9	73.6	50.4	70.1	99.9

Abbreviation: IV = intravenous

Table 43. Summary of Patient Baseline Disease Characteristics by Quartile of Ustekinumab C_{trough} at Week 8

Covariate	**Placebo**	**Q1**	**Q2**	**Q3**	**Q4**
n	319	160	159	160	160
Baseline Mayo Score	8.87	9.13	8.86	8.97	8.63
Biological Failure Status	50%	**60%**	**55%**	**51%**	**40%**
Body Weight (not significant)	72.9	74.9	73.9	72.5	72.2

Abbreviations: C_{trough} = minimum concentration; Q1-Q4 = quartiles 1 to 4

Table 44. Summary of Patient Baseline Disease Characteristics by Quartile of Ustekinumab C_{trough} at Steady-State

Covariate	**Placebo**	**Q1**	**Q2**	**Q3**	**Q4**
n	175	86	87	86	87
Baseline Mayo Score	8.72	9.00	8.79	8.97	8.70
Fraction in Remission at Randomization	29%	23%	26%	23%	41%
Biological Failure Status	50%	53%	44%	44%	44%
Body Weight (not significant)	71.7	77.8	75.0	72.8	65.2

Abbreviations: C_{trough} = minimum concentration; Q1-Q4 = quartiles 1 to 4

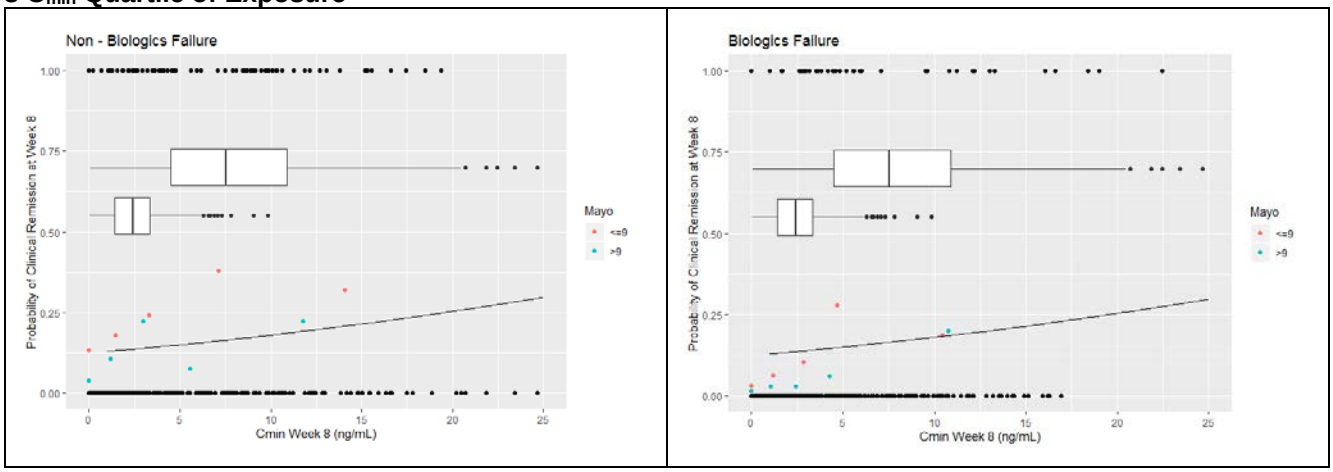
Exposure-Response Analyses Using FDA's Definition for Clinical Remission at Week 8 and Week 44

During the review the FDA clinical review team determined that efficacy endpoints should be updated to account for friability. The reviewer re-evaluated the E-R for the primary endpoints that were impacted by this change of definition. This included clinical remission at Week 8 and Week 44.

The Applicant 's final E-R models for clinical remission at Week 8 and Week 44 was run on the updated dataset with clinical remission including friability. The exposure metric did not change for each individual.

For Week 8, the reviewer's analysis suggested that a linear E-R relationship better fit the updated data than the E_{max} model, although the trends remains that higher exposures are associated with greater response. Biologics Failure status and baseline mayo score are not significant covariate on clinical remission after adjusting for the exposure. A plot of the updated E-R relationship and observed rates of response by exposure quartile are shown in Figure 20 stratified by biologics failure status (left and right panels) and baseline mayo score grouping (red and blue symbols).

Figure 20. Exposure-Response Relationships for Clinical Remission (FDA Definition) at Week 8 vs. Week 8 C_{min} Quartile of Exposure



Colored circles depict the rate of remission per exposure quartile. Black circles indicate individual responses. The left panel indicates results for patients without biologics failure. The right panel depicts results for patients with biologics failure. Color indicates baseline mayo score (red for ≤9 and blue for >9). Horizontal boxplots indicate the observed exposure range across all subjects in the 130 mg and ~6 mg/kg dose groups.

For Week 44, the updated results are shown in Table 45. A slightly decreased EC_{50} was estimated with the updated remission data, suggesting that the plateau of response may be reached at lower exposure. However, the Q8W regimen still produced a higher proportion of exposures at the plateau range compared to the Q12W regimen.

Additional sensitivity analysis was performed for Week 44 to evaluate the significance of remission at randomization status as a covariate with the updated remission dataset. The objective function increased from 630 to 643 after removing the covariate for remission at randomization, suggesting this covariate remains significant with the updated clinical endpoint.

Table 45. Updated Exposure-Response Analysis for Clinical Remission at Week 44 With FDA's Definition Endpoint and Sensitivity Analysis

Model Run	Emax	EC50	Intercept	Remission at Randomization	OFV
Original Clinical Remission Dataset	1.37	0.589	-1.63	1.21	618
FDA Updated Clinical Remission Data	0.363	0.449	-1.21	0.737	630.6
Sensitivity anlysis: minus remission at randomization status	0.451	0.97	-0.977	NA	643.5

Abbreviations: E_{max} = maximum effective concentration; EC_{50} = 50% of maximum effective concentration; OFV = objective function value

15.3.2. Review of Serum Biomarkers and Gene Expression Analyses

The Applicant evaluated serum levels of multiple serum proteins in patients with ulcerative colitis in the UCO3001 induction and maintenance study. In addition the Applicant also evaluated the levels of these analytes in healthy subjects.

15.3.2.1.1. Review of Serum Biomarkers Analysis

The Applicant evaluated serum levels of multiple serum proteins in a subset of patients (n = 574) with ulcerative colitis in the UCO3001 induction and maintenance study. In addition the Applicant also evaluated the levels of these analytes in healthy subjects (n=50). These samples were analyzed for 14 analytes across a variety of protein classes listed below:

- Cytokines and cytokine receptors: IFNγ, TNF, IL-12p70, IL-22, IL-17A, IL-10, IL-1β, IL-2R, TNFR1
- Matrix metalloproteinases: MMP1, MMP3, MMP9
- Acute Phase Reactant: serum amyloid A (SAA)
- Inflammatory marker: NGAL

The Applicant indicated that these markers were selected based on protein profiling in prior studies comparing UC patients to healthy subject controls, the treatment profile of ustekinumab in CD (CNTO1275CRD3001/3002/3003), and proteins downstream of the therapeutic target of ustekinumab, IL-12p40.

At baseline, UC patients (including both biological failure and biologic naïve) exhibited elevated levels of SAA, NGAL, IFNγ, IL-17A, IL-22, TNF, and MMP-3 compared to healthy subjects (Table 46). However, the correlation between the levels of these serum proteins and clinical endpoints was not observed for majority of these biomarkers. SAA was the only analyte which significantly correlated with the symptoms of stool number and frequency, while IL-17A was the only analyte which correlated with both endoscopic and histologic measures.

Table 46. Serum Proteins Significantly Elevated Between UCO3001 Subjects at Baseline vs. Healthy Subjects

ID	BF UC (n=287) vs. Healthy (n=50)		BN UC (n=287) vs. Healthy (n=50)		UC (n=574) vs. Healthy (n=50)	
	Fold change	p-value	Fold change	p-value	Fold change	p-value
IFN_γ	2.319	1.88E-05	2.2728	9.34E-06	2.2958	6.47E-06
IL_22	2.6942	5.83E-12	2.4969	4.12E-11	2.5937	1.99E-12
IL_17A	4.9878	2.81E-20	5.3676	3.72E-20	5.1742	1.73E-22
IL_2r	1.1321	0.0659	1.22	0.0062	1.1752	0.0182
MMP_1	1.4242	0.0033	1.5259	0.0005	1.4742	0.0008
MMP_3	2.0828	6.19E-09	1.8568	1.62E-06	1.9665	4.77E-08
MMP_9	1.3294	0.0058	1.2398	0.0441	1.2838	0.0146
NGAL	1.8349	2.56E-16	1.8666	6.66E-15	1.8507	3.06E-17
SAA	3.5961	4.76E-06	3.5425	7.54E-06	3.5692	3.39E-06
TNFR1	-1.0102	0.8377	1.0357	0.5663	1.0126	0.8201
TNF_a	1.7896	1.21E-05	1.6766	1.92E-06	1.7322	2.22E-06

≥ 1.5-fold change p-value < 0.05

BF, biologic failure subjects; BN, biologic non-failure subjects

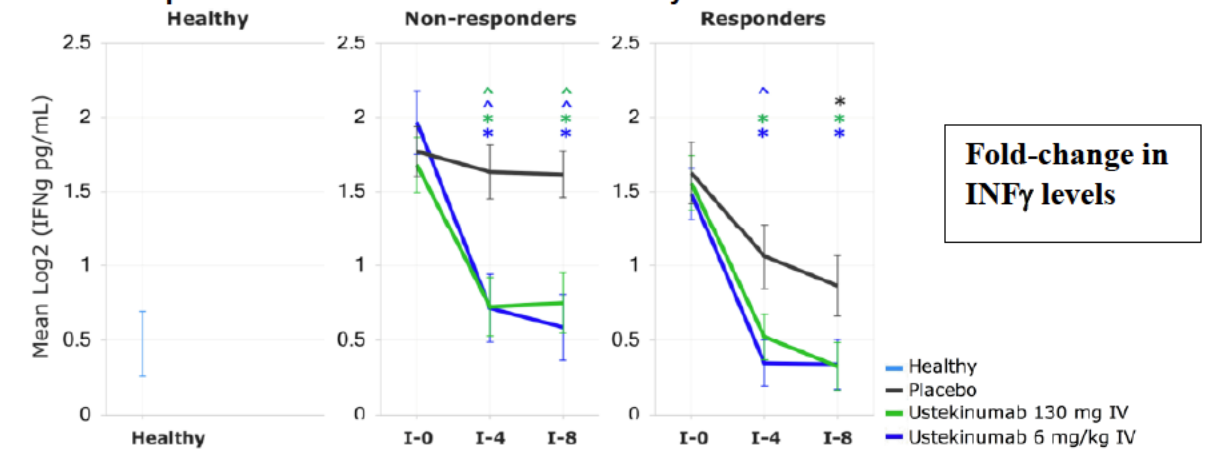
Source: Applicant's Biomarker Technical Report, Table 4

The Applicant evaluated the reductions of the forementioned disease-associated serum proteins following ustekinumab induction therapy at Week 4 and Week 8. Levels of interferon gamma (IFNɣ), IL-17A, IL-22 and SAA were decreased (Figure 21) with the changes detected as early as Week 4.

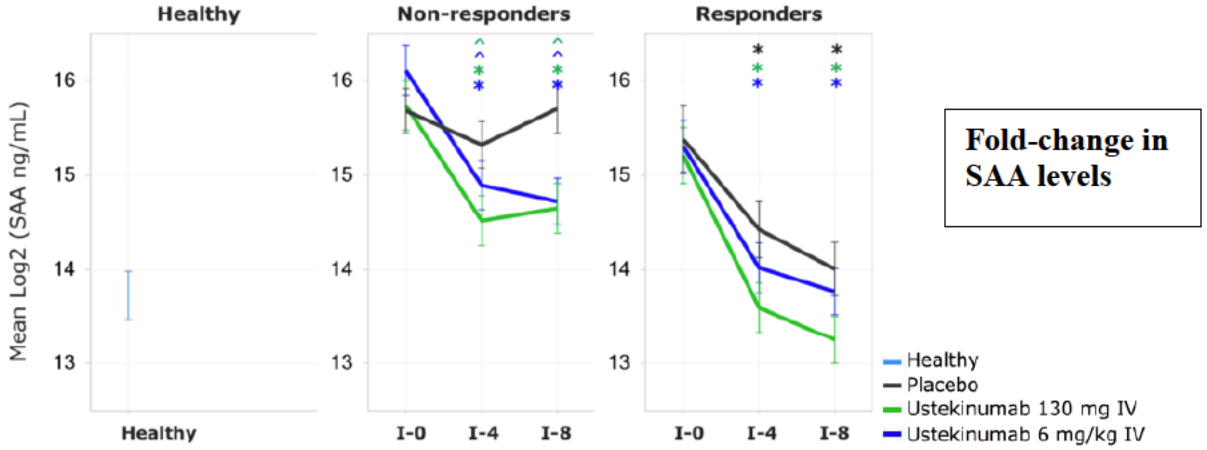
Among the patients not in response to ustekinumab at Week 8, the normalization of serum markers was less consistent or of smaller magnitude than that of ustekinumab responders at Week 8; among non-responders at Week 8, those who subsequently responded to a second dose of ustekinumab had reductions of IFNɣ, IL-17A, and IL-22 comparable to those of patients who responded to ustekinumab at Week 8. Further, the changes in these serum markers didn't exhibit any major differences across the two doses that were evaluated.

The Applicant also evaluated the effects of ustekinumab on the exploratory serum biomarkers for patients (responders from induction study) who continued to the maintenance study and were randomized to receive ustekinumab 90 mg SC every 8 weeks (Q8W), ustekinumab 90 mg SC Q12W, or placebo. Across the serum markers that were evaluated, the greatest changes were observed for IFNγ, IL-17A, and MMP3 in patients treated with either Q12W or Q8W ustekinumab compared to those treated with placebo. However, similar to the induction phase, the changes in these serum markers didn't exhibit any major differences across the two dosing regimens that were evaluated.

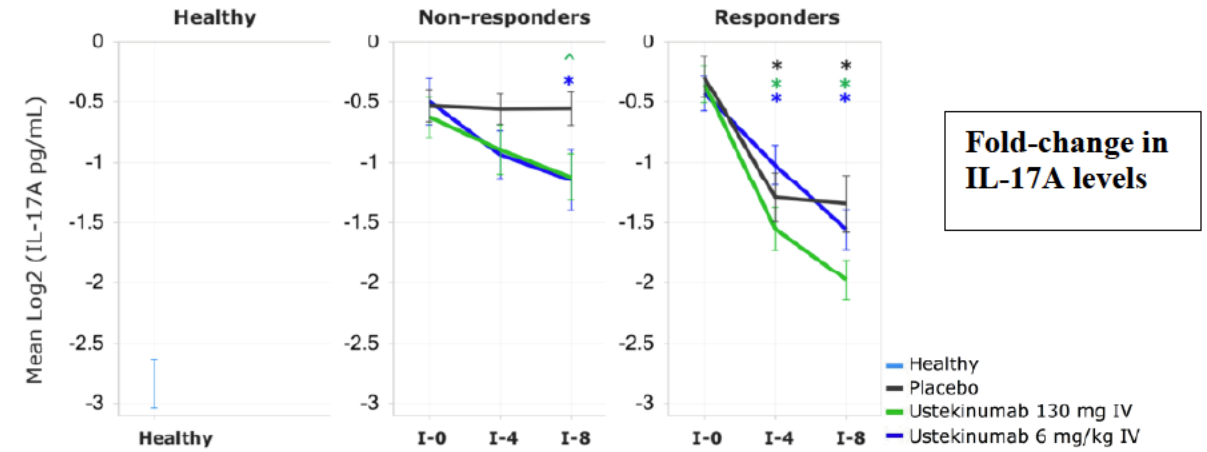
Figure 21. Changes in Serum INFɣ, SAA, and IL-17A in Healthy Subjects and Ustekinumab Responders and Non-Responders in the UCO3001 Induction Study



*p < .05 and |fold-change| > 1.5 for the comparison of I-4 or I-8 to I-0
^p < .05 and |fold-change| > 1.5 for the comparison of ustekinumab to placebo



*p < .05 and |fold-change| > 1.5 for the comparison of I-4 or I-8 to I-0
^p < .05 and |fold-change| > 1.5 for the comparison of ustekinumab to placebo



*p < .05 and |fold-change| > 1.5 for the comparison of I-4 or I-8 to I-0
^p < .05 and |fold-change| > 1.5 for the comparison of ustekinumab to placebo

Abbreviations: IL = interleukin; INFɣ = interferon gamma; SAA = serum amyloid A
Source: Applicant's Biomarker Technical Report, Figure 3, Figure 4 and Figure 5

15.3.2.1.2. Review of Gene Expression Analysis

For the gene expression analysis, the Applicant compared the gene expression profile in colon biopsies from 550 patients with UC at baseline with that of healthy subjects (n = 18). The Applicant identified a panel of 4095 probe sets with differential expression (more than +/- 2-fold change) in UC patients representing 2,454 unique genes. This included alterations in inflammatory response genes (S100 calcium-binding protein A8, S100 calcium-binding protein A9, chemokine [C-X-C motif] ligand 8, SAA1, IL-6), tissue remodeling and wound healing (MMPs), host-microbe interaction (defensin B4, dual oxidase 2), intestinal permeability (x-box binding protein 1, claudin 8), and solute transport (solute carrier genes, aquaporin).

To assess the treatment effect of ustekinumab, the Applicant evaluated the gene expression profile using biopsies obtained from patients across the various treatment groups in the study 3001 at Week 8 (induction) and Week 44 (maintenance). Compared with baseline, a change in gene expression was observed for both the placebo and the ustekinumab treatment groups for both the up- and down-regulated disease profiles at Week 8 (Table 47). The changes in the gene expression profile didn't exhibit any major differences across the two doses that were evaluated. Further, the changes in gene expression was observed in both ustekinumab and placebo treatment groups although the magnitude of effects appears to be greater with ustekinumab. Similar trends were observed at Week 44 in the maintenance phase (Table 47).

The Applicant has proposed (b) (4) , we disagree (b) (4) The changes in gene expression for both the induction and maintenance phase was seen in both the drug treated and the placebo treated groups (although the magnitude of the effect was greater in drug treated group). Therefore, we cannot be certain that the change in gene expression necessarily reflect the treatment effect of ustekinumab. Further, it is unclear how the changes in gene expression across the various pathways relate to the clinical effect of ustekinumab, limiting the utility of this information to the prescribers.

Table 47. Comparison of Changes in Gene Expression Based on GSVA Score of Up- and Down-Regulated Signatures During Induction and Maintenance Phase of Study 3001
Panel A. Induction (Week 8)

	Disease profile		UST_130mg (n=155)		UST_6mgkg (n=171)		placebo (n=145)	
	UC(n=550) vs HC(n=18)		wk8 vs BL		wk8 vs BL		wk8 vs BL	
Signatures	Mean diff.	pvalue	Mean diff.	pvalue	Mean diff.	pvalue	Mean diff.	pvalue
Up-regulated Signatures	0.873	<.0001	-0.195	<.0001	-0.220	<.0001	-0.088	0.009
Down-regulated Signatures	-0.854	<.0001	0.135	0.0001	0.169	<.0001	0.045	0.182

Panel B. Maintenance (Week 44)

	Disease profile		USTR_q12W (n=80)		USTR_q8W (n=71)		USTR_PBO (n=68)	
	UC(n=550) vs HC(n=18)		wk44 vs wk8		wk44 vs wk8		wk44 vs wk8	
Signatures	Mean diff.	P-value	Mean diff.	P-value	Mean diff.	P-value	Mean diff.	P-value
Up-regulated Signatures	0.873	<.0001	-0.210	0.0002	-0.265	<.0001	-0.137	0.021
Down-regulated Signatures	-0.854	<.0001	0.105	0.048	0.238	<.0001	0.115	0.058

Abbreviations: GSVA = Gene Set Variation Analysis; PBO = placebo
Source: Applicant's Biomarker Technical Report, Table 14 and Table 18

15.4. Efficacy Analyses: Applicant's Definitions

Induction Study: Primary and Secondary Endpoints Prespecified by Applicant

The primary endpoint of clinical remission proposed by the Applicant was defined as an absolute stool number ≤3, a Mayo rectal bleeding subscore of 0, and a Mayo endoscopy subscore of 0 or 1. At Week 8, significantly greater proportions of patients in the ustekinumab 6 mg/kg and 130 mg groups achieved clinical remission (18.9% and 16.6%, respectively) compared with patients in the placebo group (6.3%) with p-values <0.001 for both comparisons.

There were three multiplicity-controlled binary secondary endpoints evaluated at Week 8: endoscopic improvement ("healing"), clinical response, and histologic-endoscopic improvement ("mucosal healing"). The definitions of endoscopic improvement and histologic-endoscopic improvement did not exclude presence of friability.

Both treatment arms showed statistically significant improvement in all secondary endpoints when compared to Placebo (all p-values <0.001). The results were confirmed by the FDA. Table 48 and Table 49 present efficacy results of the primary and the multiplicity-controlled secondary endpoints in all randomized patients in the induction study and summarize remission rates in two subpopulations: bio-naive and prior biological failure. In both types of subgroups, the proportion of patients achieving remission was larger in the ustekinumab treatments compared to placebo.

Maintenance Study: Primary and Secondary Endpoints Prespecified by Applicant

Multiple testing procedure in the maintenance study included one primary endpoint of clinical remission at Week 44 and four secondary endpoints: maintenance of clinical response through Week 44, endoscopic improvement, corticosteroid-free clinical remission at Week 44, maintenance of clinical remission through Week 44 among patients who had achieved clinical remission at maintenance baseline.

Both treatment arms showed statistically significant improvement in all secondary endpoints when compared to placebo. The tables below present efficacy results of the primary and the multiplicity-controlled secondary endpoints in all randomized patients and summarize remission rates in two subpopulations: bio-naive and prior biological failure. In both types of subgroups, the proportion of patients achieving remission was larger in the ustekinumab treatments compared to placebo.

Table 48. Induction Study, Clinical Remission at Week 8 (Applicant's Definition)

Outcome/Population	Placebo (N=319)	Ustekinumab 130 mg (N=320)	Ustekinumab 6 mg/kg (N=322)
Clinical remission % (n/N)	6.3% (20/319)	16.6% (53/320)	18.9% (61/322)
Treatment difference (97.5% CI); p-value	—	10.3% (4.8%, 15.8%); p<0.001	12.7% (7.0%, 18.4%); p<0.001
Subpopulation: biologic naïve	10.6% (16/151)	22.1% (32/145)	25.2% (37/147)
Subpopulation: failure in prior biologic use	2.5% (4/161)	11.6% (19/164)	13.3% (22/166)

Source: Clinical Study Report CNTO1275UCO3001 Induction Table 7 (pg. 88) and FDA's Results. Applicant's results were confirmed by FDA
Abbreviation: CI = confidence interval

Table 49. Induction Study, Multiplicity-Controlled Secondary Endpoints at Week 8 (Applicant's Definition)

Endpoint	Placebo (N=319)	Ustekinumab 130 mg (N=320)	Ustekinumab 6 mg/kg (N=322)
Endoscopic improvement % (n/N)	13.8% (44/319)	26.3% (84/320)	27.0% (87/322)
Treatment difference (97.5% CI); p-value	—	12.4% (5.6%, 19.2%); p<0.001	13.3% (6.4%, 20.1%); p<0.001
Biologic naïve	21.2% (32/151)	35.2% (51/145)	33.3% (49/147)
Failure in prior biologic use	6.8% (11/161)	18.3% (30/164)	21.1% (35/166)
Clinical response % (n/N)	31.3% (100/319)	51.3% (164/320)	61.8% (199/322)
Treatment difference (97.5% CI); p-value	—	19.9% (11.4%, 28.3%); p<0.001	30.5% (22.2%, 38.8%); p<0.001
Biologic naïve	35.8% (54/151)	57.9% (84/145)	66.7% (98/147)
Failure in prior biologic use	27.3% (44/161)	45.1% (74/164)	57.2% (95/166)
Histologic-endoscopic improvement % (n/N)	8.9% (28/316)	20.3% (64/316)	18.4% (58/315)
Treatment difference (97.5% CI); p-value	—	11.3% (5.2%, 17.4%); p<0.001	9.7% (3.7%, 15.7%); p<0.001
Biologic naïve	14.2% (21/148)	27.1% (39/144)	23.6% (33/140)
Failure in prior biologic use	(/161)	(/164)	(/166)

Source: Clinical Study Report CNTO1275UCO3001 Induction Table 8 (pg. 91), Table 9 (pg.92), Table 11 (pg. 94), and FDA's Results. Applicant's results were confirmed by FDA
Abbreviation: CI = confidence interval

Table 50. Maintenance Study, Clinical Remission at Week 44 (Applicant's Definition)

Outcome/Population	Placebo SC (N=175)	Ustekinumab 90 mg SC Q12W (N=172)	Ustekinumab 90 mg SC Q8W (N=176)
Clinical remission % (n/N)	24.6% (43/175)	39.5% (68/172)	42.6% (75/176)
Treatment difference (95% CI); p-value	—	15.1% (6.0%, 24.2%) p=0.002	17.9% (8.6%, 27.2%) p<0.001
Subpopulation: biologic naïve	33.3% (28/84)	49.5% (47/95)	48.1% (38/79)
Subpopulation: failure in prior biologic use	17.1% (15/88)	25.8% (17/70)	37.4% (34/91)

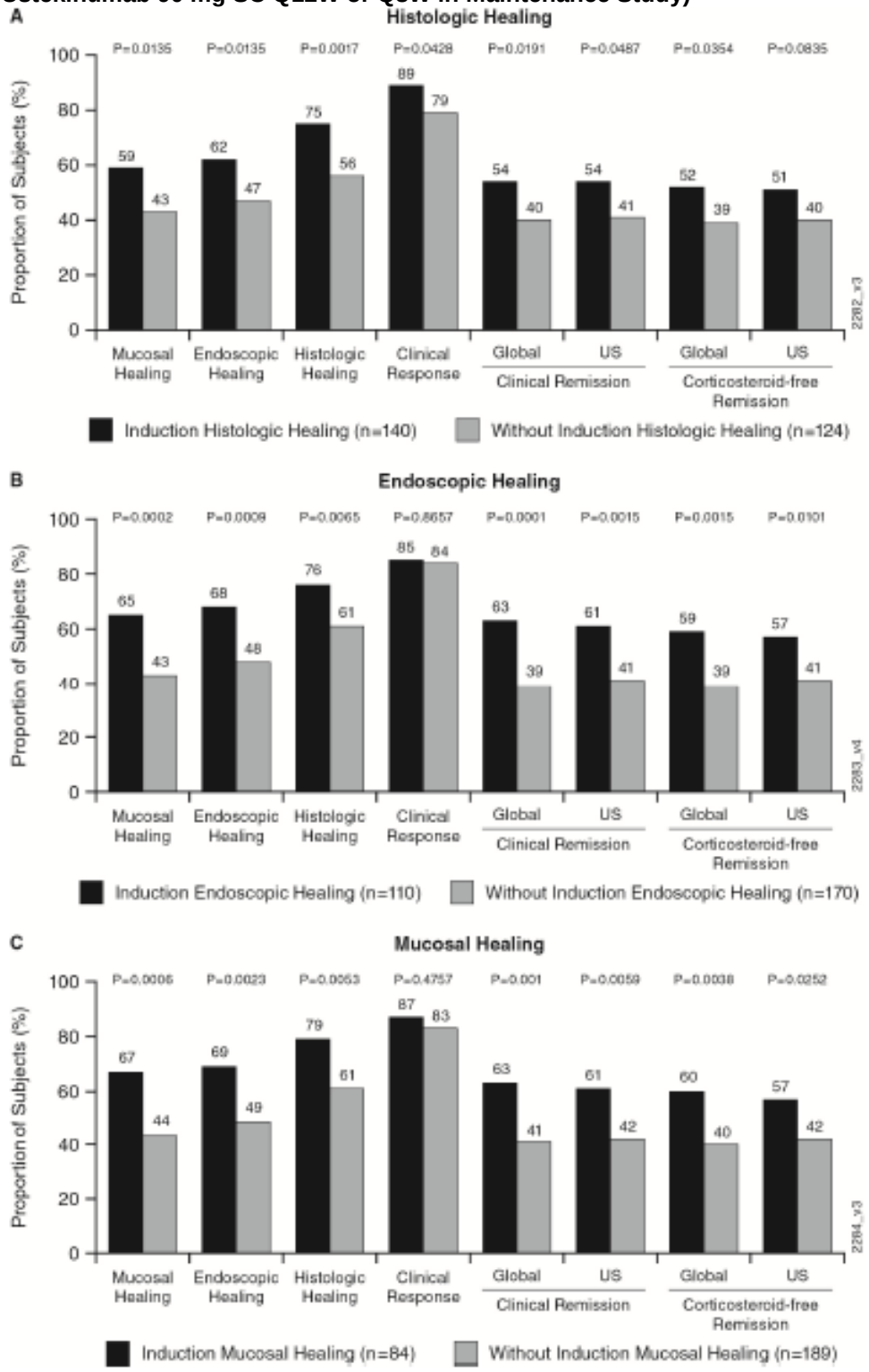
Source: Clinical Study Report Clinical Study Report CNTO1275UCO3001 Maintenance Table 7 (pg. 102) and FDA's Results. Applicant's results were confirmed by FDA
Abbreviations: CI = confidence interval; Q8/12W = every 8/12 weeks; SC = subcutaneous

Table 51. Maintenance Study, Multiplicity-Controlled Secondary Endpoints at Week 44 (Applicant's Definition)

Endpoint	Placebo SC (N=175)	Ustekinumab 90 mg SC Q12W (N=172)	Ustekinumab 90 mg SC Q8W (N=176)
Clinical response % (n/N)	44.6% (78/175)	68.0% (117/172)	71.0% (125/176)
Treatment difference (95% CI); p-value	—	23.5% (13.7%, 33.3%); p<0.001	26.4% (16.6%, 36.1%); p<0.001
Biologic naïve	52.4% (44/84)	76.8% (73/95)	77.2% (61/79)
Failure in prior biologic use	38.6% (34/88)	55.7% (39/70)	64.8% (59/91)
Endoscopic improvement % (n/N)	28.6% (50/175)	43.6% (75/172)	51.1% (90/176)
Treatment difference (95% CI); p-value	—	15.2% (5.8%, 24.6%) p=0.002	22.5% (12.8%, 32.2%) p<0.001
Biologic Naïve	35.7% (30/84)	54.7% (52/95)	58.2% (46/79)
Failure in prior biologic use	22.7% (20/88)	25.7% (18/70)	45.1% (41/91)
Corticosteroid-free clinical remission % (n/N)	24.0% (42/175)	39.0% (67/172)	40.9% (72/176)
Treatment difference (95% CI); p-value	—	15.1% (6.1%, 24.2%) p=0.002	16.8% (7.6%, 26.0%) p<0.001
Biologic naïve	33.3% (28/84)	48.4% (46/95)	46.8% (37/79)
Failure in prior biologic use	15.9% (14/88)	24.3% (17/70)	35.2% (32/91)
Maintenance of clinical remission % (n/N)	33.3% (16/48)	61.5% (32/52)	61.4% (27/44)
Treatment difference (95% CI); p-value	—	30.4% (11.9%, 48.8%); p=0.003	29.1% (10.4%, 47.9%) p=0.006
Biologic naïve	35.7% (10/28)	65.8% (25/38)	76.2% (16/21)
Failure in prior biologic use	30.0% (6/20)	41.7% (5/12)	50.0% (10/20)

Source: Clinical Study Report CNTO1275UCO3001 Maintenance Table 8 (pg. 106), Table 9 (pg. 108), Table 11 (pg. 112), Table 13 (pg. 116), and FDA's Results. Applicant's results were confirmed by FDA
Abbreviations: CI = confidence interval; Q8/12W = every 8/12 weeks; SC = subcutaneous

Figure 22. Proportion of Patients Who Achieved Histologic, Endoscopic, or Histologic-Endoscopic Improvement at Week 44 With or Without Healing at End of Induction (Randomized Patients to Ustekinumab 90 mg SC Q12W or Q8W in Maintenance Study)



Abbreviations: Q8/12W = every 8/12 weeks; SC = subcutaneous

15.5. Additional Discussion: Applicant's Histologic-Endoscopic Improvement ("Mucosal Healing") Definition

The Applicant's position paper described how the definition of histologic healing was derived, which included two steps: selection of the Geboes score (GS) features and associated cut-off values to be used, followed by assessment of the association between histologic healing and other clinical endpoints. Data from the Applicant's previously conducted study 2 and 3 clinical trials (infliximab [ACT1], golimumab, and a Janus kinase inhibitor trial) as well as the two ustekinumab study 3 trials were used in the analyses. Each of these trials evaluated patients with moderately to severely active UC, including patients who were either biologic-naïve or had failed prior biologic therapy. The Applicant evaluated which of the Geboes features were associated with endoscopic healing (Mayo endoscopy subscore of 0 or 1) and other relevant clinical outcomes. The figure below shows the Geboes scoring system.

Figure 23. Geboes Score

Grade 0: Architectural changes
0.0 No abnormality
0.1 Mild abnormality
0.2 Mild/moderate diffuse or multifocal abnormalities
0.3 Severe diffuse or multifocal abnormalities
Grade 1: Chronic inflammatory infiltrate
1.0 No increase
1.1 Mild but unequivocal increase
1.2 Moderate increase
1.3 Marked increase
Grade 2A: Eosinophils in lamina propria
2A.0 No increase
2A.1 Mild but unequivocal increase
2A.2 Moderate increase
2A.3 Marked increase
Grade 2B: Neutrophils in lamina propria
2B.0 No increase
2B.1 Mild but unequivocal increase
2B.2 Moderate increase
2B.3 Marked increase
Grade 3: Neutrophils in epithelium
3.0 None
3.1 <5% crypts involved
3.2 <50% crypts involved
3.3 >50% crypts involved
Grade 4: Crypt destruction
4.0 None
4.1 Probable–Local excess of neutrophils in part of the crypts
4.2 Probable–Marked attenuation
4.3 Unequivocal crypt destruction
Grade 5: Erosions or ulcerations
5.0 No erosion, ulceration or granulation tissue
5.1 Recovering epithelium + adjacent inflammation
5.2 Probable erosion – focally stripped
5.3 Unequivocal erosion
5.4 Ulcer or granulation tissue

* Maximum total score =22; maximum of Grades 3, 4, and 5 subscores =10
(Geboes et al. 2000)

The Applicant's selected definition of histologic healing was associated with clinical measures including Mayo endoscopic healing (subscore of 0 or 1), improved full and partial Mayo scores, reduced symptom scores of stool frequency and rectal bleeding, and improved IBDQ scores (Sandborn et al. 2014). The histologic and histologic-endoscopic improvement ("mucosal healing") findings at the end of the induction treatment were associated with attaining positive clinical outcomes (clinical response, remission, and corticosteroid-free remission) at the end of maintenance treatment. Long-term data were not available to

determine whether the histologic improvement observed is predictive of improved long-term clinical outcomes (e.g., reduced colectomy, hospitalization, malignancy rates, etc.).

In addition to the analyses provided by the Applicant, we considered whether the achievement of histologic healing, as included in the histologic-endoscopic improvement ("mucosal healing") endpoint definition, provided a clinically meaningful improvement from the baseline degree of histologic inflammation. Therefore, we issued information requests to the Applicant to obtain additional information on the total Geboes score and activity subscore (Grades 3, 4, and 5 that defined histologic healing) at baseline.

Table 52. Summary of Histologic Characteristics at Induction Baseline (Randomized Population in Induction Study)

Histologic Characteristic	Placebo N=319	Ustekinumab 130 mg IV N=320	Ustekinumab 6 mg/kg IV N=320
Total Geboes score at baseline			
n*	265	267	268
Mean (SD)	11.6 (4.7)	11.7 (4.6)	12.1 (4.1)
Median	13.0	12.0	12.0
Range	0, 20	0, 20	0, 19
Geboes activity subscore (Grades 3, 4, 5) at baseline			
n*	265	267	268
Mean (SD)	4.9 (3.0)	5.0 (2.9)	5.1 (2.7)
Median	6.0	6.0	5.0
Range	0, 10	0, 10	0,9
Patients in histologic healing at baseline, n(%)	46 (15.5%)	44 (14.8%)	29 (9.8%)

Source: Reviewer's table, adapted from Applicant response to IR, received May 17, 2019
* n: Excludes patients with an unevaluable biopsy (i.e., a biopsy that was collected but could not be assessed due to sample preparation or technical errors) at Week 8.
Maximum total score =22; maximum of Grades 3, 4, and 5 subscores =10
Abbreviations: IV = intravenous; SD = standard deviation

Based on the baseline scores shown above, most patients appeared to have moderately severe histologic inflammation, since the mean and median total scores were around 11 to 12, and the total subscores on Grades 3, 4, and 5 were around 5 to 6 points (maximum total score =22; maximum of Grades 3, 4, and 5 subscores =10). However, the degree of histologic inflammation is dependent on the location from which the biopsy is taken. There is some uncertainty as to whether the gross inflammation observed visually on endoscopy correlates with the degree of histologic inflammation because there were patients (10 to 15%) with active gross inflammation on endoscopy who met the criteria for histologic healing at baseline.

However, since a small proportion of patients met the criteria for histologic healing at baseline, the Applicant performed an additional "sensitivity analysis" of the histologic-endoscopic improvement endpoint at Week 8 in which patients with histologic healing at baseline were excluded. The results were similar to the original analyses of the histologic-endoscopic improvement at Week 8 endpoint. The comparison of the original analysis to the additional "sensitivity analysis" is shown below. In a response to an information request received July 2, 2019, a similar analysis in which patients with histologic healing at baseline were excluded was provided for the Week 44 histologic-endoscopic improvement endpoint. The results were generally similar to the original analysis (additional analyses not shown).

Table 53. Number of Patients With Histologic Healing at Week 8 in Original Analysis and in Sensitivity Analysis in Which Patients With Histologic Healing at Baseline were Excluded[1,2]

	Placebo IV	Ustekinumab IV 130 mg	Ustekinumab IV 6 mg/kg [a]
Subjects who were randomized in the induction study (CNTO1275UCO3001)	319	320	322
Week 8			
N (Original analysis) [b]	297	298	295
Subjects with histologic healing [c,d,e]	65 (21.9%)	113 (37.9%)	105 (35.6%)
p-value		< 0.001	< 0.001
N (Sensitivity analysis) [f]	251	254	266
Subjects with histologic healing [c,d,e]	48 (19.1%)	92 (36.2%)	88 (33.1%)
p-value		< 0.001	< 0.001

[a] Weight-range based ustekinumab doses approximating 6 mg/kg: 260 mg (weight ≤ 55 kg), 390 mg (weight > 55 kg and ≤ 85 kg), 520 mg (weight > 85 kg).
[b] Excludes subjects with an unevaluable biopsy (ie, a biopsy that was collected, but could not be assessed due to sample preparation or technical errors) at Week 8.
[c] Histologic healing is defined as neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue.
[d] Subjects who had a prohibited change in concomitant UC medication or an ostomy or colectomy prior to the Week 8 visit were considered not to have histologic healing.
[e] Subjects who were missing any of the components pertaining to this endpoint (ie, assessment of neutrophils in epithelium, crypt destruction, or erosions or ulcerations or granulations) at Week 8 visit were considered not to have histologic healing.
[f] Excludes subjects with histologic healing at induction baseline and subjects with an unevaluable biopsy (ie, a biopsy that was collected but could not be assessed due to sample preparation or technical errors) at Week 8.
Source: Applicant response to IR, received May 17, 2019, Table 2, page 7/11
[1] Excludes patients with histologic healing at induction baseline
[2] Randomized population in the induction study
Abbreviation: IV = intravenous

Although the histologic-endoscopic improvement endpoint was not multiplicity controlled at Week 44, we were interested in how the histologic scores changed during the maintenance trial. At maintenance baseline, the histologic scores on the Geboes Grades 3, 4, and 5 were low (after the induction dose) and showed small improvements during the maintenance trial. See table below.

Table 54. Summary of Histologic Characteristics at Maintenance Baseline and Week 44; Patients Enrolled in Maintenance Study[1]

	Randomized subjects				Nonrandomized subjects	
		Responders to ustekinumab IV induction			Responders to placebo IV induction	Delayed responders [c]
	Placebo SC [a]	90 mg SC q12w	90 mg SC q8w	Combined	Placebo SC [b]	Ustekinumab 90 mg SC q8w
Subjects enrolled in the maintenance study (excluding subjects with an unevaluable biopsy [d] at Week 44)	167	163	167	330	98	151
Total Geboes score [e]						
Maintenance baseline						
N	156	145	154	299	87	135
Mean (SD)	7.8 (4.76)	6.9 (4.53)	7.7 (4.74)	7.3 (4.65)	8.2 (5.23)	8.1 (4.70)
Median	7.0	6.0	7.0	7.0	8.0	7.0
IQ range	(4.0; 12.0)	(4.0; 10.0)	(4.0; 12.0)	(4.0; 11.0)	(4.0; 12.0)	(4.0; 12.0)
Range	(0; 18)	(0; 19)	(0; 17)	(0; 19)	(0; 19)	(0; 19)
Week 44 [g]						
N	115	134	143	277	61	117
Mean (SD)	7.5 (5.15)	6.0 (4.87)	5.6 (4.28)	5.8 (4.57)	7.9 (5.77)	6.6 (4.43)
Median	6.0	4.0	4.0	4.0	7.0	5.0
IQ range	(3.0; 12.0)	(3.0; 9.0)	(3.0; 8.0)	(3.0; 9.0)	(3.0; 13.0)	(3.0; 10.0)
Range	(0; 18)	(0; 19)	(0; 17)	(0; 19)	(0; 19)	(0; 18)
Geboes activity subscore [f]						
Maintenance baseline						
N	156	145	154	299	87	135
Mean (SD)	2.5 (2.74)	2.0 (2.47)	2.5 (2.74)	2.3 (2.62)	2.9 (2.93)	2.5 (2.93)
Median	1.5	0.0	1.0	1.0	2.0	2.0
IQ range	(0.0; 5.0)	(0.0; 4.0)	(0.0; 4.0)	(0.0; 4.0)	(0.0; 6.0)	(0.0; 5.0)
Range	(0; 9)	(0; 9)	(0; 9)	(0; 9)	(0; 9)	(0; 9)
Week 44 [g]						
N	115	134	143	277	61	117
Mean (SD)	2.4 (2.90)	1.7 (2.74)	1.4 (2.38)	1.6 (2.56)	2.8 (3.13)	1.8 (2.41)
Median	1.0	0.0	0.0	0.0	1.0	0.0
IQ range	(0.0; 5.0)	(0.0; 3.0)	(0.0; 2.0)	(0.0; 3.0)	(0.0; 6.0)	(0.0; 3.0)
Range	(0; 10)	(0; 10)	(0; 10)	(0; 10)	(0; 9)	(0; 8)

[a] Subjects who were in clinical response to ustekinumab IV induction dosing and were randomized to placebo SC on entry into the maintenance study.
[b] Subjects who were in clinical response to placebo IV induction dosing and received placebo SC on entry into the maintenance study.
[c] Subjects who were not in clinical response to ustekinumab IV at I-8 but were in clinical response at I-16 after a SC administration of ustekinumab at I-8.
[d] Excludes subjects with an unevaluable biopsy (ie, a biopsy that was collected, but could not be assessed due to sample preparation or technical errors) at Week 44.
[e] Total Geboes score: the continuous histology score (range 0-22) was derived as the sum of all Geboes Grades. The numeric score of each GS feature was regarded as continuous to derive numerical histologic scores, meaning that an increase of 1-grade categorically was translated into a 1-point increase in a continuous transformation of the GS score.
[f] Geboes activity subscore: the continuous histology score (range 0-10) was derived as the sum of Geboes Grades 3, 4, and 5 that defined histologic healing. The numeric score of each GS feature was regarded as continuous to derive numerical histologic scores, meaning that an increase of 1-grade categorically was translated into a 1-point increase in a continuous transformation of the GS score.
[g] Subjects who had a prohibited change in UC medication, an ostomy or colectomy, or used a rescue medication after clinical flare, or discontinued study agent due to lack of therapeutic effect or due to an AE of worsening of UC prior to the Week 44 visit had their induction baseline value carried forward to Week 44.

Source: Applicant response to IR, received July 2, 2019, Table 1, page 7/18
[1] Excluding patients with an unevaluable biopsy at Week 44
Abbreviations: IV = intravenous; Q8/12W = every 8/12 weeks; SC = subcutaneous; SD = standard deviation

We were also interested to learn more about how the Geboes score performs to better inform future trials. Therefore, we requested additional analyses that describes the summary of histologic characteristics for the other categories in the Geboes score (Grades 0, 1, 2A, and

2B) for scores at induction baseline, Week 8, and Week 44. This information was provided in a response to an information request, received July 2, 2019. Overall, the scores on Grades 0, 1, 2A, and 2B did not change or showed small (1 to 2 point) improvements from induction baseline to Week 8 and Week 44. We acknowledge that the elements in Grades 0, 1, 2A, and 2B of the Geboes score are generally more reflective of chronic inflammation. However, the stability/small improvements suggests that the histologic inflammation was not worsening in any the other components of the Geboes score that was not included in the definition of histologic healing.

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/s/

JESSICA J LEE
10/18/2019 08:59:19 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761044Orig1s003

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: October 3, 2019

To: Kelly Richards, RN, MSN, Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products (DGIEP)

From: Adewale Adeleye, Pharm.D., MBA, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Pharm.D., RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for STELARA (ustekinumab)

BLA: 761044 / Supplement 003

In response to DGIEP's consult request dated January 14, 2019, OPDP has reviewed the proposed product labeling (PI), Medication Guide/Instructions for Use (IFU), and carton and container labeling for STELARA (ustekinumab) injection, for subcutaneous or intravenous use (Stelara). This supplement (S003) provides for the addition of ulcerative colitis indication to the labeling.

PI and Medication Guide/IFU: OPDP's comments on the proposed labeling are based on the draft PI and Medication Guide/IFU received by electronic mail from DGIEP (Kelly Richards) on September 20, 2019, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide/IFU were sent under separate cover on October 2, 2019.

Carton and Container Labeling: Reference is made to electronic mail from DGIEP (Kelly Richards) on October 2, 2019, stating that there are no proposed changes to the carton and container labeling at this time. Therefore, OPDP will not provide comments on the carton and container labeling at this time.

Thank you for your consult. If you have any questions, please contact Adewale Adeleye at (240) 402-5039 or adewale.adeleye@fda.hhs.gov.

41 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

ADEWALE A ADELEYE
10/03/2019 09:48:15 AM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Templates
Version: 2018-01-24

Date:	September 18, 2019
Reviewer:	Joel L. Weissfeld, MD MPH, Medical Officer Division of Epidemiology I
Team Leader:	Patricia L. Bright, MSPH PhD, Team Leader Division of Epidemiology I
Division Director:	Sukhminder K. Sandhu, PhD MPH MS, Deputy Director Division of Epidemiology I
Subject:	ARIA Sufficiency Memo
Drug Name:	ustekinumab (Stelara®)
Application Type/Number:	BLA 761044/S-003
Submission Number:	eCTD 0074
Applicant/sponsor:	Janssen
OSE RCM #:	2019-1687

EXECUTIVE SUMMARY

Memo type		
-Initial		
-Interim		
-Final	X	
Source of safety concern		
-Peri-approval	X	
-Post-approval		
Is ARIA sufficient to help characterize the safety concern?	Infection	Malignancy
-Yes	X	
-No		X
If "No", please identify the area(s) of concern.		
-Surveillance or Study Population		
-Exposure		
-Outcome(s) of Interest		X
-Covariate(s) of Interest		
-Surveillance Design/Analytic Tools		

1. BACKGROUND INFORMATION

1.1. Medical Product

Ustekinumab is a human interleukin-12 and -23 antagonist approved by FDA for psoriasis, psoriatic arthritis, and Crohn's disease (CD). The most recent (September 23, 2016) ustekinumab approval for CD introduced high-dose intravenous (IV) dosing for induction and more frequent subcutaneous (SQ) dosing for maintenance (every 8 instead of 12 weeks). Because of this new dosing schedule in a different disease setting (CD) and incompletely resolved concerns about malignancy and infection from ustekinumab, FDA implemented at CD approval (1) PMR 3112-1 for a post-market study of malignancy in CD and (2) ARIA-directed analysis in Sentinel for serious infection in CD.

BLA 761044/S-003 now seeks FDA approval for ulcerative colitis (UC) with same ustekinumab dosing as CD. Other FDA-approved biologic or small molecule treatments for UC include tumor necrosis factor-alpha (TNF-α) inhibitors (infliximab, adalimumab, and golimumab), anti-integrins (vedolizumab), and JAK inhibitors (tofacitinib).

1.2. Describe the Safety Concern

The UC clinical program for BLA 761044/S-003 included 825 UC patients, including 491 and 442 treated with ustekinumab IV/SQ for ≥6 months and ≥1 year, respectively. Malignancy other than non-melanoma skin cancer (NMSC) occurred during treatment in 4 of 825 patients with 626 patient-years in cumulative exposure to ustekinumab.[1] Malignancy other than NMSC occurred in 1 of 446 patients with 250 patient-years in cumulative follow-up on placebo (possibly after ustekinumab induction).[2] The clinical review division (Division of Gastroenterology and Inborn Error Products, DGIEP) assessed this safety experience as providing inadequate information about long-term malignancy risk in UC after treatment with ustekinumab.

Treatment-emergent serious infection occurred in three and nine patients on ustekinumab for induction and maintenance, respectively (Table 1). DGIEP assessed this safety experience as providing inadequate information about serious infection risk in UC during sustained treatment with ustekinumab.

Table 1: Number of UC patients with 1 or more treatment-emergent serious infections during induction and maintenance with placebo or ustekinumab (CNTO1275UCO3001).

	Induction (8 weeks)			**Maintenance (44 weeks)**		
	Placebo	**130 mg**	**6 mg/kg**	**Placebo**	**90 mg SC q12w**	**90 mg SC q8w**
Patients, N	319	321	320	175	172	176
Mean exposure, weeks	7.96	8.11	8.16	35.30	32.53	37.29

[1] Weissfeld, JL, PL Bright, and SK Sandhu, Sponsor Presentation of Malignancy Events in an Efficacy Supplement for Ulcerative Colitis, filed under BLA 761044 on May 28, 2019 (DARRTS Reference ID: 4438800).

[2] TSFMAL71C in Integrated Summary of Safety (ISS), submitted to BLA 761044 (eCTD 0074) on December 20, 2018.

	Induction (8 weeks)			Maintenance (44 weeks)		
	Placebo	130 mg	6 mg/kg	Placebo	90 mg SC q12w	90 mg SC q8w
Patients with serious infection, N (%)	4 (1.3)	2 (0.6)	1 (0.3)	4 (2.3)	6 (3.5)	3 (1.7)

Source: Assembled by DEPI from TSFINFE02A and TSFINFE02B in Integrated Summary of Safety (ISS), submitted to BLA 761044 (eCTD 0074) on December 20, 2018.

Furthermore, DGIEP determined that the rationale for seeking post-market studies of ustekinumab is similar for UC and CD. Specifically, DGIEP identified clinical grounds for post-market studies in UC to resolve concerns about malignancy or serious infection attributable to,

- A different patient population (UC) with unique susceptibility to malignancy and serious infection.
- The higher dose IV induction and more frequent SQ maintenance dosing proposed for UC.

The current FDA label for ustekinumab displays Warnings and Precautions for Infections and Malignancies, as reproduced below:

- Infections: Serious infections have occurred. Do not start STELARA® during any clinically important active infection. If a serious infection or clinically significant infection develops, consider discontinuing STELARA® until the infection resolves.

- Malignancies: STELARA® may increase risk of malignancy. The safety of STELARA® in patients with a history of or a known malignancy has not been evaluated.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose	Infection	Malignancy
Assess a known serious risk	X	X
Assess signals of serious risk		
Identify unexpected serious risk when available data indicate potential for serious risk		

1.4. Statement of Purpose

Comparative analysis to assess long-term (7-year) risks for serious infection and malignancy in UC patients on treatment or previously treated with ustekinumab. DGIEP regards infection and malignancy as known serious risks because of previous FDA labeling decisions resulting in the currently active Warnings and Precautions for Infections and Malignancies. See Section 1.2, above.

The following analysis for ARIA sufficiency relies on an assessment previously completed as part of the BLA 761044 approval of ustekinumab for CD.[3]

[3] Weissfeld, JL, SK Sandhu, C Wang, and R Ball, ARIA Sufficiency Memo for ustekinumab (Stelara®), filed under BLA 761044 on August 19, 2016 (DARRTS Reference ID: 3973530).

1.5. Effect Size of Interest or Estimated Sample Size Desired

To detect 2-fold malignancy risk with 80% power (alpha 0.05, two-sided) from ustekinumab in UC and CD patients followed ≥7 years after first exposure.[4]

2. SURVEILLANCE OR DESIRED STUDY POPULATION

2.1 Population

Adults with UC severe enough to require treatment with a biologic.

2.2 Is ARIA sufficient to assess the intended population?

Yes. DEPI regards outpatient and inpatient diagnosis codes and pharmacy and procedure codes in ARIA as a sufficient means for identifying patients with at least moderately severe UC. Hou, et al., 2014,[5] reviewed medical charts in the Department of Veterans Affairs to confirm inflammatory bowel disease in 1,298 of 1,871 patients (positive predictive value, PPV, 0.69) with ≥1 ICD-9 inpatient or outpatient administrative code for CD or UC. Hou, et al., measured PPV at 0.87 by requiring ≥2 outpatient codes or ≥1 inpatient code. Following Hou, et al., ARIA establishes UC with reasonable confidence by excluding patients with a diagnosis code for any biologic treatment indication other than UC and by requiring ≥1 diagnosis code for UC AND ≥1 pharmacy or procedure code for a UC biologic.

3 EXPOSURES

3.1 Treatment Exposure(s)

Treatment with ustekinumab in outpatient setting.

3.2 Comparator Exposure(s)

Treatment with non-ustekinumab biologic (TNF-α inhibitor or anti-integrin) in outpatient setting.

3.3 Is ARIA sufficient to identify the exposure of interest?

Yes. DEPI regards pharmacy and procedure codes in ARIA as a sufficient means for identifying treatment with a biologic.[6]

4 OUTCOME(S)

4.1 Outcomes of Interest

DEPI defines Serious Infection by infection that requires hospitalization. DEPI defines Malignancies by malignancy with long latency, that is, malignancy first apparent 3 to 7 years after first exposure to ustekinumab.

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[4] Weissfeld, JL, PL Bright, and W Hua, An Observational Study to Assess the Long-term Safety of Ustekinumab versus Other Biologic Therapies among Patients with Crohn's Disease: A New-User Cohort Study Using the Department of Defense Electronic Health Records Database (Protocol RRA-18896), filed under IND 011632 on August 23, 2018 (DARRTS Reference ID: 4310960).

[5] Hou, JK, M Tan, RW Stidham, J Colozzi, D Adams, H El-Serag and AK Waljee, 2014, Accuracy of diagnostic codes for identifying patients with ulcerative colitis and Crohn's disease in the Veterans Affairs Health Care System, Dig Dis Sci, 59:2406-10.

[6] Pending results from a confirmatory study of a method for defining ustekinumab or comparator treatment episodes in Sentinel. See, Sentinel Query Portal, Stelara and Serious Infections - Utilization (Type 5), SOC ID QF-2072.

4.2 Is ARIA sufficient to assess the outcome of interest?

For Serious Infection: Yes. Though results vary by type of infection,[7] diagnostic codes in hospital claims can identify many types of serious infection with acceptable accuracy (>70% positive predictive value). For example, Schneeweiss, et al., 2007,[8] used an administrative database for the Department of Veterans Affairs to identify 158 patients hospitalized with a primary ICD-9 diagnosis code for a bacterial infection, including, by type, pneumonia, bacteremia or septicemia, cellulitis, encephalitis or meningitis, endocarditis or myocarditis, pyelonephritis, septic arthritis, or osteomyelitis. A physician examined the complete electronic medical record for each hospitalization and extracted pre-prespecified items of clinical information to a standardized abstraction form. For validation, 126 of 158 abstracts (PPV 0.80, 95% CI 0.74-0.86) satisfied type-specific diagnostic criteria for bacterial infection, as defined by a specialist in infectious diseases.[9]

For Malignancies: No. Complex algorithms based on codes identify malignancy with marginally acceptable accuracy.[10] However, ARIA currently relies heavily on information submitted by private healthcare providers on behalf of patients with commercial health insurance. Because of instability in the U.S. marketplace for medical insurance, ARIA cannot satisfy regulatory requirements for long-term follow-up.

5 COVARIATES

5.1 Covariates of Interest

Essential covariates include age, sex, personal history of malignancy, personal history of infection, and concomitant treatment for inflammatory bowel disease (CD and UC).

5.2 Is ARIA sufficient to assess the covariates of interest?

Yes. ARIA provides sex and age. ARIA uses codes appearing over time on outpatient, hospital, or pharmacy claims to define medical history and comorbidity variables. Because of the time-limited coverages typical in ARIA, patient-level identification of medical history and comorbidity variables typically relies on claims submitted over brief (6- to 12-month) look-back periods. However, to control for confounding by indication, DEPI attaches importance to preceding events occurring relatively close in time to ustekinumab exposure. DEPI assesses the brief look-back periods possible in ARIA as a sufficient means for identifying essential covariates.

6 SURVEILLANCE DESIGN / ANALYTIC TOOLS

6.1 Surveillance or Study Design

Covariate-controlled analysis by propensity-score-matched proportional hazards regression.

6.2 Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?

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[7] Barber, C, D Lacaille, PR Fortin, 2013, Systematic review of validation studies of the use of administrative data to identify serious infections, Arthritis Care Res, 65:1343-1357.

[8] Schneeweiss, S, A Robicsek, R Scranton, D Zuckerman and DH Solomon, 2007, Veteran's Affairs hospital discharge databases coded serious bacterial infections accurately, J Clin Epidemiol, 60:397-409.

[9] To support ARIA, the OSE Sentinel Team opened a study through the University of Pennsylvania (Vincent Lo Re, Workgroup Leader) to validate algorithms for serious bacterial infection in Sentinel.

[10] Setoguchi, S, DH Solomon, RJ Glynn, EF Cook, R Levin and S Schneeweiss, 2007, Agreement of diagnosis and its date for hematologic malignancies and solid tumors between Medicare Claims and cancer registry data, Cancer Causes Control, 18:561-9.

Yes. ARIA provides sufficient tools for covariate-controlled analysis by propensity-score-matched proportional hazards regression.

7 NEXT STEPS

Determining ARIA sufficient for Serious Infection, DEPI plans to conduct ARIA-directed analysis of serious infections in UC patients on ustekinumab.

Determining ARIA not sufficient for Malignancies, FDA may issue a PMR under FDAAA for a Sponsor-directed long-term study of latent malignancy in UC patients exposed to ustekinumab. FDA might issue this PMR by using the following text, modeled after PMR 3112-1 for CD.[11]

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 ulcerative colitis. 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.

The Sponsor might satisfy this UC PMR by amending RRA-18896, *An Observational Study to Assess the Long-term Safety of Ustekinumab versus Other Biologic Therapies among Patients with Crohn's Disease: A New-User Cohort Study Using the Department of Defense Electronic Health Records Database*.[12] FDA might communicate this possibility by including the following statement in an Approval Letter for BLA 761044/S-003.

The existing observational study in patients with Crohn's disease with the same objectives may be expanded to also enroll patients with ulcerative colitis.

[11] Per DEPI policy and practice, ARIA analysis for sufficiency excluded the secondary outcome of opportunistic infections.

[12] FDA received the Final Protocol for PMR 3112-1 on October 3, 2018. See, Acknowledge Final Protocol for Postmarketing Requirement, filed under IND 011632 on November 11, 2018 (DARRTS Reference ID: 4343669

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/s/

JOEL L WEISSFELD
09/18/2019 11:25:36 AM

PATRICIA L BRIGHT
09/18/2019 12:36:33 PM

SUKHMINDER K SANDHU
09/18/2019 12:47:24 PM

JUDITH W ZANDER
09/20/2019 12:00:43 PM

MICHAEL D NGUYEN
09/20/2019 12:09:58 PM

ROBERT BALL
09/20/2019 12:51:53 PM

Clinical Inspection Summary

Date	August 20, 2019
From	Susan Leibenhaut, M.D., OSI/DCCE/GCPAB Susan Thompson, M.D., Team Leader, OSI/DCCE/GCPAB Kassa Ayalew, M.D., M.P.H., Branch Chief, OSI/DCCE/GCPAB
To	Frank Anania, M.D., Medical Officer, DGIEP
BLA #	761044/S-003
Applicant	Janssen Biotech, Inc.
Drug	Ustekinumab
NME	No
Division Classification	Ulcerative colitis
Proposed Indication	Treatment for ulcerative colitis
Consultation Request Date	February 14, 2019
Summary Goal Date	August 28, 2019
Action Goal Date	October 20, 2019
PDUFA Date	October 20, 2019

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Inspections for this NDA were conducted at three clinical investigator (CI) sites. No significant regulatory findings or data integrity issues were noted. The study data generated by these sites are acceptable in support of the application.

II. BACKGROUND

The sponsor submitted this supplemental BLA for ustekinumab for the indication of treatment of adult patients with moderately to severely active ulcerative colitis (UC) (b) (4)

(b) (4)

The product is a human monoclonal antibody directed against interleukin 12 and interleukin 23, naturally occurring proteins that regulate the immune system and immune-mediated inflammatory disorders. It was approved by the FDA for psoriasis in 2008 and for Crohn's Disease in 2016.

Biologic: Ustekinumab

Studies– Protocol numbers and titles for all studies that were inspected

1. Protocol CNTO1275UCO3001 entitled "A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Induction and Maintenance Therapy in Subjects with Moderately to Severely Active Ulcerative Colitis"

Number of subjects: 961 subjects (induction); 783 subjects (maintenance)
Number of sites: 244 sites (induction); 201 sites (maintenance)
Number of countries where subjects were enrolled: 24
Dates that study was conducted: August 19, 2015 to December 11, 2017 (induction)
August 19, 2015 to August 12, 2018 (maintenance)
Efficacy Endpoint: Proportion of subjects who achieved clinical remission defined for the U.S. population as:

- absolute stool number ≤ 3
- Mayo rectal bleeding subscore of 0
- Mayo endoscopy subscore of 0 or 1.

For Induction, this was determined at Week 8 (or 16) and for Maintenance, this was measured at Week 44.

Sites were chosen based on enrollment, inspectional history, and number of INDs in the OSI database.

III. RESULTS (by site):

1. **Michael Chiorean, M. D.**
   Site # A96-US00043
   Virginia Mason Medical Center, 1100 9th Ave, Seattle, WA 98101

   At this site, for Protocol CNTO1275UCO3001 induction, there were 9 subjects screened, 7 subjects were randomized, and 6 subjects completed through maintenance. A total of 7 subject records were reviewed. The records were reviewed for informed consent process, staff training, test article accountability, efficacy parameters, protocol deviations, concomitant medications, eligibility criteria, and adverse events. Source documents for protocol adherence and data verification were compared to line listings from the BLA. No significant deviations or discrepancies were noted, and no Form 483 was issued. There was no evidence of under reporting of adverse events.

   The study appears to have been conducted adequately at this site and the data generated by this site may be used in support of the respective indication.

2. Naresh Gunaratnam, M.D.
Site # A96-US00037
Huron Gastroenterology Associates Center for Digestive Care, 5300 Elliott Drive, Ypsilanti, MI 48197

At this site, for Protocol CNTO1275UCO3001 induction, there were 9 subjects screened, 7 subjects were randomized, and 6 subjects completed through maintenance. Subject (b) (6) in the placebo group withdrew because of worsening of ulcerative colitis. A total of 7 subject records were reviewed. The records were reviewed for informed consent process, staff training, test article accountability, efficacy parameters, protocol deviations, concomitant medications, eligibility criteria, and adverse events. Source documents for protocol adherence and data verification were compared to line listings from the BLA. No significant deviations or discrepancies were noted, and no Form 483 was issued. There was no evidence of under reporting of adverse events.

The study appears to have been conducted adequately at this site and the data generated by this site may be used in support of the respective indication.

3. Timothy Ritter, M.D.
Site # A96-US00018
Texas Digestive Disease Consultants, 2485 E. Southlake Blvd Suite 100, Southlake, TX 76092

At this site, for Protocol CNTO1275UCO3001 induction, there were 8 subjects screened, 6 subjects were randomized, and 2 subjects completed through maintenance. All randomized subjects' records were reviewed. The records were reviewed for informed consent process, subject disposition, randomization; primary efficacy endpoint, safety endpoint, discontinuations, concomitant medications adverse events protocol deviations; and test article administration. All records were complete, and deviations were reported as appropriate to the sponsor and IRB. The primary endpoint was verifiable, and all data matched with the listings provided with this assignment. There was no evidence of under reporting of adverse events.

The study appears to have been conducted adequately at this site and the data generated by this site may be used in support of the respective indication.

{See appended electronic signature page}

Susan Leibenhaut, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:
Central Doc. Rm.
Review Division /Acting Division Director/Dragos Roman
Review Division /Medical Team Leader/Juli Tomaino
Review Division /Project Manager/Kelly Richards
Review Division/Medical Officer/Frank Anania
OSI/Office Director/David Burrow
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/ Susan D. Thompson
OSI/DCCE/GCPAB Reviewer/ Susan Leibenhaut
OSI/ GCPAB Program Analysts/ Joseph Peacock/Yolanda Patague
OSI/Database PM/Dana Walters

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SUSAN LEIBENHAUT
08/20/2019 05:03:01 PM

SUSAN D THOMPSON
08/20/2019 05:56:09 PM

KASSA AYALEW
08/20/2019 10:08:21 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology Review (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology Review of Study Report

Date:	May 24, 2019
Reviewer(s):	Joel L. Weissfeld, MD MPH Division of Epidemiology I
Team Leader:	Patricia L. Bright, MSPH PhD Division of Epidemiology I
Deputy Director:	Sukhminder K. Sandhu, PhD MPH MS Division of Epidemiology I
Drug Name(s):	ustekinumab (Stelara®)
Subject:	Sponsor Presentation of Malignancy Events in an Efficacy Supplement for Ulcerative Colitis
Application Type/Number:	BLA 761044/S-003 (eCTD 0074)
Applicant/sponsor:	Janssen
OSE RCM #:	2019-771 (Due Date: 9/13/19)

TABLE OF CONTENTS

EXECUTIVE SUMMARY

To advise the Division of Gastroenterology and Inborn Error Products (DGIEP) about labeling, the Division of Epidemiology I (DEPI) reviewed a sponsor's presentation of malignancy events in an efficacy supplement that seeks FDA approval for ustekinumab as a treatment for ulcerative colitis (UC).

Ustekinumab is a human interleukin-12 and -23 antagonist approved in (1) 2009 for psoriasis (BLA 125261), (2) 2013 for psoriatic arthritis (BLA 125261), and (3) 2016 for Crohn's disease (BLA 761044). In December 2018, the ustekinumab sponsor (Janssen) submitted an efficacy supplement (BLA 761044/S-003) for UC.

Janssen presented results from an analysis that included 19 patients with an incident malignancy event other than non-melanoma skin cancer (NMSC). Qualifying events occurred during the first year of patient participation in an ustekinumab clinical trial program across four disease populations, including UC, Crohn's disease, psoriasis, and psoriatic arthritis. Seventeen events occurred during treatment with ustekinumab. For comparison, Janssen used sex-, age-, and race-specific cancer incidence rates for the general U.S. population to calculate 23.48 as the number of malignancy events expected during ustekinumab treatment. Observing fewer events than expected, Janssen concluded by finding no evidence for increased risk of malignancy from ustekinumab.

DEPI validated Janssen's analysis of malignancy events. Though considered appropriate for FDA use as a data point in a benefit-risk assessment for BLA 761044/S-003, DEPI determined that Janssen's comparative analysis against the general U.S. population provided too little information about possible malignancy risks in UC to merit specific mention in the ustekinumab label.

1 INTRODUCTION

To advise the Division of Gastroenterology and Inborn Error Products (DGIEP) about labeling, the Division of Epidemiology I (DEPI) reviews a sponsor's presentation of malignancy events in an efficacy supplement that seeks FDA approval for ustekinumab as a treatment for ulcerative colitis (UC).

Ustekinumab is a human interleukin-12 and -23 antagonist approved in (1) 2009 for psoriasis (BLA 125261), (2) 2013 for psoriatic arthritis (BLA 125261), and (3) 2016 for Crohn's disease (BLA 761044). In December 2018, the ustekinumab sponsor (Janssen) submitted an efficacy supplement (BLA 761044/S-003) for UC.

Table 1 shows core results for malignancy other than non-melanoma-skin cancer (NMSC) during the UC induction and maintenance trials for BLA 761044/S-003. The Janssen presentation

limited analysis to the first year of follow-up.[a]

Table 1: Core results for malignancy other than non-melanoma-skin cancer (NMSC) during the UC induction and maintenance trials for BLA 761044/S-003. See FOOTNOTES.

	PLO	UST
All Patients		
Patients, N	446	825
Patient-years	250	626
Patients with ≥1 malignancy other than NMSC	1	4
SEER-Eligible Patients		
Patients, N	417	757
Patient-years	203	577
Patients with ≥1 malignancy other than NMSC	1	4

SOURCE: ISS Table TSFMAL72C
ABBREVIATIONS: PLO – placebo; UST – ustekinumab
FOOTNOTES:
1. Placebo (PLO) follow-up includes time up to the first ustekinumab dose for patients assigned placebo for induction and ustekinumab for maintenance.
2. Placebo (PLO) follow-up also includes time after week 16 for patients assigned ustekinumab for induction and placebo for maintenance.
3. Ustekinumab (UST) follow-up includes time up to 16 weeks for patients assigned ustekinumab for induction and placebo for maintenance.
4. SEER eligibility determined by information about race. SEER analysis presumably excluded patients with race coded as MULTIPLE, OTHER, NOT REPORTED, or UNKNOWN.

Finding too few events for comparative analysis (one patient with malignancy during placebo follow-up and four patients with malignancy during ustekinumab follow-up), Janssen supplemented malignancy results from the UC trials with results from Crohn's disease (CD), psoriasis (PSO), and psoriatic arthritis (PSA) trials. Using an indirect adjustment method, Janssen combined results from UC and CD trials to present results for all Inflammatory Bowel Disease (IBD). In addition, Janssen combined results from UC, CD, PSO, and PSA trials to presents results for All Diseases Pooled. The Janssen presented results in Integrated Summary of Safety (ISS) Table TSFMAL72C. See **APPENDIX 1** for a copy of this table.

The U.S. Surveillance, Epidemiology, and End Results (SEER) Program provided Janssen with the external standard for indirect adjustment. Following SEER convention, Janssen excluded *in situ* cervical cancer and NMSC.

Acknowledging interpretation "limited by the small number of events and the overall duration of exposure," Janssen assessed results in ISS Table TSFMAL72C as showing no "evidence of an

[a] The study timeframe extended through week 60 for subjects entering maintenance after 16 weeks of induction.

increased risk of malignancy in subjects with UC, IBD, or for all diseases pooled treated with ustekinumab, over the period studied."[b]

The draft label uses the following statement to summarize results shown above in Table 1.[c]

> **With up to one year of treatment in the ulcerative colitis clinical studies, … [m]alignancies other than non-melanoma skin cancers occurred in 0.5% of STELARA®-treated patients (0.64 events per hundred patient-years) and 0.2% of placebo-treated patients (0.40 events per hundred patient-years).**

The current label presents results from a different SEER analysis, previously conducted in psoriasis patients with "median follow-up of 3.2 years, representing 8998 subject-years of exposure," as follows.[d]

> **Malignancies other than non-melanoma skin cancer in STELARA®-treated patients during the controlled and uncontrolled portions of [psoriasis clinical] studies were similar in type and number to what would be expected in the general U.S. population according to the SEER database (adjusted for age, gender and race).**

The draft label does not mention the SEER analysis conducted for BLA 761044/S-003.

2 REVIEW METHODS AND MATERIALS

2.1 Documents Reviewed

This review references the following documents and datasets submitted to BLA 761044 (eCTD 0074) on December 20, 2018.

Reference	Module	Description
SCS	2.7.4	Summary of Clinical Safety
ISS	5.3.5.3	Integrated Summary of Safety
adseer.xpt	5.3.5.3	SEER Malignancy Analysis Dataset
all-malignancies-age-sex-race-2000-2015.txt	5.3.5.3	SEER Standard Rates

2.2 Criteria Applied to Review

DEPI uses the Standardized Incidence Ratio (SIR) to express the ratio between the observed and

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[b] Summary of Clinical Safety, Section 2.3.1.8.1.3, p 107.

[c] Prescribing Information for STELARA® (ustekinumab) injection, for subcutaneous or intravenous use, Section 6.1 Clinical Trials Experience (p 15), submitted to BLA 761044 (eCTD 0074) on December 20, 2018.

[d] Prescribing Information for STELARA® (ustekinumab) injection, for subcutaneous or intravenous use, Section 6.1 Clinical Trials Experience (p 11), accessed at Drugs@FDA on May 15, 2019.

expected number of patients with malignancy other than NMSC.

DEPI used (1) SEER*Stat Software (Version 8.3.5) to generate sex-, race-, and age-specific standard incidence rates for malignancy, (2) SAS (Version 9.4) to tabulate sex-, race-, and age-specific malignancy counts and patient-years in adseer.xpt, and (3) Microsoft Excel to calculate expected malignancy counts from patient-years and SEER incidence,[e] and (4) Ulm's method to calculate confidence intervals for the SIR.[f]

3 REVIEW RESULTS

3.1 Standard Rates

As shown in **APPENDIX 2**, DEPI used a 2000-2015 SEER database and SEER*Stat to reproduce the sex-, race-, and age-specific standard incidence rates submitted by the Sponsor.

DEPI generated additional standard rates for sensitivity analysis. The first set selected the malignant behavior option in SEER*Stat. The second set further restricted analysis to events incident in 2007-2010.

3.2 Malignancy Counts and Patient-Years

DEPI used methods summarized in **APPENDIX 3** and **APPENDIX 4** to reproduce the malignancy event counts and patient-years shown in ISS Table TSFMAL72C and Table 2, below.

Table 2: Observed malignancy event counts (OBS) and patient-years (PYS), by disease program and exposure.

	PLACEBO		USTEKINUMAB	
Disease Program	**OBS**	**PYS**	**OBS**	**PYS**
Ulcerative Colitis	1	203.1	4	577.3
Crohn's Disease	0	334.1	2	1,048.0
Inflammatory Bowel Diseases	**1**	**537.2**	**6**	**1,625.3**
Psoriasis	1	179.1	10	2,496.8
Psoriatic Arthritis	0	143.2	1	839.3
Psoriatic Diseases	**1**	**322.3**	**11**	**3,336.1**
All Diseases Pooled	**2**	**859.5**	**17**	**4,961.4**

SOURCE: Results generated by DEPI from adseer.xpt.

Within each disease program, patient-years distributed similarly by exposure (Table 3). When

[e] SEER Workbook.xls, filed in OSE Agency Information Management System (AIMS) under RCM 2019-771 on <date to be determined>.

[f] Ulm K. Simple method to calculate the confidence interval of a standardized mortality ratio (SMR). Am J Epidemiol 131(2):373-375, 1990.

evaluated across programs, however, patient-years distributed differently on,

- Sex, with patient-years from men relatively more frequent in the UC and psoriasis programs.
- Race, with patient-years from Asian and Pacific Islanders most frequent in the UC program.
- Age, with patient-years during young-adult age (15-39 years) most frequent in the Crohn's disease program.
- Country, with patient-years from U.S. clinical sites accounting for 17, 40, 39, and 25 percent of patient-years in the UC, Crohn's disease, psoriasis, and psoriatic arthritis programs, respectively.

Table 3: Patient-years, percent distribution according to each of five factors, by disease program and exposure. See Table 2 for patient-year totals.

		UC		CD		PSO		PSA	
Factor	**Value**	**PLO**	**UST**	**PLO**	**UST**	**PLO**	**UST**	**PLO**	**UST**
Sex	Men	62.5	60.1	45.2	43.3	70.7	68.3	51.7	52.1
	Women	37.5	39.9	54.8	56.7	29.3	31.7	48.3	47.9
Race	White	82.1	83.0	91.2	89.4	93.2	94.6	98.7	98.1
	Black	1.0	1.0	4.1	2.9	2.2	2.2	0.3	0.5
	AI/AN	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0
	AS/PI	16.9	16.0	4.7	7.6	4.6	3.1	1.0	1.4
Age, years	15-39	45.0	47.3	54.5	56.4	29.7	30.8	25.1	24.7
	40-64	49.4	47.7	41.7	40.3	63.6	63.4	69.4	68.9
	≥65	5.6	5.0	3.7	3.3	6.7	5.7	5.5	6.5
Country	United States	14.8	18.4	39.5	39.7	42.0	38.3	24.4	25.2
	Canada	1.4	1.6	6.6	8.5	45.8	48.2	15.1	12.7
	Japan or Korea	15.5	14.9	4.2	6.7	0.0	0.0	0.0	0.0
	Other	68.3	65.2	49.7	45.1	12.2	13.5	60.5	62.1
Duration of follow-up in years	<0.5	68.1	57.7	78.6	68.3	99.6	58.8	97.9	58.1
	≥0.5, <1.0	31.4	38.1	21.0	31.2	0.4	40.7	2.1	38.4
	≥1.0	0.5	4.2	0.4	0.6	0.0	0.5	0.0	3.5

SOURCE: Results generated by DEPI from adseer.xpt.
ABBREVIATIONS: UC – ulcerative colitis; CD – Crohn's disease; PSO – psoriasis; PSA – psoriatic arthritis; PLO – placebo; UST – ustekinumab; AI/AN – American Indian or Alaska Native; AS/PI – Asian or Pacific Islander

Of note, only 4.2% of total patient-years (24.5 of 577.3 patient-years) accrued after one year on ustekinumab in the UC program (Table 3).

The UC program accumulated patient-years during a period not in temporal overlap with the other three programs (Table 4).

Table 4: Year and month of minimum start date and maximum end date, by disease program.

PROGRAM	START	END
Psoriasis	2003-JUL	2008-NOV
Crohn's disease	2004-MAY	2015-JUN
Psoriatic arthritis	2006-JAN	2012-NOV
Ulcerative colitis	2015-AUG	2018-JUL

SOURCE: Results generated by DEPI from ASTDT and AENDT variable fields in adseer.xpt.

3.3 Final Calculations

Table 5 shows the number of malignancies expected (EXP) and the standardized incidence ratios (SIR) determined by each of three sets of standard rates (**APPENDIX 2**). **APPENDIX 5** demonstrates use of **BLA** standard rates from **APPENDIX 2** and patient-years (PYS) from **APPENDIX 4** to calculate the number of malignancies expected from ustekinumab in the UC program. Table 5 shows this expected count (2.338) in italics.

Table 5: Results from final calculations.

	UC		CD		IBD		PS		ALL	
	PLO	**UST**	**PLO**	**UST**	**PLO**	**UST**	**PLO**	**UST**	**PLO**	**UST**
PYS	203	577	334	1,048	537	1,625	322	3,336	860	4,961
OBS	1	4	0	2	1	6	1	11	2	17
SET 1 Standard Rates [1,2]										
EXP	0.856	*2.338*	1.162	3.494	2.018	5.832	1.759	17.644	3.777	23.476
SIR	1.17	1.71	0.00	0.57	0.50	1.03	0.57	0.62	0.53	0.72
95% CI	0.03-6.51	0.47-4.38	0.00-**3.17**	0.07-2.07	0.01-2.76	0.38-2.24	0.01-3.17	0.31-1.12	0.06-1.91	0.42-1.16
SET 2 Standard Rates [3]										
EXP	0.772	2.098	1.016	3.051	1.787	5.150	1.579	15.875	3.366	21.025
SIR	1.30	1.91	0.00	0.66	0.56	1.17	0.63	0.69	0.59	0.81
95% CI	0.03-7.22	0.52-4.88	0.00-3.63	0.08-2.37	0.01-3.12	0.43-2.54	0.02-3.53	0.35-1.24	0.07-2.15	0.47-1.29
SET 3 Standard Rates [4]										
EXP	0.814	2.217	1.063	3.197	1.877	5.414	1.667	16.780	3.544	22.195
SIR	1.23	1.80	0.00	0.63	0.53	1.11	0.60	0.66	0.56	0.77
95% CI	0.03-6.84	0.49-4.62	0.00-3.47	0.08-2.26	0.01-2.97	0.41-2.41	0.02-3.34	0.33-1.17	0.07-2.04	0.45-1.23

SOURCE: Results generated by DEPI from adseer.xpt.
ABBREVIATIONS: UC – ulcerative colitis; CD – Crohn's disease; IBD – inflammatory bowel diseases (UC and CD programs combined); PS – psoriatic diseases (psoriasis and psoriatic arthritis programs combined); PLO – placebo; UST – ustekinumab; PYS – patient-years; OBS – number of malignancy events observed; EXP – number of malignancy events expected; SIR – standardized incidence ratio; CI– confidence interval
FOOTNOTES:
1. Results produced with SEER standard rates for malignant and non-malignant events incident in 2000 through 2015 (**APPENDIX 2)**.
2. Results reproduce ISS Table TSFMAL72C, except for the bolded upper 95% confidence limit. ISS Table TSFMAL72C incorrectly shows this limit as 2.58.

3. Results produced with SEER standard rates for malignant events incident in 2000 through 2015 (**APPENDIX 2**).
4. Results produced with SEER standard rates for malignant events incident in 2007 through 2010 (**APPENDIX 2**).

3.4 Case-Based Analysis

Malignancy occurred in four UC patients during exposure to ustekinumab, including rectal cancer in a 32-year-old man, colon cancer in 48-year-old woman, prostate cancer in a 61-year-old man, and renal cancer in a 70-year-old man (Table 6). Table 6 lists malignancy types observed in the Crohn's and psoriatic disease programs.

Table 6: List of patients with malignancy.

STUDY ID	PGM	SEX	AGE	RX	MALIGNANCY TYPE	DAY
CNTO1275UCO3001 (b) (6)	UC	M	25	PLO	testicular	302
CNTO1275UCO3001	UC	M	32	UST	rectal	159
CNTO1275UCO3001	UC	F	48	UST	colon	59
CNTO1275UCO3001	UC	M	61	UST	prostate	69
CNTO1275UCO3001	UC	M	70	UST	renal	92
CNTO1275CRD3001	CD	M	57	UST	myeloma	199
CNTO1275CRD3001	CD	M	68	UST	small intestinal adenocarcinoma	255
C0743T (b) (6)	PS	M	63	PLO	hepatocellular carcinoma	12
C0743T	PS	F	41	UST	breast	367
C0743T	PS	M	44	UST	thyroid	236
C0743T	PS	M	54	UST	chronic lymphocytic leukemia	288
C0743T	PS	F	58	UST	breast	52
C0743T	PS	M	59	UST	prostate	220
C0743T	PS	M	61	UST	renal	350
CNTO1275PsA3002- (b) (6)	PS	F	62	UST	breast	215
C0379T (b) (6)	PS	M	64	UST	prostate	44
C0743T	PS	M	65	UST	mycosis fungoides	125
C0743T	PS	M	69	UST	tongue	246
C0743T	PS	M	69	UST	oral	267

SOURCE: DEPI extracted malignancy type and study day of onset from ISS Table LSFMAL72C.
ABBREVIATIONS: PGM – disease program; UC – ulcerative colitis; CD – Crohn's disease; PS – psoriatic diseases (psoriasis or psoriatic arthritis); RX – treatment; PLO – placebo; UST – ustekinumab; DAY – study day of onset

4 DISCUSSION

Janssen presented results from an analysis that included 19 patients with an incident malignancy event other than NMSC (Table 6). Qualifying events occurred during the first year (≤367 days) of patient participation in a UC, CD, PSO, or PSA clinical trial program for ustekinumab.[g] Seventeen events occurred during treatment with ustekinumab. Using sex-, age-, and race-

[g] The ustekinumab clinical trials included one UC trial (CNTO1275UCO3001), three CD trials (CD C0379T07, C0743T26, and CNTO1275CRD3003), four psoriasis trials (PSOC0379T04, C0743T08, C0743T09, and C0743T12), and three psoriatic arthritis trials (C0743T10, CNTO1275PsA3001, and CNTO1275PsA3002).

specific cancer incidence rates from SEER, Janssen calculated the number of events expected at 23.48 (SIR 0.72, 95% CI 0.42-1.16). Observing fewer events than expected, Janssen concluded by finding no evidence for increased risk of malignancy from ustekinumab.

Janssen presented complete results in ISS Table TSFMAL72C (**APPENDIX 1**). DEPI validated results in this table by,

- Independently identifying the set of standard incidence rates used for indirect adjustment (**APPENDIX 2**).

- Using a Janssen-submitted dataset (adseer.xpt) to verify event counts and patient-year totals observed in each disease program by exposure grouping (**APPENDIX 4**).

- Using sex-, age-, and race-specific incidence rates from SEER and patient-years from adseer.xpt to reproduce Janssen's calculation of the number of events expected in each disease program by exposure grouping (**APPENDIX 5**).

- Using observed and expected event counts to reproduce Janssen's SIR calculations.

DEPI identified one error in ISS Table TSFMAL72C, an incorrect SIR upper 95% confidence limit for CD patients during placebo follow-up (incorrect limit 2.38, correct limit 3.17; Table 5).

Favoring the malignant behavior option in SEER*Stat, DEPI evaluated a more proper set of standard incidence rates.[h] This correction reduced the number of events expected overall from 23.48 to 21.02 and changed the final SIR from 0.72 (95% CI 0.42-1.16) to 0.81 (95% CI 0.47-1.29). Because of other concerns, as discussed below, DEPI assessed this correction as having no meaningful impact on interpretation.

Technical problems with the Janssen analysis included (1) using a U.S. standard (SEER) to provide background rates for an international drug development program and (2) missing adjustments for calendar-time differences across the UC, CD, PSO, and PSA disease programs (Table 4). Despite these problems, DEPI viewed Janssen's approach as pragmatic and reasonable.

With this understanding, DEPI assessed the number of malignancy events presented by Janssen as not unexpected or surprising. A comparable number of events might reasonably occur in a

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[h] SEER requires ICD-O-3 histology and behavior coding. Permitted ICD-O-3 codes for behavior include 0 (benign), 1 (uncertain behavior), 2 (carcinoma *in situ*), 3 (malignant, primary site), 6 (malignant, metastatic site), and 9 (malignant, uncertain whether primary or metastatic site). The "Select Only Malignant Behavior" option in SEER*Stat identifies cases reported to SEER with ICD-O-3 behavior coded as malignant, primary site. Moreover, SEER mandates reporting of all cases with ICD-O-3 behavior coded as malignant, primary site, or carcinoma *in situ*. Central reporting of cases with other behavior codes is optional. These factors prohibit the use of SEER as a source of background rates for benign tumors and tumor metastasis, entities often included in adverse event reports to FDA. See https://seer.cancer.gov/behavrecode/ and https://codes.iarc fr/usingicdo.php.

general population sample with the same demographic and follow-up characteristics as the SEER-eligible patients in Janssen's analysis.

Another problem to interpretation included small sample size (*e.g.*, 825 UC patients with 626 patient-years in exposure to ustekinumab; Table 1). With follow-up limited to one year, the Janssen analysis offered no information about long latency malignancy or long-term (>60-week) treatment with ustekinumab.

Finally, DEPI accepted without question the derived adseer.xpt dataset. This dataset organized information sourced from separate clinical trial datasets. DEPI undertook no effort to validate adseer.xpt against these sources. Validating adseer.xpt against source datasets might assume importance if FDA's benefit-risk assessment for BLA 761044/S-003 hinges on the Janssen presentation of results for malignancy.

The draft label currently shows non-NMSC malignancy risks during the first year of UC clinical studies as 0.64 and 0.40 events per 100 patient-years in ustekinumab and placebo patients, respectively. These results agree with the event counts and patient-year totals shown in ISS Table TSFMAL72C for all UC patients (Table 1). With the many limits to interpretation listed above, however, particularly analysis limited to the first year of follow-up, the draft label appropriately omits results from SIR analysis in UC patients.

5 CONCLUSIONS

DEPI reproduced Janssen's analysis of malignancy events in an efficacy supplement that seeks FDA-approval for ustekinumab as a UC treatment. Janssen used SEER as an external standard. Though appropriate for FDA use as a data point in a benefit-risk assessment for BLA 761044/S-003, the SEER-referenced results presented by Janssen provided too little information about possible malignancy risks in UC to merit specific mention in the ustekinumab label.

6 RECOMMENDATIONS FOR DGIEP

DEPI recommends that DGIEP accept a draft ustekinumab label without mention of new results from SEER-referenced analysis.

CC: Pinheiro S / Sandhu S / Hua W / Bright P / Iannacone M / Billings M / Dunson A / Calloway P (OSE)

Tomaino J / Anania F / Richards K (DGIEP)

APPENDIX 1: ISS Table TSFMAL72C

TSFMAL72C: Number of Subjects with 1 or More Malignancies Per Hundred Subject-Years of Follow-Up Through One Year[a] of Follow Up (Comparing with SEER Data); Treated Subjects in Inflammatory Bowel Disease (Ulcerative Colitis and Crohn's Disease) and Psoriatic Diseases (Psoriasis and Psoriatic Arthritis) Studies[b]

	Ulcerative Colitis		Crohn's Disease		Inflammatory Bowel Disease		Psoriatic Diseases		All Diseases Pooled	
	Placebo[c]	Ustekinumab[d]	Placebo[c]	Ustekinumab[d]	Placebo[c]	Ustekinumab[d]	Placebo[e]	Ustekinumab[f]	Placebo[c,e]	Ustekinumab[d,f]
Subjects treated	446	825	943	1749	1389	2574	1112	4135	2501	6709
N[g]	417	757	914	1689	1331	2446	1095	4038	2426	6484
Total subject-years of follow-up	203	577	334	1048	537	1625	322	3336	860	4961
Median subject-years of follow-up	0.4	1.0	0.2	0.6	0.2	0.7	0.2	0.9	0.2	0.8
Observed number of subjects with event	1	4	0	2	1	6	1	11	2	17
Expected number of subjects[h] with event	0.86	2.34	1.16	3.49	2.02	5.83	1.76	17.64	3.78	23.48
SIR[i]	1.17	1.71	0.00	0.57	0.50	1.03	0.57	0.62	0.53	0.72
SIR 95% confidence interval[j]	(0.03, 6.51)	(0.47, 4.38)	(0.00, 2.58)	(0.07, 2.07)	(0.01, 2.76)	(0.38, 2.24)	(0.01, 3.17)	(0.31, 1.12)	(0.06, 1.91)	(0.42, 1.16)

APPENDIX 2: SEER standard rates

The following tables show sex-, age-, and race-specific incidence rates (per 1000) from 18 population-based cancer registries in the Surveillance, Epidemiology, and End Results (SEER) Program.[i] The Sponsor submitted the results shown under the heading **BLA**.[j]

DEPI used SEER*Stat to produce the results shown under the headings **SET 1**, **SET 2**, and **SET 3**.[k] The sex-, age-, and race-specific malignancy and population counts in **SET 1** and **BLA** matched exactly (results not shown in this review). Rounding explains the small differences shown between **BLA** and **SET 1** with respect to the sex-, age-, and race-specific incidence rates calculated from these malignancy and population counts. DEPI produced,

- **SET 1** by selecting malignant and non-malignant events incident in 2000 through 2015.[l]
- **SET 2** by selecting malignant events incident in 2000 through 2015.
- **SET 3** by selecting malignant events incident in 2007 through 2010.

RACE: WHITE

	MEN				WOMEN			
AGE	**BLA**	**SET 1**	**SET 2**	**SET 3**	**BLA**	**SET 1**	**SET 2**	**SET 3**
15-19	0.27	0.27	0.25	0.25	0.28	0.28	0.22	0.22
20-24	0.41	0.41	0.37	0.38	0.50	0.50	0.40	0.41
25-29	0.58	0.58	0.52	0.53	0.85	0.85	0.69	0.71
30-34	0.77	0.77	0.68	0.69	1.37	1.37	1.14	1.16
35-39	1.06	1.06	0.92	0.93	2.12	2.12	1.76	1.82
40-44	1.66	1.67	1.46	1.51	3.48	3.48	2.80	2.87
45-49	2.93	2.93	2.65	2.78	5.09	5.09	4.15	4.31
50-54	5.47	5.47	5.04	5.32	6.76	6.76	5.65	5.82
55-59	9.18	9.18	8.59	9.12	8.62	8.62	7.42	7.53
60-64	14.02	14.02	13.22	14.23	11.14	11.14	9.75	10.18
65-69	20.17	20.18	19.08	20.94	14.34	14.35	12.69	13.50
70-74	24.53	24.53	23.20	25.62	16.64	16.64	14.93	15.98
75-79	27.61	27.61	25.99	28.85	18.81	18.81	17.07	18.29
80-84	28.55	28.55	26.69	29.72	19.65	19.65	17.97	19.37
85+	28.47	28.47	26.53	29.83	18.50	18.50	17.07	18.54

[i] Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2017 Sub (2000-2015) <Katrina/Rita Population Adjustment> - Linked To County Attributes - Total U.S., 1969-2016 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2018, based on the November 2017 submission.

[j] Summary of Clinical Safety – Ulcerative Colitis (Module 5.3.5.3), all-malignancies-age-sex-race-2000-2015.txt, submitted to BLA 761044 (eCTD 00764) on December 20, 2018.

[k] SEER*Stat Software, Version 8.3.5, accessed at https://seer.cancer.gov/seerstat/ on May 13, 2019.

[l] DEPI requested malignant events by selecting the Malignant Behavior user option in SEER*Stat.

RACE: BLACK

	MEN				WOMEN			
AGE	**BLA**	**SET 1**	**SET 2**	**SET 3**	**BLA**	**SET 1**	**SET 2**	**SET 3**
15-19	0.17	0.17	0.15	0.15	0.18	0.18	0.14	0.14
20-24	0.24	0.24	0.20	0.22	0.33	0.33	0.24	0.24
25-29	0.39	0.39	0.34	0.34	0.60	0.60	0.48	0.50
30-34	0.57	0.57	0.50	0.50	1.09	1.09	0.91	0.94
35-39	0.88	0.88	0.78	0.76	1.78	1.78	1.51	1.51
40-44	1.70	1.70	1.55	1.57	3.03	3.03	2.51	2.60
45-49	3.47	3.47	3.28	3.37	4.55	4.55	3.87	3.93
50-54	7.10	7.10	6.82	7.25	6.47	6.47	5.59	5.81
55-59	12.44	12.44	12.07	12.85	8.45	8.45	7.39	7.63
60-64	18.38	18.38	17.93	19.48	11.05	11.05	9.83	10.32
65-69	24.49	24.49	23.92	26.21	13.86	13.86	12.37	13.31
70-74	26.65	26.65	25.96	28.72	15.75	15.75	14.18	15.26
75-79	27.82	27.82	26.98	29.98	17.64	17.65	16.10	17.22
80-84	28.20	28.20	27.18	29.90	18.23	18.23	16.78	17.95
85+	26.84	26.84	25.73	29.25	17.98	17.98	16.67	18.00

RACE: AMERICAN INDIAN/ALASKA NATIVE

	MEN				WOMEN			
AGE	**BLA**	**SET 1**	**SET 2**	**SET 3**	**BLA**	**SET 1**	**SET 2**	**SET 3**
15-19	0.11	0.11	0.09	0.07	0.17	0.17	0.11	0.11
20-24	0.18	0.18	0.16	0.14	0.24	0.24	0.17	0.18
25-29	0.28	0.28	0.25	0.23	0.41	0.42	0.33	0.30
30-34	0.34	0.34	0.31	0.33	0.66	0.67	0.55	0.56
35-39	0.53	0.53	0.48	0.45	1.07	1.07	0.90	0.85
40-44	0.72	0.72	0.63	0.58	1.62	1.62	1.33	1.45
45-49	1.36	1.36	1.25	1.32	2.41	2.41	2.08	2.25
50-54	2.57	2.57	2.42	2.57	3.35	3.35	2.93	3.01
55-59	4.36	4.36	4.11	4.08	4.60	4.60	4.09	4.00
60-64	6.69	6.69	6.41	7.03	6.17	6.17	5.58	5.61
65-69	9.84	9.84	9.37	10.76	7.84	7.84	7.05	7.55
70-74	12.80	12.80	12.46	13.82	9.69	9.69	8.81	9.41
75-79	13.97	13.97	13.43	15.17	10.79	10.79	10.02	10.72
80-84	15.40	15.40	14.79	16.93	11.91	11.91	11.18	11.64
85+	14.66	14.66	13.59	16.60	10.70	10.70	9.98	9.06

RACE: ASIAN OR PACIFIC ISLANDER

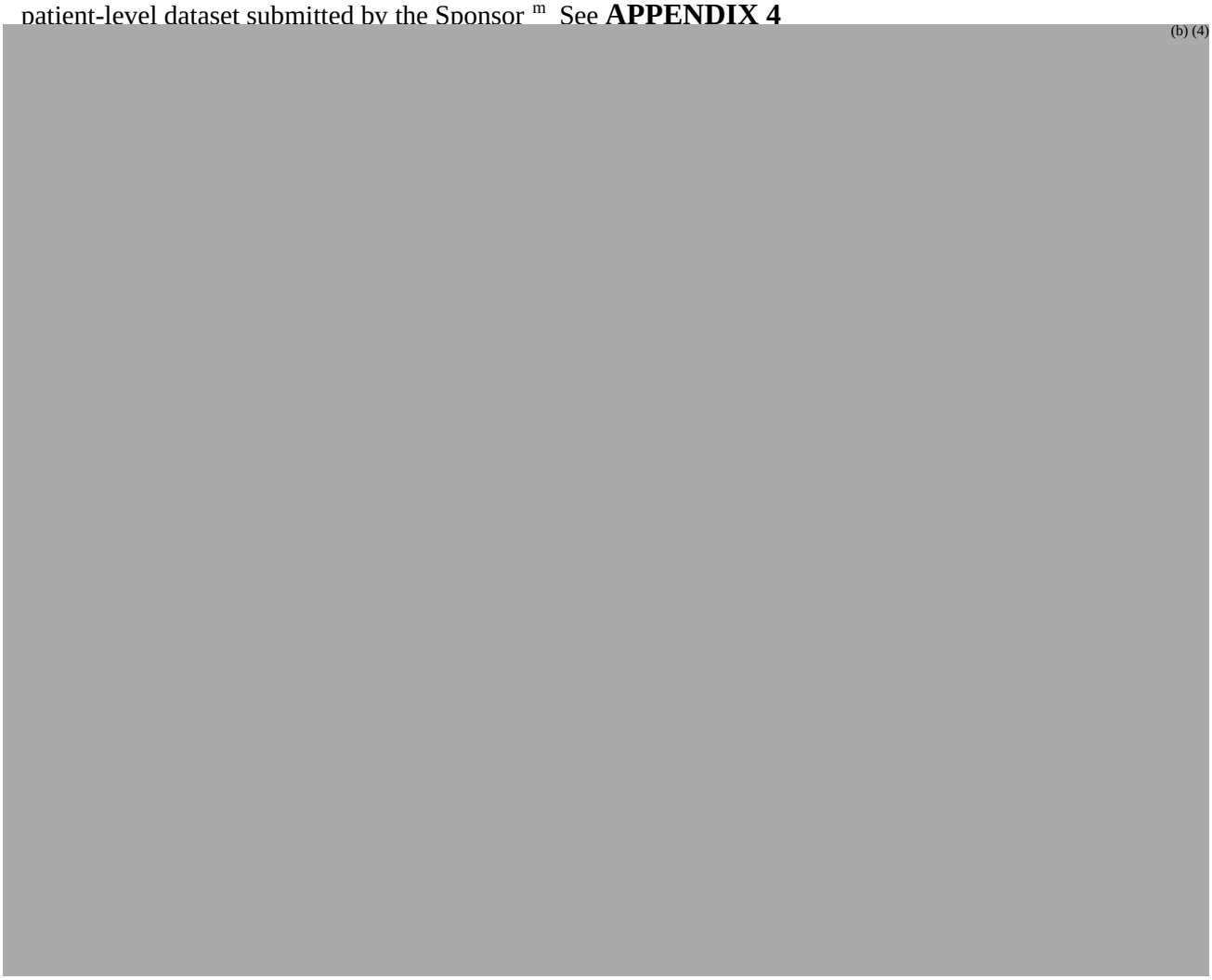
	MEN				WOMEN			
AGE	**BLA**	**SET 1**	**SET 2**	**SET 3**	**BLA**	**SET 1**	**SET 2**	**SET 3**
15-19	0.19	0.19	0.17	0.17	0.19	0.19	0.16	0.17
20-24	0.23	0.23	0.21	0.21	0.31	0.31	0.25	0.26
25-29	0.31	0.31	0.28	0.28	0.50	0.51	0.43	0.43
30-34	0.46	0.46	0.41	0.43	0.92	0.92	0.81	0.80
35-39	0.65	0.65	0.58	0.58	1.58	1.58	1.38	1.40
40-44	1.04	1.04	0.94	0.94	2.84	2.84	2.33	2.40
45-49	1.73	1.73	1.61	1.61	4.13	4.13	3.44	3.48
50-54	3.13	3.13	2.94	3.10	5.20	5.20	4.38	4.62
55-59	5.17	5.17	4.93	5.12	6.23	6.23	5.37	5.47
60-64	8.07	8.07	7.76	8.26	7.54	7.54	6.54	6.82
65-69	12.50	12.50	12.04	12.85	9.40	9.40	8.24	8.75
70-74	15.84	15.84	15.25	16.16	10.92	10.92	9.70	10.28
75-79	19.04	19.04	18.25	19.56	12.21	12.21	10.97	11.77

AGE	MEN				WOMEN			
	BLA	**SET 1**	**SET 2**	**SET 3**	**BLA**	**SET 1**	**SET 2**	**SET 3**
80-84	20.64	20.64	19.79	21.70	13.72	13.73	12.57	13.49
85+	20.75	20.75	19.65	22.19	13.99	13.99	12.89	14.05

APPENDIX 3: SAS code and output

APPENDIX FIGURE 3.1: SAS code used by DEPI to tabulate malignancy events and patient-years in a patient-level dataset submitted by the Sponsor [m] See **APPENDIX 4**

(b) (4)



[m] Summary of Clinical Safety – Ulcerative Colitis (Module 5.3.5.3), adseer.xpt, submitted to BLA 761044 (eCTD 00764) on December 20, 2018.

APPENDIX FIGURE 3.2: Output produced by SAS code in APPENDIX FIGURE 3.1.

Reproduces Observed Counts and Total Patient-Years in TSFMAL72C

DISPOP	EXPOS	MALIG	PY
Crohn's Disease	PLO	0	334.13
Crohn's Disease	UST	2	1048.00
Psoriasis	PLO	1	179.14
Psoriasis	UST	10	2496.77
Psoriatic Arthritis	PLO	0	143.16
Psoriatic Arthritis	UST	1	839.33
Ulcerative Colitis	PLO	1	203.08
Ulcerative Colitis	UST	4	577.33

APPENDIX 4: Malignancy event counts and patient-years in ulcerative colitis

DEPI used adseer.xpt and SAS code in **APPENDIX 3** to tabulate malignancy events (**CASES**) and patient-years (**PYS**), by race, sex, age, disease program (ulcerative colitis, Crohn's disease, psoriasis, and psoriatic arthritis), and exposure (placebo or ustekinumab). The following tables contain results for the ulcerative colitis (UC) disease program.

RACE: WHITE

	MEN				WOMEN			
	PLACEBO		USTEKINUMAB		PLACEBO		USTEKINUMAB	
AGE	CASES	PYS	CASES	PYS	CASES	PYS	CASES	PYS
15-19	0	2.551	0	3.586	0	1.159	0	3.203
20-24	0	9.409	0	21.811	0	5.721	0	13.190
25-29	1	10.466	0	47.489	0	7.925	0	24.340
30-34	0	11.235	1	34.869	0	11.100	0	31.693
35-39	0	11.546	0	27.024	0	5.180	0	22.689
40-44	0	11.421	0	26.016	0	2.069	0	22.303
45-49	0	15.085	0	32.404	0	9.124	0	28.163
50-54	0	8.780	0	31.945	0	4.431	0	18.513
55-59	0	9.399	0	24.226	0	8.608	0	11.684
60-64	0	7.265	1	16.815	0	5.384	0	13.135
65-69	0	3.973	0	9.951	0	2.540	0	3.882
70-74	0	1.473	1	4.880	0	0.862	0	1.887
75-79	0	0.000	0	2.195	0	0.000	0	1.000
80-84	0	0.000	0	0.000	0	0.000	0	0.019
ALL	1	102.602	3	283.211	0	64.102	0	195.701

RACE: BLACK

	MEN				WOMEN			
	PLACEBO		USTEKINUMAB		PLACEBO		USTEKINUMAB	
AGE	CASES	PYS	CASES	PYS	CASES	PYS	CASES	PYS
15-19	0	0.000	0	0.000	0	0.000	0	0.000
20-24	0	0.000	0	0.000	0	0.000	0	1.000
25-29	0	0.714	0	0.879	0	0.000	0	1.209
30-34	0	0.000	0	0.000	0	0.332	0	0.000
35-39	0	0.157	0	0.310	0	0.000	0	0.000
40-44	0	0.000	0	0.000	0	0.000	0	0.000
45-49	0	0.000	0	1.030	0	0.723	0	0.310
50-54	0	0.151	0	1.049	0	0.000	0	0.000
55-59	0	0.000	0	0.000	0	0.000	0	0.000
60-64	0	0.000	0	0.000	0	0.000	0	0.000
65-69	0	0.000	0	0.000	0	0.000	0	0.000
70-74	0	0.000	0	0.000	0	0.000	0	0.000
75-79	0	0.000	0	0.000	0	0.000	0	0.000
80-84	0	0.000	0	0.000	0	0.000	0	0.000
ALL	0	1.022	0	3.269	0	1.055	0	2.519

RACE: ASIAN OR PACIFIC ISLANDER (AS/PI)

	MEN				WOMEN			
	PLACEBO		USTEKINUMAB		PLACEBO		USTEKINUMAB	
AGE	CASES	PYS	CASES	PYS	CASES	PYS	CASES	PYS
15-19	0	0.157	0	1.396	0	0.313	0	3.365
20-24	0	1.261	0	3.863	0	1.015	0	2.486

	MEN				WOMEN			
	PLACEBO		USTEKINUMAB		PLACEBO		USTEKINUMAB	
AGE	CASES	PYS	CASES	PYS	CASES	PYS	CASES	PYS
25-29	0	2.813	0	5.953	0	2.562	0	2.126
30-34	0	0.313	0	7.674	0	0.731	0	2.599
35-39	0	1.742	0	4.810	0	3.003	0	5.475
40-44	0	4.476	0	6.723	0	0.997	0	4.772
45-49	0	4.285	0	11.162	0	1.854	1	3.081
50-54	0	2.027	0	6.731	0	0.195	0	2.008
55-59	0	1.489	0	4.316	0	0.159	0	1.011
60-64	0	2.093	0	6.898	0	0.255	0	1.184
65-69	0	2.560	0	1.107	0	0.000	0	0.541
70-74	0	0.000	0	0.000	0	0.000	0	2.343
75-79	0	0.000	0	0.000	0	0.000	0	1.000
80-84	0	0.000	0	0.000	0	0.000	0	0.003
ALL	0	23.217	0	60.632	0	11.085	1	31.997

ALL AGE

	MEN				WOMEN			
	PLACEBO		USTEKINUMAB		PLACEBO		USTEKINUMAB	
RACE	CASES	PYS	CASES	PYS	CASES	PYS	CASES	PYS
WHITE	1	102.602	3	283.211	0	64.102	0	195.701
BLACK	0	1.022	0	3.269	0	1.055	0	2.519
AS/PI	0	23.217	0	60.632	0	11.085	1	31.997
ALL	1	126.841	3	347.112	0	76.242	1	230.217

ALL AGE

	MEN AND WOMEN			
	PLACEBO		USTEKINUMAB	
RACE	CASES	PYS	CASES	PYS
WHITE	1	166.704	3	478.912
BLACK	0	2.077	0	5.788
AS/PI	0	34.302	1	92.629
ALL	1	203.083	4	577.329

APPENDIX 5: Sample calculation

The following table demonstrates use of **BLA** standard rates (**APPENDIX 2)** and ustekinumab patient-years (PYS) in the ulcerative colitis program (**APPENDIX 4)** to calculate the number of malignancy events expected (EXP).

AGE	SEX	RACE	RATE per 1000	PYS	EXP
15-19	Men	White	0.27	3.586	0.001
20-24	Men	White	0.41	21.811	0.009
25-29	Men	White	0.58	47.489	0.028
30-34	Men	White	0.77	34.869	0.027
35-39	Men	White	1.06	27.024	0.029
40-44	Men	White	1.66	26.016	0.043
45-49	Men	White	2.93	32.404	0.095
50-54	Men	White	5.47	31.945	0.175
55-59	Men	White	9.18	24.226	0.222
60-64	Men	White	14.02	16.815	0.236
65-69	Men	White	20.17	9.951	0.201
70-74	Men	White	24.53	4.880	0.120
75-79	Men	White	27.61	2.195	0.061
80-84	Men	White	28.55	0.000	0.000
85+	Men	White	28.47	0.000	0.000
15-19	Women	White	0.28	3.203	0.001
20-24	Women	White	0.50	13.190	0.007
25-29	Women	White	0.85	24.340	0.021
30-34	Women	White	1.37	31.693	0.044
35-39	Women	White	2.12	22.689	0.048
40-44	Women	White	3.48	22.303	0.078
45-49	Women	White	5.09	28.163	0.143
50-54	Women	White	6.76	18.513	0.125
55-59	Women	White	8.62	11.684	0.101
60-64	Women	White	11.14	13.135	0.146
65-69	Women	White	14.34	3.882	0.056
70-74	Women	White	16.64	1.887	0.031
75-79	Women	White	18.81	1.000	0.019
80-84	Women	White	19.65	0.019	0.000
85+	Women	White	18.50	0.000	0.000
15-19	Men	Black	0.17	0.000	0.000
20-24	Men	Black	0.24	0.000	0.000
25-29	Men	Black	0.39	0.879	0.000
30-34	Men	Black	0.57	0.000	0.000
35-39	Men	Black	0.88	0.310	0.000
40-44	Men	Black	1.70	0.000	0.000
45-49	Men	Black	3.47	1.030	0.004
50-54	Men	Black	7.10	1.049	0.007
55-59	Men	Black	12.44	0.000	0.000
60-64	Men	Black	18.38	0.000	0.000
65-69	Men	Black	24.49	0.000	0.000
70-74	Men	Black	26.65	0.000	0.000
75-79	Men	Black	27.82	0.000	0.000
80-84	Men	Black	28.20	0.000	0.000
85+	Men	Black	26.84	0.000	0.000

AGE	SEX	RACE	RATE per 1000	PYS	EXP
15-19	Women	Black	0.18	0.000	0.000
20-24	Women	Black	0.33	1.000	0.000
25-29	Women	Black	0.60	1.209	0.001
30-34	Women	Black	1.09	0.000	0.000
35-39	Women	Black	1.78	0.000	0.000
40-44	Women	Black	3.03	0.000	0.000
45-49	Women	Black	4.55	0.310	0.001
50-54	Women	Black	6.47	0.000	0.000
55-59	Women	Black	8.45	0.000	0.000
60-64	Women	Black	11.05	0.000	0.000
65-69	Women	Black	13.86	0.000	0.000
70-74	Women	Black	15.75	0.000	0.000
75-79	Women	Black	17.64	0.000	0.000
80-84	Women	Black	18.23	0.000	0.000
85+	Women	Black	17.98	0.000	0.000
15-19	Men	AS/PI	0.19	1.396	0.000
20-24	Men	AS/PI	0.23	3.863	0.001
25-29	Men	AS/PI	0.31	5.953	0.002
30-34	Men	AS/PI	0.46	7.674	0.004
35-39	Men	AS/PI	0.65	4.810	0.003
40-44	Men	AS/PI	1.04	6.723	0.007
45-49	Men	AS/PI	1.73	11.162	0.019
50-54	Men	AS/PI	3.13	6.731	0.021
55-59	Men	AS/PI	5.17	4.316	0.022
60-64	Men	AS/PI	8.07	6.898	0.056
65-69	Men	AS/PI	12.50	1.107	0.014
70-74	Men	AS/PI	15.84	0.000	0.000
75-79	Men	AS/PI	19.04	0.000	0.000
80-84	Men	AS/PI	20.64	0.000	0.000
85+	Men	AS/PI	20.75	0.000	0.000
15-19	Women	AS/PI	0.19	3.365	0.001
20-24	Women	AS/PI	0.31	2.486	0.001
25-29	Women	AS/PI	0.50	2.126	0.001
30-34	Women	AS/PI	0.92	2.599	0.002
35-39	Women	AS/PI	1.58	5.475	0.009
40-44	Women	AS/PI	2.84	4.772	0.014
45-49	Women	AS/PI	4.13	3.081	0.013
50-54	Women	AS/PI	5.20	2.008	0.010
55-59	Women	AS/PI	6.23	1.011	0.006
60-64	Women	AS/PI	7.54	1.184	0.009
65-69	Women	AS/PI	9.40	0.541	0.005
70-74	Women	AS/PI	10.92	2.343	0.026
75-79	Women	AS/PI	12.21	0.000	0.000
80-84	Women	AS/PI	13.72	1.000	0.014
85+	Women	AS/PI	13.99	0.003	0.000
ALL	**ALL**	**ALL**		**577.329**	**2.338**

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JOEL L WEISSFELD
05/24/2019 03:53:06 PM

PATRICIA L BRIGHT
05/28/2019 08:30:44 AM

SUKHMINDER K SANDHU
05/28/2019 08:52:53 AM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	March 11, 2019
Requesting Office or Division:	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Application Type and Number:	BLA 761044/S-03
Product Name and Strength:	Stelara (ustekinumab) injection 130 mg/26 mL (5 mg/mL), 45 mg/0.5 mL, 90 mg/mL
Product Type:	Single Ingredient Combination Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Janssen Biotech, Inc.
FDA Received Date:	December 20, 2018, January 15, 2019
OSE RCM #:	2019-110
DMEPA Safety Evaluator:	Idalia E. Rychlik, PharmD
DMEPA Team Leader:	Sarah K. Vee, PharmD.

1 REASON FOR REVIEW

Janssen Biotech, Inc. submitted a supplement for Stelara (ustekinumab) injection to support the approval of a new indication for the treatment of adult patients with moderately to severely active ulcerative colitis (UC). Subsequently, the Division of Gastroenterology and Inborn Errors Products (DGIEP) requested that we review the proposed Stelara prescribing information, medication guide and instructions for use for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Labeland Labeling Review	
Material Reviewed	**Appendix Section (for Methods and Results)**
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters	C-N/A
FDA Adverse Event Reporting System (FAERS)*	D-N/A
Other	E-N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

Tables 2 below includes the identified medication error issue with the submitted prescribing information, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Division of Gastroenterology and Inborn Errors Products (DGIEP)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
Full Prescribing Information – Section 2 Dosage and Administration			
1.	Dose information expressed with the use of trailing zeros in Table 2: Injection volumes of Stelara 45 mg/0.5mL single-dose vials for	The use of trailing zeros should be avoided to prevent to possibility of medication dosing errors; per the Agency's *Draft Guidance: Container and*	Remove all instances of trailing zeros (e.g. 24.0 mg, 0.40 mL) to avoid a ten-fold misinterpretation.

Table 2. Identified Issues and Recommendations for Division of Gastroenterology and Inborn Errors Products (DGIEP)		
IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
adolescent psoriasis patients less than 60 kg.	*Carton, April 2013 (lines 469-472)* and *ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations.*	

4 CONCLUSION

Our evaluation of the proposed Stelara Prescribing information identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division.

Our evaluation of the proposed Stelara medication guide and instructions for use did not identify areas of vulnerability that may lead to medication errors. We have no recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Stelara that Janssen Biotech, Inc. submitted on December 20, 2018.

Table 3. Relevant Product Information for Stelara

Product Name	Stelara (BLA 761044)	Stelara (BLA 125261)
Initial Approval Date	September 23, 2016	September 15, 2009
Active Ingredient	Ustekinumab	
Indication	Adult patients with: • moderate to severe plaque psoriasis (Ps) who are candidates for phototherapy or systemic therapy. • active psoriatic arthritis (PsA), alone or in combination with methotrexate. • moderately to severely active Crohn's disease (CD) who have • failed or were intolerant to treatment with immunomodulators or corticosteroids, but never failed a tumor necrosis factor (TNF) blocker or • failed or were intolerant to treatment with one or more TNF blockers. Adolescent patients (12 years or older) with: • moderate to severe plaque psoriasis, who are candidates for phototherapy or systemic therapy. **Proposed Indication under review:** *Adult patients: moderately to severely active ulcerative colitis* (b) (4) (b) (4)	
Route of Administration	Intravenous[a]	Subcutaneous
Dosage Form	Injection	
Strength	130 mg/26 mL (5 mg/mL)	45 mg/0.5 mL 90 mg/mL

[a] Note: new intravenous formulation is intended only for use as induction therapy in CD. Maintenance dose is administered using the subcutaneous formulation.

Dose and Frequency

Psoriasis Adult Subcutaneous Recommended Dosage:

Weight Range (kilogram)	Dosage Regimen
less than or equal to 100 kg	45 mg administered subcutaneously initially and 4 weeks later, followed by 45 mg administered subcutaneously every 12 weeks
greater than 100 kg	90 mg administered subcutaneously initially and 4 weeks later, followed by 90 mg administered subcutaneously every 12 weeks

Psoriasis Adolescent (12 years and older) Subcutaneous Recommended Dosage:

Weight based dosing is recommended at the initial dose, 4 weeks later, then every 12 weeks thereafter.

Weight Range (kilogram)	Dosage Regimen
less than 60 kg	0.75 mg/kg
60 kg to 100 kg	45 mg
greater than 100 kg	90 mg

Psoriatic Arthritis Adult Subcutaneous Recommended Dosage:

- The recommended dosage is 45 mg administered subcutaneously initially and 4 weeks later, followed by 45 mg administered subcutaneously every 12 weeks.
- For patients with co-existent moderate-to-severe plaque psoriasis weighing greater than 100 kg, the recommended dosage is 90 mg administered subcutaneously initially and 4 weeks later, followed by 90 mg administered subcutaneously every 12 weeks.

Crohn's Disease and Ulcerative Colitis Initial Adult Intravenous Recommended Dosage:

A single intravenous infusion using weight-based dosing:

Weight Range (kilogram)	Recommended Dosage
up to 55 kg	260 mg (2 vials)
greater than 55 kg to 85 kg	390 mg (3 vials)
greater than 85 kg	520 mg (4 vials)

	Crohn's Disease and Ulcerative Colitis Maintenance Adult Subcutaneous Recommended Dosage: A subcutaneous 90 mg dose 8 weeks after the initial intravenous dose, then every 8 weeks thereafter.	
How Supplied	Single-dose vials 130 mg/26 mL (5 mg/mL)	Single-dose prefilled syringes: 45 mg/0.5 mL or 90 mg/mL or single- dose vials: 45 mg/0.5 mL
Storage	Vials and prefilled syringes must be refrigerated at 2ºC to 8ºC (36ºF to 46ºF). Store vials upright. Keep the product in the original carton to protect from light until the time of use. Do not freeze. Do not shake. Does not contain a preservative; discard any unused portion.	

APPENDIX B. PREVIOUS DMEPA REVIEWS

On March 4, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, Stelara. Our search identified 9 previous reviews[bcdefghij] and we considered our previous recommendations to see if they are applicable for this current review.

[b] Holmes, L. Label and Labeling Review for Stelara (BLA 125261). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2008 Dec 01. RCM No.: 2008-812.

[c] Holmes, L. Label and Labeling Review for Stelara (BLA 125261). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2009 Aug 12. RCM No.: 2009-1308.

[d] Holmes, L. Label and Labeling Review for Stelara (BLA 125261). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2009 Dec 01. RCM No.: 2009-1686.

[e] Tobenkin, A. Label and Labeling Review for Stelara (BLA 125261). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2011 May 11. RCM No.: 2011-1376.

[f] Mena-Grillasca, C. Labeling Review for Stelara (BLA 125261). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 Mar 07. RCM No.: 2012-2088.

[g] McMillan, T. Label, Labeling, and Packaging Review for Stelara (BLA 125261). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 Aug 09. RCM No.: 2013-266.

[h] McMillan, T. Label and Labeling Review for Stelara (BLA 125261). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 Jan 24. RCM No.: 2013-2551.

[i] Abraham, S. Label and Labeling Review for Stelara (BLA 761044). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 Jul 18. RCM No.: 2015-2724.

[j] Mena-Grillasca, C. Label and Labeling Review for Stelara (BLA 125261/S-138 and S-142). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 AUG 10. RCM No.: 2016-2979 and 2017-1574.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed (Images not shown)

Using the principles of human factors and Failure Mode and Effects Analysis,[k] along with postmarket medication error data, we reviewed the following Stelara labels and labeling submitted by Janssen Biotech, Inc.

- Instructions for Use received on January 15, 2019
- Medication Guide received on January 15, 2019
- Prescribing Information received on December 20, 2018

[k] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI: 2004.

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IDALIA E RYCHLIK
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SARAH K VEE
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