CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125261Orig1s086

Trade Name: STELARA

Generic Name: ustekinumab

Sponsor: Janssen Biotech, Inc.

Approval Date: May 21, 2013

Indications: STELARA® is a human interleukin-12 and -23 antagonist indicated for the treatment of adult patients (18 years or older) with

moderate to severe plaque psoriasis (Ps) who are candidates for phototherapy or systemic therapy.

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125261/86

SUPPLEMENT APPROVAL

Janssen Biotech, Inc.
Attention: Joseph Lallier, MS, MBA
Associate Director, Global Regulatory Affairs
Welsh & McKean Roads, P.O. Box 776
Spring House, PA 19477

Dear Mr. Lallier:

Please refer to your Supplemental Biologics License Application (sBLA) dated and received July 27, 2012, submitted under section 351(a) of the Public Health Service Act for Stelara® (ustekinumab).

We acknowledge receipt of your amendments dated January 16 and 30, February 6 and 15, April 23, May 10 and 16, 2013.

This Prior Approval supplemental biologics application proposes to allow for patients to self administer the product and provides updates to the long term safety data in the prescribing information.

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

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 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert, text for the Medication Guide, text for the patient instructions for use) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes 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 MS Word format that includes the changes approved in this supplemental application.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

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 package insert(s) to:

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

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

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, call Paul Phillips, Regulatory Project Manager, at (301) 796-3935.

Sincerely,

{See appended electronic signature page}

Susan J. Walker, MD, FAAD
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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

/s/

SUSAN J WALKER
05/21/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

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<u>LABELING</u>

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 use
Initial U.S. Approval: 2009

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

Dosage and Administration (2.2)	05/2013
Contraindications (4)	06/2012
Warnings and Precautions, Malignancies (5.4)	01/2013
Warnings and Precautions, Hypersensitivity Reactions (5.5)	06/2012

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

STELARA® is a human interleukin-12 and -23 antagonist indicated for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. (1)

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

STELARA® is administered by subcutaneous injection. (2)

- For patients weighing ≤100 kg (220 lbs), the recommended dose is 45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks. (2.1)
- For patients weighing >100 kg (220 lbs), the recommended dose is 90 mg initially and 4 weeks later, followed by 90 mg every 12 weeks. (2.1)

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

- Injection: 45 mg/0.5 mL in a single-use prefilled syringe (3)
- Injection: 90 mg/1 mL in a single-use prefilled syringe (3)
- Injection: 45 mg/0.5 mL in a single-use vial (3)
- Injection: 90 mg/1 mL in a single-use 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 develops, stop 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)
- 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)

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

Most common adverse reactions (incidence >3% and greater than with placebo): Nasopharyngitis, upper respiratory tract infection, headache, and fatigue. (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.*

----------DRUG INTERACTIONS----------

- Live vaccines: Live vaccines should not be given with STELARA®. (7.1)
- Concomitant therapy: The safety of concomitant use of STELARA® with immunosuppressants or phototherapy has not been evaluated. (7.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 05/2013

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- 2.1 Dosing
- 2.2 General Considerations for Administration
- 2.3 Instructions for Administration of STELARA® Prefilled Syringes Equipped with Needle Safety Guard

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

STELARA® is indicated for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing

STELARA® is administered by subcutaneous injection.

- For patients weighing ≤100 kg (220 lbs), the recommended dose is 45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks.
- For patients weighing >100 kg (220 lbs), the recommended dose is 90 mg initially and 4 weeks later, followed by 90 mg every 12 weeks.

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

2.2 General Considerations for Administration

STELARA® is for subcutaneous 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.

After proper training in subcutaneous injection technique, a patient may self inject with STELARA® if a physician determines that it is appropriate. Patients should be instructed to follow the directions provided in the Medication Guide *(see Medication Guide)*.

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

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-use vial, a 27 gauge, ½ inch needle is recommended.

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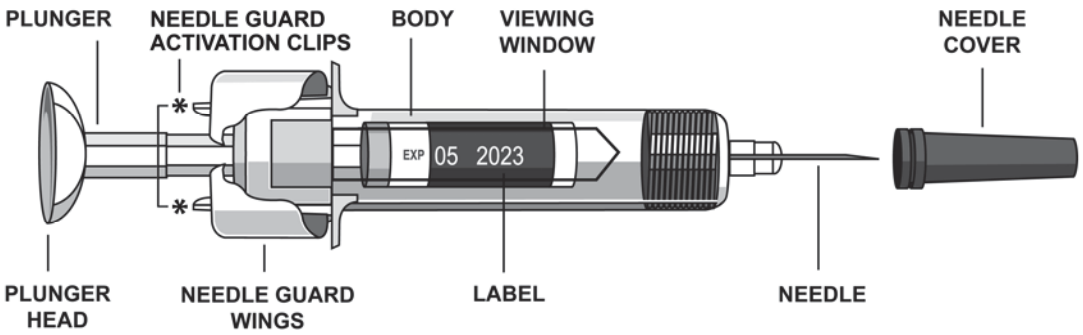
2.3 Instructions for Administration of STELARA® Prefilled Syringes Equipped with Needle Safety Guard

Refer to the diagram below for the provided instructions.

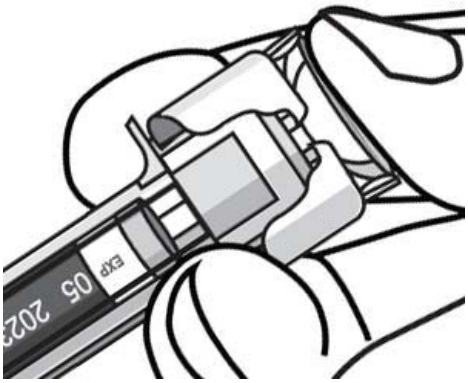
To prevent premature activation of the needle safety guard, do not touch the NEEDLE GUARD ACTIVATION CLIPS at any time during use.



- 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 (2.2)]*.

- 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:

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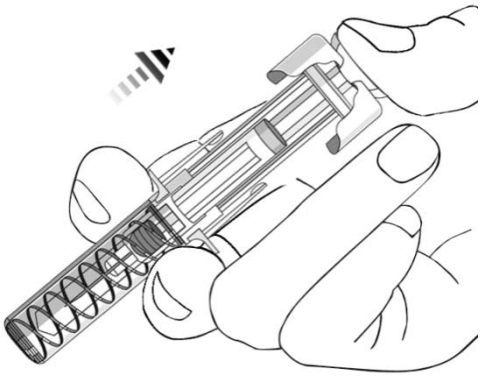

- Used syringes should be placed in a puncture-resistant container.

3 DOSAGE FORMS AND STRENGTHS

STELARA® solution is colorless to slightly yellow in appearance and contains 90 mg ustekinumab per mL.

- Injection: 45 mg/0.5 mL in a single-use prefilled syringe
- Injection: 90 mg/1 mL in a single-use prefilled syringe
- Injection: 45 mg/0.5 mL in a single-use vial
- Injection: 90 mg/1 mL in a single-use vial

4 CONTRAINDICATIONS

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)]*.

STELARA® should not be given to patients with any clinically important active infection. STELARA® should not be administered until the infection resolves or is adequately treated. Instruct patients to seek medical advice if signs or symptoms suggestive of an infection occur. Exercise caution when considering the use of STELARA® in patients with a chronic infection or a history of recurrent infection.

Serious infections requiring hospitalization occurred in the psoriasis development program. These serious infections included cellulitis, diverticulitis, osteomyelitis, viral infections, gastroenteritis, pneumonia, and urinary tract infections.

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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® will 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. 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. Patients receiving STELARA® should be monitored closely 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 post-marketing. If an anaphylactic or other clinically significant hypersensitivity reaction occurs, discontinue STELARA® and institute appropriate therapy *[see Adverse Reactions (6.3)]*.

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5.6 Reversible Posterior Leukoencephalopathy Syndrome

One case of reversible posterior leukoencephalopathy syndrome (RPLS) was observed during the clinical development program which included 3523 STELARA®-treated subjects. 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.

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, STELARA® should be discontinued and appropriate treatment administered.

5.7 Immunizations

Prior to initiating therapy with STELARA®, patients should receive all immunizations appropriate for age 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

The safety of STELARA® in combination with other immunosuppressive agents or phototherapy has not been 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)]*.

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)]*
- Reversible Posterior Leukoencephalopathy Syndrome *[see Warnings and Precautions (5.6)]*

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6.1 Clinical Studies 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.

The safety data reflect exposure to STELARA® in 3117 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 1 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 STUDY 1 and STUDY 2 *[see Clinical Studies (14)]*.

Table 1. Adverse reactions reported by ≥1% of subjects through Week 12 in STUDY 1 and 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 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 trials *[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)

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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 trials (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 trials (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 trials 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]

6.2 Immunogenicity

The presence of ustekinumab in the serum can interfere with the detection of anti-ustekinumab antibodies resulting in inconclusive results due to assay interference. In STUDIES 1 and 2, antibody testing was done at time points when ustekinumab may have been present in the serum. Table 2 summarizes the antibody results from STUDIES 1 and 2 through Year 5.

Table 2. Presence of anti-ustekinumab antibodies in STUDIES 1 and 2 through Year 5.

Antibody Results	STUDY 1 (N=746)	STUDY 2 (N=1202)
Positive	39 (5%)	65 (5%)
Negative	365 (49%)	431 (36%)
Inconclusive	342 (46%)	706 (59%)

The majority of patients who were positive for antibodies to ustekinumab had neutralizing antibodies.

The data above reflect the percentage of subjects whose test results were positive for antibodies to ustekinumab in a bridging immunoassay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of the incidence of antibodies to ustekinumab with the incidence of antibodies to other products may be misleading.

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6.3 Post-marketing Experience

Adverse reactions have been reported during post-approval use with 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).

Skin reactions: Pustular psoriasis, erythrodermic psoriasis

7 DRUG INTERACTIONS

Drug interaction studies have not been conducted with STELARA®.

7.1 Live Vaccines

Live vaccines should not be given concurrently with STELARA® *[see Warnings and Precautions (5.7)]*.

7.2 Concomitant Therapies

The safety of STELARA® in combination with immunosuppressive agents or phototherapy has not been evaluated *[see Warnings and Precautions (5.8)]*.

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 Category B

There are no studies of STELARA® in pregnant women. STELARA® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. No teratogenic

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effects were observed in the developmental and reproductive toxicology studies performed in cynomolgus monkeys at doses up to 45 mg/kg ustekinumab, which is 45 times (based on mg/kg) the highest intended clinical dose in psoriasis patients (approximately 1 mg/kg based on administration of a 90 mg dose to a 90 kg psoriasis patient).

Ustekinumab was tested in two embryo-fetal development toxicity studies. Pregnant cynomolgus monkeys were administered ustekinumab at doses up to 45 mg/kg during the period of organogenesis either twice weekly via subcutaneous injections or weekly by intravenous injections. No significant adverse developmental effects were noted in either study.

In an embryo-fetal development and pre- and post-natal development toxicity study, three groups of 20 pregnant cynomolgus monkeys were administered subcutaneous doses of 0, 22.5, or 45 mg/kg ustekinumab twice weekly from the beginning of organogenesis in cynomolgus monkeys to Day 33 after delivery. There were no treatment-related effects on mortality, clinical signs, body weight, food consumption, hematology, or serum biochemistry in dams. Fetal losses occurred in six control monkeys, six 22.5 mg/kg-treated monkeys, and five 45 mg/kg-treated monkeys. Neonatal deaths occurred in one 22.5 mg/kg-treated monkey and in one 45 mg/kg-treated monkey. No ustekinumab-related abnormalities were observed in the neonates from birth through six months of age in clinical signs, body weight, hematology, or serum biochemistry. There were no treatment-related effects on functional development until weaning, functional development after weaning, morphological development, immunological development, and gross and histopathological examinations of offsprings by the age of 6 months.

8.3 Nursing Mothers

Caution should be exercised when STELARA® is administered to a nursing woman. The unknown risks to the infant from gastrointestinal or systemic exposure to ustekinumab should be weighed against the known benefits of breast-feeding. Ustekinumab is excreted in the milk of lactating monkeys administered ustekinumab. IgG is excreted in human milk, so it is expected that STELARA® will be present in human milk. It is not known if ustekinumab is absorbed systemically after ingestion; however, published data suggest that antibodies in breast milk do not enter the neonatal and infant circulation in substantial amounts.

8.4 Pediatric Use

Safety and effectiveness of STELARA® in pediatric patients have not been evaluated.

8.5 Geriatric Use

Of the 3117 psoriasis subjects exposed to STELARA®, a total of 183 were 65 years or older, and 21 subjects were 75 years or older. Although no differences in safety or efficacy were observed between older and younger subjects, the number of subjects aged 65 and over is not sufficient to determine whether they respond differently from younger subjects.

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10 OVERDOSAGE

Single doses up to 4.5 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

STELARA® is a human IgG1κ monoclonal antibody against the p40 subunit of the IL-12 and IL-23 cytokines. Using DNA recombinant technology, STELARA® 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. STELARA® is comprised of 1326 amino acids and has an estimated molecular mass that ranges from 148,079 to 149,690 Daltons.

STELARA®, for subcutaneous use, is available as: 45 mg of ustekinumab in 0.5 mL and 90 mg of ustekinumab in 1 mL. STELARA® is supplied as a sterile solution in a single-use prefilled syringe with a 27 gauge fixed ½ inch needle, or a single-use 2 mL Type I glass vial with a coated stopper. The syringe is fitted with a passive needle guard and a needle cover that is manufactured using a dry natural rubber (a derivative of latex).

Each 45 mg ustekinumab prefilled syringe also contains: L-histidine and L-histidine monohydrochloride monohydrate (0.5 mg), Polysorbate 80 (0.02 mg), and sucrose (38 mg) to fill to a final volume of 0.5 mL.

Each 90 mg ustekinumab prefilled syringe also contains: L-histidine and L-histidine monohydrochloride monohydrate (1 mg), Polysorbate 80 (0.04 mg), and sucrose (76 mg) to fill to a final volume of 1 mL.

Each 45 mg ustekinumab vial also contains: L-histidine and L-histidine monohydrochloride monohydrate (0.5 mg), Polysorbate 80 (0.02 mg), and sucrose (38 mg) to fill to a final volume of 0.5 mL.

Each 90 mg ustekinumab vial also contains: L-histidine and L-histidine monohydrochloride monohydrate (1 mg), Polysorbate 80 (0.04 mg), and sucrose (76 mg) to fill to a final volume of 1 mL.

The STELARA® solution is colorless to slightly yellow in appearance and has a pH of 5.7-6.3. STELARA® does not contain preservatives.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ustekinumab is a human IgG1κ monoclonal antibody that binds with high affinity and specificity to the p40 protein subunit used by both the interleukin (IL)-12 and IL-23 cytokines. IL-12 and

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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-12 β1.

12.2 Pharmacodynamics

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 psoriatic subjects.

12.3 Pharmacokinetics

Absorption

In psoriasis subjects, 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 psoriasis subjects. Following multiple subcutaneous doses of STELARA®, the steady-state serum concentrations of ustekinumab were achieved by Week 28. The mean (±SD) steady-state trough serum concentration ranged from 0.31 ± 0.33 mcg/mL (45 mg) to 0.64 ± 0.64 mcg/mL (90 mg). There was no apparent accumulation in serum ustekinumab concentration over time when given subcutaneously every 12 weeks.

Distribution

Following subcutaneous administration of 45 mg (N=18) and 90 mg (N=21) of ustekinumab to psoriasis subjects, the mean (±SD) apparent volume of distribution during the terminal phase (Vz/F) was 161 ± 65 mL/kg and 179 ± 85 mL/kg, respectively. The mean (± SD) volume of distribution during the terminal phase (Vz) following a single intravenous administration to subjects with psoriasis ranged from 56.1 ± 6.5 to 82.1 ± 23.6 mL/kg.

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.

Elimination

The mean (± SD) systemic clearance (CL) following a single intravenous administration of ustekinumab to psoriasis subjects ranged from 1.90 ± 0.28 to 2.22 ± 0.63 mL/day/kg. The mean (±SD) half-life ranged from 14.9 ± 4.6 to 45.6 ± 80.2 days across all psoriasis studies following intravenous and subcutaneous administration.

Weight

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When given the same dose, subjects weighing >100 kg had lower median serum ustekinumab concentrations compared with those subjects weighing ≤100 kg. The median trough serum concentrations of ustekinumab in subjects of higher weight (>100 kg) in the 90 mg group were comparable to those in subjects of lower weight (≤100 kg) in the 45 mg group.

Hepatic and Renal Impairment
No pharmacokinetic data are available in patients with hepatic or renal impairment.

Elderly
A population pharmacokinetic analysis (N=106/1937 subjects 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.

Drug-Drug Interactions
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)]*.

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.

A male fertility study was conducted with only 6 male monkeys per group administered subcutaneous doses of 0, 22.5, or 45 mg/kg ustekinumab twice weekly prior to mating and during the mating period for 13 weeks, followed by a 13-week treatment-free period. Although fertility and pregnancy outcomes were not evaluated in mated females, there were no treatment-related effects on parental toxicity or male fertility parameters.

A female fertility study was conducted in mice using an analogous IL-12/IL-23p40 antibody by subcutaneous administration at doses up to 50 mg/kg, twice weekly, beginning 15 days before cohabitation and continuing through GD 7. There were no treatment-related effects on maternal toxicity or female fertility parameters.

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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

Two multicenter, randomized, double-blind, placebo-controlled studies (STUDY 1 and 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.

STUDY 1 enrolled 766 subjects and 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 STUDY 1 and 40% of subjects in 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 study subjects had a history of psoriatic arthritis.

Clinical Response

The results of STUDY 1 and STUDY 2 are presented in Table 3 below.

Table 3. Clinical Outcomes STUDY 1 and STUDY 2

Week 12	STUDY 1			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%)

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Table 3. Clinical Outcomes STUDY 1 and STUDY 2

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, response rates were similar with both the 45 mg and 90 mg doses; however, in subjects who weighed >100 kg, higher response rates were seen with 90 mg dosing compared with 45 mg dosing (Table 4 below).

Table 4. Clinical Outcomes by Weight STUDY 1 and STUDY 2

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

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

Subjects in 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.

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,

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DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2010, based on the November 2009 submission.

16 HOW SUPPLIED/STORAGE AND HANDLING

STELARA® does not contain preservatives. STELARA® is available in single-use prefilled syringes or single-use vials containing 45 mg or 90 mg of ustekinumab. Each prefilled syringe is equipped with a needle safety guard.

The NDC number for the 45 mg prefilled syringe is 57894-060-03.

The NDC number for the 90 mg prefilled syringe is 57894-061-03.

The NDC number for the 45 mg vial is 57894-060-02.

The NDC number for the 90 mg vial is 57894-061-02.

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. STELARA® does not contain a preservative; discard any unused portion.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide and Instructions for Use)

Instruct patients to read the Medication Guide before starting STELARA® therapy and to reread the Medication Guide each time the prescription is renewed.

Infections

Inform patients that STELARA® may lower the ability of their immune system to fight infections. Instruct patients of the importance of communicating any history of infections to the doctor, and contacting their doctor if they develop any symptoms of infection.

Malignancies

Patients should be counseled about the risk of malignancies while receiving STELARA®.

Allergic Reactions

Advise patients to seek immediate medical attention if they experience any symptoms of serious allergic reactions.

17.1 Instruction on Injection Technique

The first self-injection should be performed under the supervision of a qualified healthcare professional. If a patient or caregiver is to administer STELARA®, he/she should be instructed in injection techniques and their ability to inject subcutaneously should be assessed to ensure the proper administration of STELARA® *[see Medication Guide and Instructions for Use]*.

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Patients should be instructed to inject the full amount of STELARA® according to the directions provided in the Medication Guide and Instructions for Use. 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.

Needles and syringes should be disposed of in a puncture-resistant container. Patients or caregivers should be instructed in the technique of proper syringe and needle disposal, and be advised not to reuse these items.

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

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MEDICATION GUIDE
STELARA® (stel ar' a**)**
(ustekinumab)
Injection

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 during treatment 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, sweats, or chills
- muscle aches
- cough
- shortness of breath
- blood in your 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 who has 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. It is not known if people who take STELARA® will get any of these infections, because of the effects of STELARA® on these proteins in your body.

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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 18 years and older with moderate or severe psoriasis that involves large areas or many areas of their body, who may benefit from taking injections or pills (systemic therapy) or phototherapy (treatment using ultraviolet light alone or with pills).

STELARA® may improve your psoriasis but may also lower the ability of your immune system to fight infections. This may also increase your risk for certain types of cancer.

It is not known if STELARA® is safe and effective in children.

Who should not take STELARA®?

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®.

What should I tell my doctor before receiving STELARA®?

Before you receive STELARA®, tell your doctor 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 vaccine. The viruses used in some types of 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 taking STELARA® or one year after you stop taking 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

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STELARA®. STELARA® may also increase your risk of having an allergic reaction to an allergy shot.

- receive or have received phototherapy for your psoriasis.
- have any other medical conditions.
- are pregnant or planning to become pregnant**.** It is not known if STELARA® will harm your unborn baby. You and your doctor should decide if you will take STELARA®.
- are breast-feeding or plan to breast-feed. It is thought that STELARA® passes into your breast milk. You should not breast-feed while taking STELARA® without first talking with your doctor.

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 prescribed by your doctor.
- 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®. Do not try to inject STELARA® yourself until you or your caregiver have been shown how to inject STELARA® by your doctor or nurse.
- STELARA® is given by injection 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.**

What should I avoid while using STELARA®?

You should not receive a live vaccine while taking STELARA®. See **"What should I tell my doctor before receiving STELARA®?"**

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®. 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
  - trouble breathing, throat tightness

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- chest tightness
- skin rash

Common side effects of STELARA® include:

- upper respiratory infections
- headache
- tiredness

These are not all of the possible side effects of STELARA®. Tell your doctor about any side effect that bothers you or that does not go away. For more information, ask your doctor or pharmacist.

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 do I store STELARA®?

- Store STELARA® in a refrigerator, between 36ºF to 46ºF (2ºC to 8ºC) in the original carton until it is used.
- Store STELARA® vials upright.
- Protect from light.
- Do not freeze STELARA®.
- Do not shake STELARA®.
- Throw away (dispose of) any unused STELARA.

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

General information about 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.
If you would like more information, talk with your doctor. 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: L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, and sucrose.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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

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

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INSTRUCTIONS FOR USE
STELARA® (stel ar' a**)**
(ustekinumab)
injection

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:

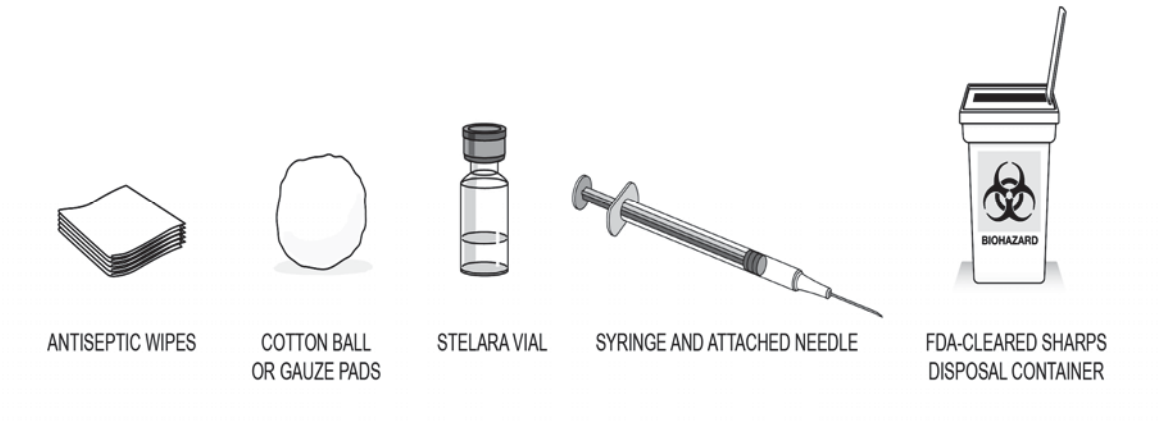
- Before you start, check the carton to make sure that it is the right dose. You will have either 45 mg or 90 mg as prescribed by your doctor.
  - If your dose is 45 mg you will receive one 45 mg vial.
  - If your dose is 90 mg, you will receive either one 90 mg vial or two 45 mg vials. **If you receive two 45 mg vials for a 90 mg dose, you will need to give yourself two injections, one right after the other.**
- 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. 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, provided by your pharmacy
- antiseptic wipes
- cotton balls or gauze pads
- your prescribed dose of STELARA®

- FDA-cleared sharps disposal container. See "**Step 6: Dispose of needles and syringes.**"

Figure A



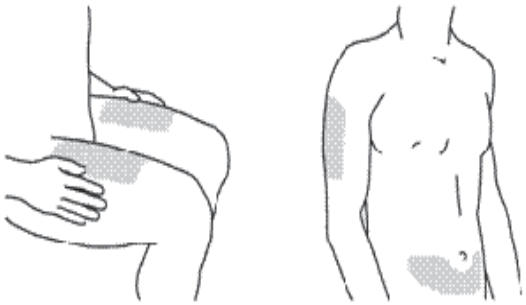
Step 1: Prepare the injection.

- 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)**
- 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.

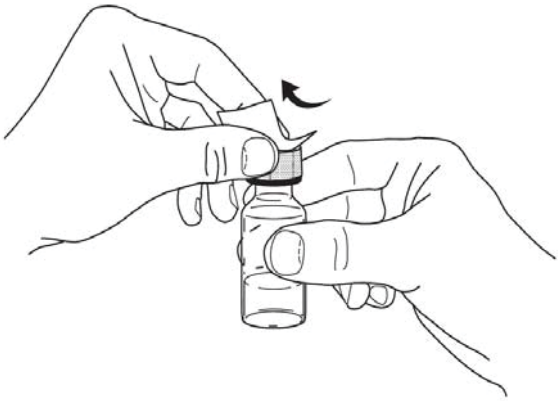
Step 3: Prepare the vial.

- 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

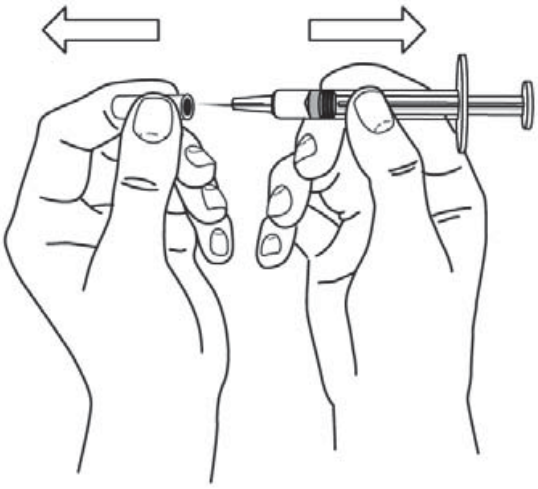


- Do not touch the rubber stopper after you clean it.
- Put the vial on a flat surface.

Step4: Prepare the needle

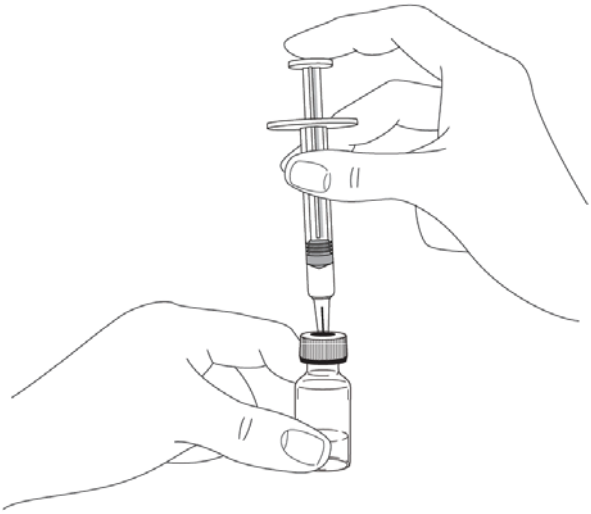
- Pick up the syringe with the needle attached.
- Remove the cap that covers the needle. **(See Figure E)**
- Throw the needle cap away. Do not touch the needle or allow the needle to touch anything.

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)**

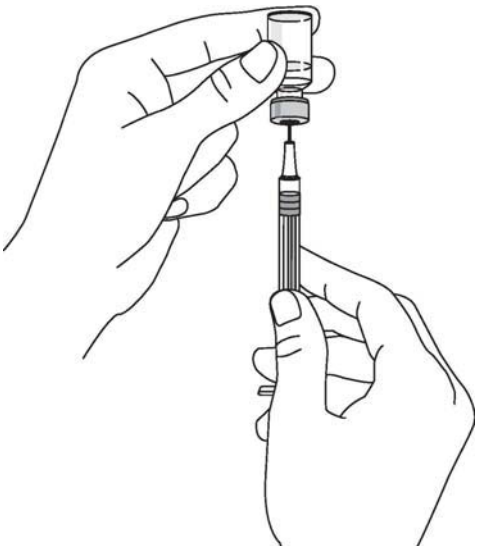
Figure F



- 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.

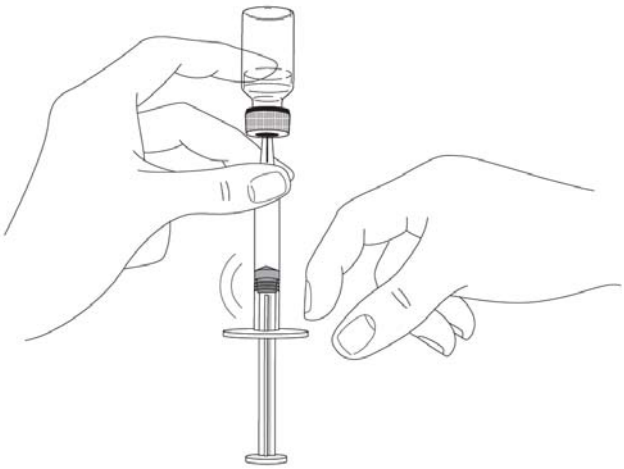
- Fill the syringe until the black tip of the plunger lines up with the mark that matches your prescribed dose.

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.

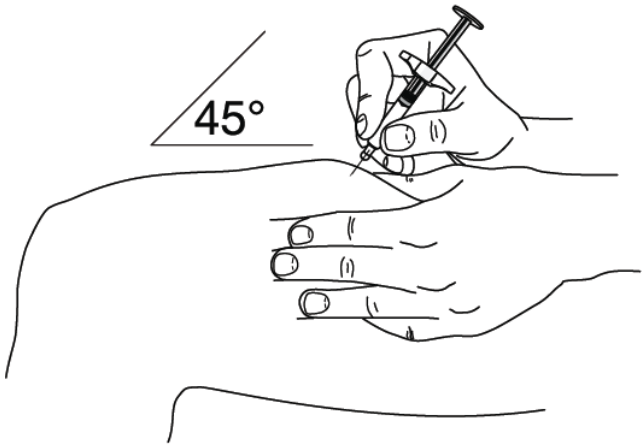
Figure H



Step 5: Inject STELARA®

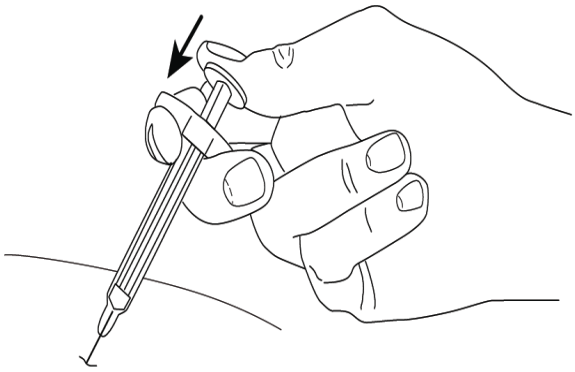
- Hold the barrel of the syringe in one hand, between the thumb and index fingers.
- **Do not** pull back on the plunger at any time.
- Use the other hand to gently pinch the cleaned area of skin. Hold firmly.
- Use a quick, dart-like motion to insert the needle into the pinched skin at about a 45-degree 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, and you received two 45 mg vials you will need to give 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

Issued 05/2013

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INSTRUCTIONS FOR USE
STELARA® (stel ar' a**)**
(ustekinumab)
injection

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 45mg 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.**
- Check the expiration date on the pre-filled 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.
- 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
- your prescribed dose of STELARA® **(See Figure B)**
- FDA-cleared sharps disposal container. **See "STEP 4: Dispose of syringe."**

Figure A

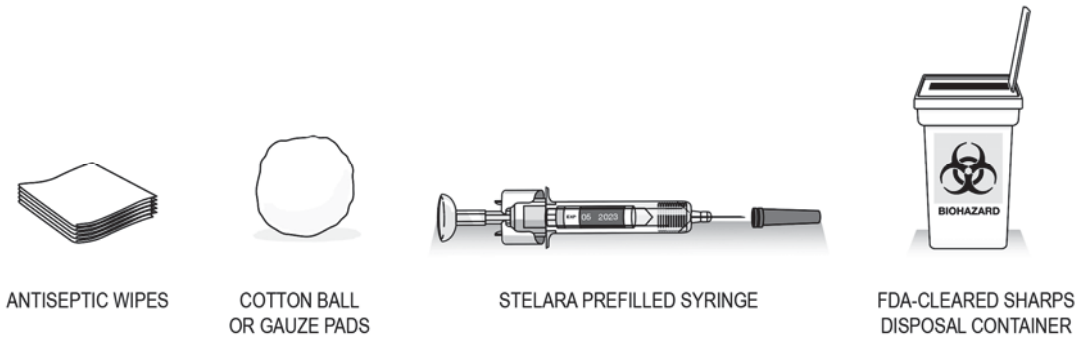
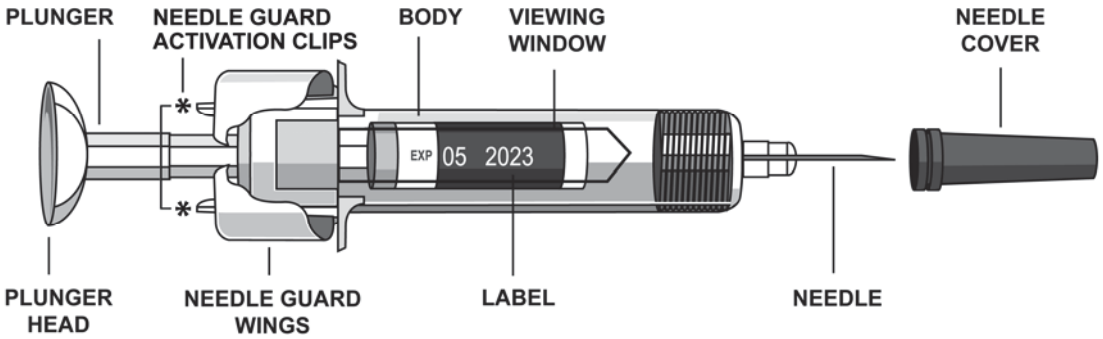


Figure B



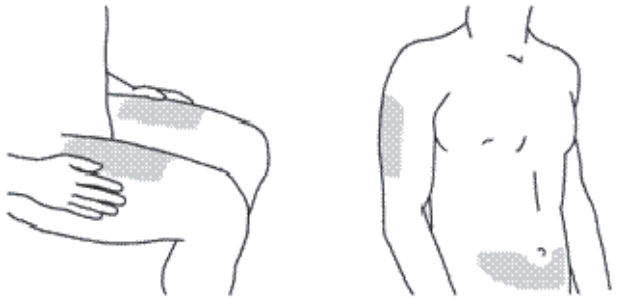
Step 1: Prepare the injection.

- 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)**
- 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

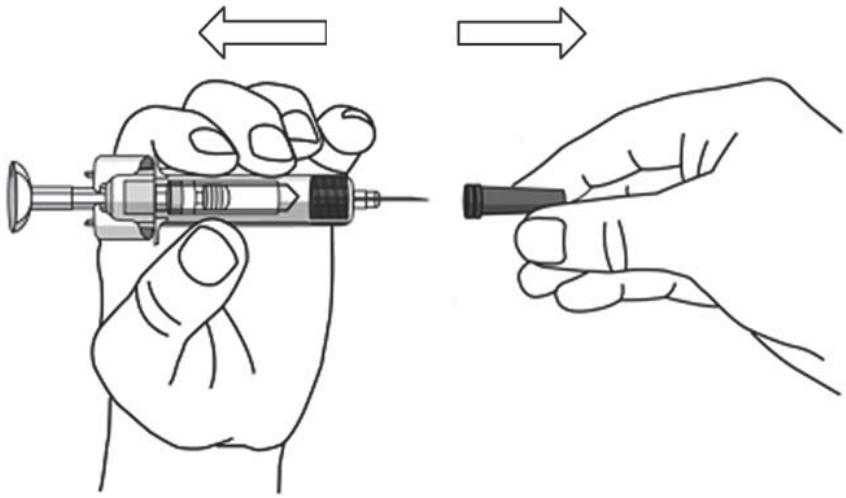


*Areas in gray are recommended injection sites.

Step 3: Inject STELARA®

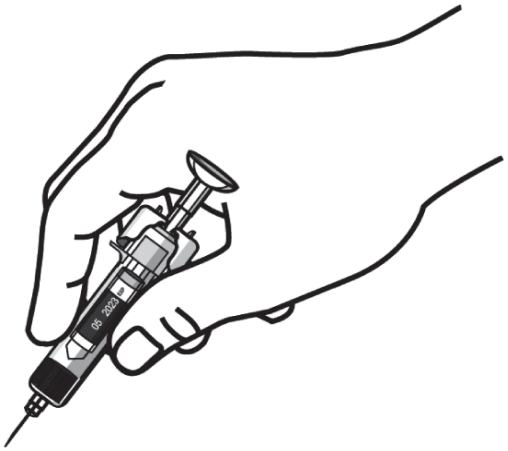
- Remove the needle cover when you are ready to inject your STELARA®.
- **Do not** touch the plunger while removing the needle cover.
- Hold the body of the prefilled syringe with one hand, and pull the needle cover straight off. **(see Figure D)**
- Put the needle cover in the trash.
- You may also 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



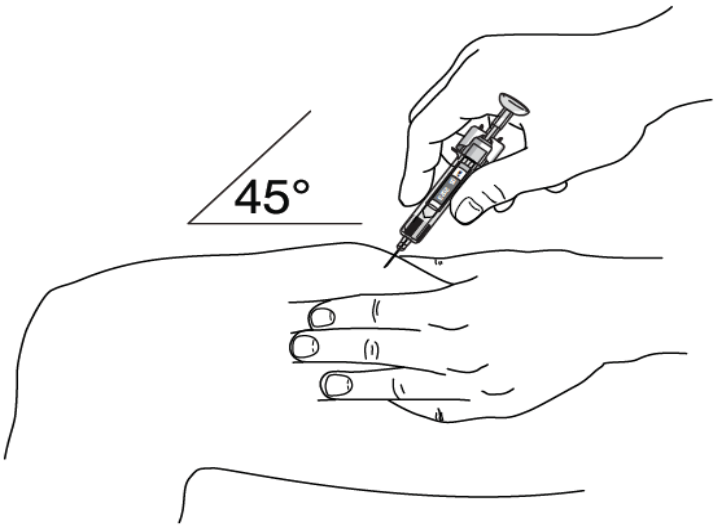
- Hold the body of the prefilled syringe in one hand between the thumb and index fingers. **(See Figure E)**

Figure E



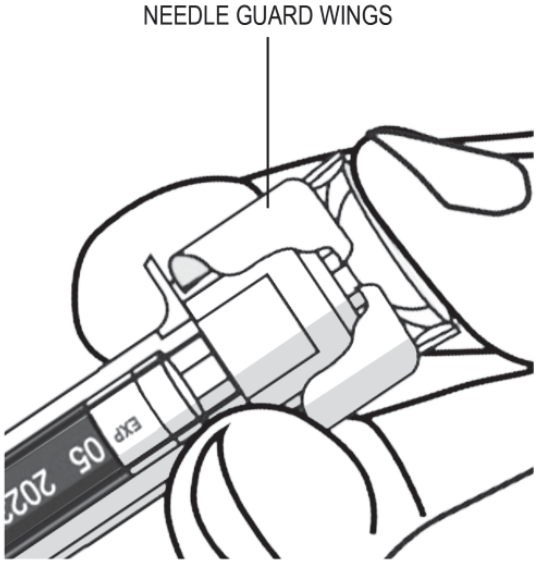
- **Do not** pull back on the plunger at any time.
- Use the other hand to gently pinch the cleaned area of skin. Hold firmly.
- Use a quick, dart-like motion to insert the needle into the pinched skin at about a 45-degree angle. **(See Figure F)**

Figure F



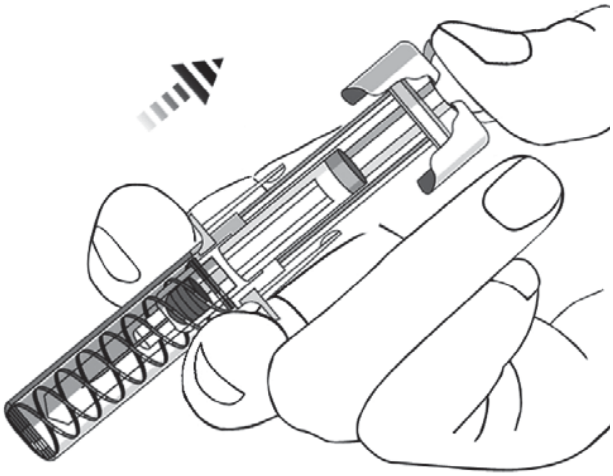
- Inject all of the liquid by using your thumb to push in the plunger until the plunger head is completely between the needle guard wings. **(See Figure G)**

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.

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

Issued 05/2013

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125261Orig1s086

OFFICER/EMPLOYEE LIST

Officer/Employee List
Application: sBLA 125261/86

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified:

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Graham, Laurie
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Prabhakara, Ranjani
Brodsky, Eric
Adebowale, Abimbola

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125261Orig1s086

MEDICAL REVIEW(S)

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/s/

BRENDA CARR
05/06/2013

CLINICAL REVIEW

Application Type	BLA
Submission Number	125261
Submission Code	SE-8
Letter Date	July 27, 2012
Stamp Date	July 27, 2012
PDUFA Goal Date	May 27, 2012
Reviewer Name	Brenda Carr, M.D.
Review Completion Date	April 10, 2013
Established Name	Ustekinumab
(Proposed) Trade Name	Stelara
Therapeutic Class	IL-12/IL-23 antagonist
Applicant	Janssen Biotech, Inc.
Formulation(s)	solution for subcutaneous administration
Dosing Regimen	Weeks 0, 4 then every 12 weeks
Indication(s)	treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy
Intended Population(s)	adult patients (18 years or older)

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Reference ID: 3295325

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The Medical Officer recommends approval of efficacy supplement 86 (S-86), with labeling language as recommended by the agency. Approval of this supplement would include provisions for self-administration of ustekinumab.

1.2 Risk Benefit Assessment

Self-administration

The applicant, Janssen Biotech, Inc. (Janssen), proposed labeling for self-administration of ustekinumab. They submitted data from evaluation of off-site self-administration with the prefilled syringe (PFS); however, they proposed labeling for self-administration of the PFS and the liquid in vial (LIV) presentations. The applicant did not evaluate off-site self-administration with the LIV presentation.

The applicant initially proposed self-injection with launch of ustekinumab, a first-in-class new molecular entity, when the LIV was the only presentation proposed for marketing. However, the applicant had only evaluated self-injection by subjects who were at the investigative site and under medical supervision. The agency advised the applicant that, to support approval of self-administration, they needed to provide data which reflected self-treatment independent of medical supervision. The agency expressed no concerns about self-administration by subcutaneous injection per se: This is not a technically-complex procedure, and numerous products are approved for self-administration by this route. The agency's principle expressed concern was in the context of ustekinumab therapy and pertained to patients' ability to become adept with self-injection procedures, given the relatively long intervals (three months) recommended for maintenance dosing.

The Medical Officer has concluded that the applicant provided sufficient information to support approval for self-administration of ustekinumab with the PFS. The data adequately support that subjects could safely self-administer treatment with the PFS outside of medical supervision. There were no errors in transport or administration of the product. There were no discontinuations associated with self-administration. There were no adverse events associated with self-injection, including no injection site reactions reported with self-injection.

The Medical Officer has concluded that sufficient information is available to support approval of the LIV for self-administration, as discussed below.

Reference ID: 3295325

Evaluation of Self-administration with the LIV
The applicant has formally evaluated self-administration with the LIV presentation. The applicant assessed self-administration with the LIV in the pivotal trials and referenced those data in the annotated label provided with submission of the marketing application (application submission date: December 13, 2007). However, all subjects self-administered study treatment under medical supervision at the investigative site. No efficacy or safety concerns were identified in the context of medically-supervised self-injection with the LIV.

Post-marketing Experience
A summary of the post-market safety experience for ustekinumab was completed on October 5, 2012 (signature date October 12, 2012), in accordance with Title IX, section 915 of the Food and Drug Administration Amendments Act of 2007 (FDAAA). For the 915 review, Carlos M. Mena-Grillasca, RPh, Safety Evaluator in the Division of Medication Error Prevention and Analysis (DMEPA), searched the (then) Adverse Event Reporting System (AERS) database for reports of medication errors. Of the 17 cases returned under the terms of the search, nine were foreign reports. The Medical Officer considers that these nine reports merit some discussion in this supplement review, as (per the applicant) self-administration with the PFS and LIV have been approved in several other jurisdictions, including the European Union, Canada and Australia, since 2009. In the Medical Officer's opinion, none of the foreign reports appear to pertain to self-administration; they are described below:

- Wrong patient population (n=2); product was administered to patients with latent tuberculosis.
- Dose omission (n=5); product not administered due to hospitalization in two cases, unspecified causality in two cases, and tonsillitis in one case.
- Wrong frequency of administration (n=1); product was administered monthly.
- Dispensing error (n=1); patient was dispensed one 45 mg vial, rather than the prescribed two vials.

Ultimately, Mr. Mena-Grillasca "identified no potential safety issues from the reported medication error cases involving Stelara (Ustekinumab) injection, for subcutaneous use."
The Medical Officer concurs with this assessment and also concludes that the search identified no potential safety issues pertaining to self-administration.

For this supplement, S-86, Mr. Mena-Grillasca searched the FDA Adverse Event Reporting System (FAERS) database for ustekinumab medication error reports. The search was time limited from the AERS search performed as part of the 915 NME Post Marketing evaluation (discussed above).

Three ustekinumab medication error cases qualified for detailed analysis from the FAERS search. Two were foreign cases, and one was domestic:

- In two cases (one foreign; one domestic) "wrong route of administration" was the cited error. In both cases, ustekinumab was administered via the intramusuclar route, and in neither case was causality provided.

Reference ID: 3295325

- "Wrong dose error" was the cited error in one case (foreign), in which a patient received a 90 mg dose, rather than 45 mg dose.

The description of the FAERS cases that were excluded from the detailed analysis raised no concerns that would impact the Medical Officer's recommendation for this supplement. The events reported in the foreign cases raised no concerns about self-administration.

Medication Error Mitigation
This reviewer believes that, with proper adherence, the instructions for use (IFUs) are sufficiently-detailed to serve as effective reference aids for self-administration. The training by healthcare providers in conjunction with the IFUs should decrease the potential for dosing and/or administration errors with self-treatment. Also, the reviewer notes that the protocol for one long-term extension trial, C0743T09, allowed for dose escalation (i.e. increase in dose amount and/or frequency) at the investigator's discretion, such that some subjects eventually and deliberately received 90mg when 45mg was the dosage group to which they had been originally randomized. In fact, after Week 52, a subject who began treatment on a regimen of 45mg every 12 weeks may ultimately have ended up on 90mg every 8 weeks. No safety issues were identified from dosing under this regimen.

The Medical Officer believes that the packaging of both presentations will decrease the likelihood of dosing errors, since both presentations are for single-use, with volume sufficient for one 45mg or 90mg dose. Because of the product's cost, the Medical Officer believes it distinctly unlikely that 90mg would be routinely dispensed to a patient for an intended 45mg dose (with wastage of the unused portion). Therefore, patients would generally not have to administer a partial volume from a larger one (PFS), nor withdraw a partial volume from a larger one (LIV). Even were a patient, intended for 45mg dosing, to be erroneously dispensed and administer 90mg, the safety and well-being of that patient may not be at risk from such an error (see above discussion regarding dose escalation in C0743T09).

Self-administration by Intravenous Injection
The agency has approved products for self-administration via the intravenous route, one of which is Cinryze, a C1 esterase inhibitor (BLA 125267; approved October 9, 2008). It is indicated for routine prophylaxis against angioedema attacks in adolescent and adult patients with hereditary angioedema and can be administered every three to four days. The single pivotal trial is specifically described in the clinical review (reviewer: Charles Maplethorpe M.D., Ph.D.) as having been "conducted at clinical centers (not at home)." This Medical Officer could find no information to indicate that self-administration (or caretaker administration) was evaluated, including under supervision at the investigative site. Additionally, this Medical Officer did not find information to indicate that the agency required evaluation of unsupervised self-administration to support approval of this option. Further, it is not clear that the applicant proposed labeling for self-administration of Cinryze; from Dr. Maplethorpe's review recommendations (Section 13.1):

"I recommend licensure of CINRYZE for the routine prophylaxis indication. Due to the expected home use of routine prophylaxis, I recommend that the sponsor be required to submit a Patient Package Insert (PPI) that includes

Reference ID: 3295325

Directions for Use within 30 days of licensure. The PPI does not need to be a post-marketing requirement (PMR) under Title IX section 901 of FDAAA."

Consistent with Dr. Maplethorpe's recommendation, patient labeling for self-administration was not listed as a post-marketing requirement in the posted approval letter.

This Medical Officer considers the procedures for self-administration of Cinryze to be far more complex than those for self-administration of ustekinumab LIV. Cinryze is a freeze-dried powder that first requires reconstitution with sterile water into liquid form that is then drawn into a syringe for injection. The reconstitution process alone constitutes steps one through six of the patient instructions for use and are steps not required with the ustekinumab LIV. (Per the Full Prescribing Information, reconstitution and administration are to be done under aseptic technique.) Other self-administration instructions for Cinryze include tourniquet placement, insertion of the butterfly needle of the infusion set tubing into the vein, slow injection over 10 minutes (at a rate of approximately 1mL/min), etc.

Self-administration of Cinryze may or may not have been evaluated independent of medical supervision to support approval for self-administration. Irrespective of that history, it is approved for self-administration. Further, irrespective of that history, training by healthcare providers, reinforced by patient labeling, have been determined to be sufficient support for patients (not subjects) in the self- administration of Cinryze, i.e. sufficient support for real-world use.

If training by healthcare providers buttressed by adequate patient labeling have been determined to be sufficient support for self-administration of Cinryze for real-world use, then training by healthcare providers buttressed by adequate patient labeling should, with other available information (discussed above), be sufficient support for self-administration of ustekinumab LIV. In the Medical Officer's opinion, training, patient labeling and other available information are sufficient to support approval of the LIV in the absence of off-site evaluation of the LIV and with consideration of the recommended three-month dosing intervals for ustekinumab. Self-administration with the ustekinumab LIV is far less technique-intensive than self-administration of Cinryze.

Self-administration of ustekinumab would be available to patients believed (by themselves and their providers) to be appropriate candidates for this option. The Medical Officer believes that, generally, practitioners would agree to this option only after initial safety and efficacy have been demonstrated. Psoriasis of a severity that qualifies for treatment with ustekinumab (or other systemic treatment or phototherapy) is not trivial disease. Therefore, in the Medical Officer's opinion, patients who elect for self-administration would likely generally be confident in their abilities to properly administer treatment and be highly motivated to adhere to procedures in order to achieve or maintain optimal therapeutic benefit(s). The on-site training and IFUs should provide sufficient support for self-injection of both presentations. The Medical Officer concludes that the preponderance of evidence supports approval of self-administration of ustekinumab with the PFS and LIV presentations.

Reference ID: 3295325

Labeling Updates (including information reflecting completion of the five-year extension trials)

The applicant has submitted data sufficient to support updates to subject exposures and adverse event rates in the Clinical Trials Experience (6.1) and to the Immunogenicity (6.2) discussion in the label.

The applicant also proposed to update a paragraph in the Clinical Studies Experience section to add events that were identified as adverse reactions during the original BLA (but not included in the label). The applicant proposed the following revision (proposed new language underscored):

Adverse reactions that occurred at rates less than 1% in the controlled period of STUDIES 1 and 2 through week 12 included: cellulitis, (b) (4), herpes zoster, diverticulitis and certain injection site reactions (pain, swelling, pruritus, induration, hemorrhage, bruising, and irritation).

The Medical Officer believes that adding (b) (4) to the paragraph would be somewhat redundant to existing information in the label, (b) (4) (b) (4) The list of adverse reactions in the label is not intended to be exhaustive; it reads "Adverse reactions that occurred at rates less than 1% in the controlled period of STUDIES 1 and 2 through week 12 *included*…." (emphasis added). The Medical Officer does not believe that listing " (b) (4) would add meaningful new information to the label. In the Medical Officer's opinion, lengthening the list, by adding information sufficiently imparted elsewhere, risks obscuring the communication of the following clinically important adverse reactions: cellulitis, herpes zoster, diverticulitis and certain injection site reactions (pain, swelling, pruritus, induration, hemorrhage, bruising, and irritation).

2 Introduction and Regulatory Background

2.1 Product Information

Stelara liquid in vial (LIV) was approved on September 25, 2009, and the prefilled syringe (PFS) presentation was approved on December 30, 2009. In the supplement under review (S-86), the applicant has submitted data intended to support revisions to the ustekinumab label as below:

- Addition of provisions for self-administration.
- Updates with information reflecting completion of the five-year extension trials, C0743T08 (T08; PHOENIX 1) and C0743T09 (T09; PHOENIX 2).

Self-Administration

Janssen Biotech, Inc. (Janssen) proposed labeling for self-administration of treatment with the liquid in vial (LIV) and prefilled syringe (PFS) presentations. They initially proposed self-injection with launch of ustekinumab, a first-in-class new molecular entity, when the LIV was the only presentation proposed for marketing. However, the applicant had only evaluated self-treatment by subjects who were at the investigative site and under medical supervision. The

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agency advised the applicant that to support approval of self-administration, they needed to provide data which reflected self-treatment independent of medical supervision.

The agency expressed no concerns about self-treatment by subcutaneous injection per se: This is not a technically-complex procedure, and numerous products are approved for self-administration by this route. The agency's principle expressed concern was in the context of ustekinumab therapy and pertained to patients' ability to become adept with self-injection procedures, given the relatively long intervals (three months) recommended for maintenance dosing.

The applicant later proposed self-administration with submission of the efficacy supplement for the PFS (submit date: March 3, 2009). Again, however, they provided no data from evaluation of self-treatment off site, relying on the same data as had been referenced in support of the initial proposal for self-administration.

In the current supplement, S-86, the applicant provided data from evaluation of off-site self-administration with the PFS and proposed labeling for self-administration of both presentations, i.e. the PFS and LIV. The applicant had not evaluated off-site self- administration using the LIV presentation. Janssen does not currently distribute the LIV in the United States, and they seek approval of self-administration with that presentation "based on potential patient needs and/or future clinical indications", relying in part on the PFS data. The applicant provided supportive arguments (in response to an Information Request January 16, 2013) for labeling of the LIV presentation for self-administration when they had provided data only for the PFS; arguments included:

- Discussion of liquid products which are currently approved for self-administration and require withdrawal from a vial (the applicant did not claim that unsupervised use had been evaluated with the cited products).
- The LIV and PFS presentations have been approved in "most markets" since 2009 (including the European Union, Canada and Australia), with no safety concerns identified from post-marketing experience.
- Data on self-injection with the LIV had been provided with submission of the marketing application (injections were done under medical supervision at the investigative site).

The applicant amended the protocol for the C0743T08 trial (T08; PHOENIX 1) to incorporate the option for subjects to self-administer study agent away from the investigational site (Amendment 4). The five-year trial was then in the open-label, long-term extension phase. The efficacy supplement under review provides for data generated from conduct of the trial under Amendment 4 and is intended to support self-administration. The supplement would provide for revisions to the Dosage and Administration (2.2) and Patient Information (17) sections of the Full Prescribing Information (FPI) portion of the label, as well as the Medication Guide. The supplement would also provide for new patient labeling in the form of instructions for use (IFUs) as aids for self-administration.

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Updates from of the five-year extension trials

The applicant also proposed to revise the Clinical Studies Experience (6.1), Immunogenicity (6.2) [redacted] (b) (4) sections of the label to reflect completion of the five-year trials C0743T08 (T08; PHOENIX 1) and C0743T09 (T09; PHOENIX 2), the open-label, long-term extension of the pivotal trials.

On May 31, 2012, the agency approved efficacy supplement 49 (S-49), which provided updates to the Clinical Studies Experience section of the label reflecting data through 3 years for T08 and 4 years for T09 (The applicant submitted those data and analyses as the "4-Year Update").

In the supplement that is the subject of this review, S-86, the applicant proposed to again update the sections that were revised with approval of S-49. In the current supplement, the applicant relied on data through Year 5/Week 264 from T08 and T09 (data and analyses submitted as the "5-Year Update"). Specifically, the applicant proposed to revise:

- safety information, e.g. adverse event rates (Clinical Studies Experience (6.1):
- immunogenicity data (6.2)

Additionally, the applicant proposed a statement pertaining to [redacted] (b) (4). Specifically, the applicant proposed the following statement for the Clinical Studies section (14) of the label: [redacted] (b) (4) where [redacted] (b) (4) was not defined.

The statement is somewhat similar to one that the applicant proposed in S-49 [redacted] (b) (4) That is, in S-49, the applicant had proposed adding [redacted] (b) (4) however, the agency did not consider those data adequate for inclusion in the label and did not approve that statement.

2.2 Availability of Proposed Active Ingredient in the United States

The applicant submitted a supplemental BLA for psoriatic arthritis (PsA) to the Division of Pulmonary, Allergy and Rheumatology Products on November 21, 2012. Per draft labeling provided in that supplement, the proposed indication is for use "alone or in combination with methotrexate (MTX)…for the treatment of adult patients (18 years or older) with active psoriatic arthritis."

The proposed dosing regimens for PsA are below (and are similar to those for psoriasis):

- The recommended dose is 45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks.
- [redacted] (b) (4)

The applicant submitted data from the PsA development program in the four-month safety update for the efficacy supplement that is the subject of this review (See Sec. 7.6 of this review).

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2.3 Summary of Presubmission Regulatory Activity Related to Submission

The applicant had a pre-sBLA teleconference with the review division pertaining to this supplement on May 23, 2012. Agreement was reached on the content and format of the supplement.

2.4 Other Relevant Background Information

Postmarketing Requirements (PMRs) 8 and 9 of the approval letter mandated completion of the five-year extension trials T08 and T09, respectively. Each study report was submitted in accordance with the timeline detailed in the approval letter. The final study report for each of those trials is individually addressed under separate cover for assessment of fulfillment of the specific terms of the PMRs.

Consults for Patient Labeling for Self-Administration

The Medication Guide and Instructions for Use reflect consultation from the following divisions:

- Division of Medical Policy Programs (DMPP) Patient Labeling Review (consult dated February 8, 2013; follow-up on April 3, 2013)
- Division of Professional Drug Promotion (DPDP; consult dated February 12, 2013)
- Division of Medication Error Prevention and Analysis (DMEPA; consult dated March 7, 2013)

The DPDP also reviewed the FPI.

The Medical Officer has reviewed all labeling in its entirety; labeling negotiations with the applicant were pending as this review was being finalized.

5 Sources of Clinical Data

The applicant relied on data from T08 to support labeling for self-administration. The applicant also relied on T08 to support the proposed new language for the Clinical Studies section, specifically referencing sub-section 6.4.1.2 of the final study report T08. (b) (4) [redacted] hich is the outcome the applicant proposes to describe in the label. The referenced sub-section of the study report discusses outcomes during the uncontrolled, open-label phase of the trial.

New data from T08 and T09 were the basis for the updated analyses of integrated safety data, which were data pooled from four trials: C0379T04 (T04), T08, T09 and C0379T12 (T12). Final data analyses had been previously submitted for trials T04 and T12 (dates for final reports: June 13, 2006 and August 15, 2009, respectively). For the proposed updates to the Clinical Studies Experience section of the label, the applicant is largely relying on the updated integrated safety

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analyses. However, the applicant is relying only on data from T08 and T09 for 1) the proposed addition of new events to the list of events occurring at < 1% through Week 12 and 2) for the proposed updates to the immunogenicity discussion.

5.1 Tables of Clinical Studies

The applicant considered the four trials in Table 1 as being key in their global psoriasis clinical development program. The applicant analyzed pooled safety data from these four trials for the integrated safety analyses. However, new data were provided only from T08 and T09 in the updated analyses.

Table 1: Key global ustekinumab clinical studies in psoriasis

Study Number (Name)	Study Duration Placebo/Active-Comparator Period	Number of Subjects Randomized	Study Status	Data included in longer-term analyses (current submission)	
				Efficacy Pharmacology	Safety
PHASE 2					
C0379**T04**	36 Weeks 20 Weeks (placebo)	320	Completed	None	36 Weeks
PHASE 3					
C0743**T08** (PHOENIX 1)	264 Weeks 12 Weeks (placebo)	766	Completed	Week 40 to Week 244	Up to 264 Weeks (Year 5)
C0743**T09** (PHOENIX 2)	264 Weeks 12 Weeks (placebo)	1230	Completed	Week 52 to Week 244	Up to 264 Weeks (Year 5)
C0743**T12** (ACCEPT)	64 Weeks 12 Weeks (etanercept)	903	Completed	None	64 Weeks

Source: Table 1 Clinical Overview

5.2 Review Strategy

Pertaining to the proposed (b) (4) self-administration, the review will focus on T08, as the applicant is relying only on this trial to support the proposed labeling revisions pertaining to efficacy and self-administration.

Pertaining to the safety analyses, the review will focus on the sections of the submission intended and referenced to support the proposed updates to the label. See Section 2.4 pertaining to review of final study reports for the five-year trials T08 and T09.

5.3 Discussion of Individual Studies

Protocol Amendment 4 of the protocol for T08 provided the option for subjects to self-administer study agent away from the investigative site. The applicant submitted the amendment to IND 9590 on February 25, 2010. Although the protocol allowed for self-administration prior to implementation of Amendment 4, self-treatment was done under medical supervision at the

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investigative site. Per amendment 4, Section 7.1.2 of the protocol was revised as below (the bolded language was provided by the amendment):

After Week 12 and at the discretion of the investigator and subject, and after appropriate training, study agent may be self-administered at the investigative site by the subject under the supervision of an appropriately licensed and authorized health professional. All subjects will be strongly encouraged to self-inject by Week 40. Specific instructions for self-injection will be supplied in the Study Reference Manual. **After Protocol Amendment 4 is implemented, subjects who have demonstrated that they are capable of self-administration and are comfortable with self-administration may, at the discretion of the investigator and subject, begin administration of study agent away from the investigative site. Instructions for administration of study agent away from the investigative site will be supplied in the (Subject Take Away Package) STAP.**

The Subject Take Away Package (STAP) included patient instructions, an insulated travel pack, cooling blocks, study treatment, alcohol pad, cotton ball, sharps container, and adhesive bandage.

The protocol amendment included no endpoints specific to self-injection. There were no protocol-specified procedures for assessment of efficacy or safety of off-site self-administration. The efficacy and safety analyses sections of the protocol were only revised to include the following statements:

- "The efficacy of ustekinumab when administered away from the investigative site will be evaluated" (Section 10.4.1 of protocol).
- "The safety of ustekinumab when administered away from the investigative site will be evaluated" (Section 10.4.3 of protocol).

Study procedures implemented under Amendment 4 all pertained to the PFS presentation, i.e. off-site self-administration of the LIV was not addressed under the amendment nor evaluated in the trial.

6 Review of Efficacy

Efficacy Summary

The applicant proposed (b) (4) (b) (4)). Specifically, the applicant proposed the following new statement for the Clinical Studies section of the label:

(b) (4)

The Medical Officer does not find the proposed statement to be adequate for inclusion in the label. (b) (4) (b) (4)

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(b) (4)

The applicant submitted analyses comparing pharmacokinetics (PK) data from subjects categorized as "On-site Administration" and "Off-site Administration" (Note: It is not clear to this reviewer whether "on-site" refers to subjects who self-administered treatment on-site or those who had treatment administered on-site or both). In one analysis, the applicant compared trough ustekinumab concentrations between these two groups at Weeks 232 and 244. The mean trough ustekinumab concentration for the "off-site" group appeared to be lower at Week 244 (≥ one injection off-site) compared to the "on-site" group, irrespective of dose group, i.e. 45mg or 90mg. However, the clinical pharmacology reviewer, Dr. Jie Wang, concluded that the data were not sufficient to permit assessment of any potential impact of off-site treatment on trough PK. The applicant proposed no labeling claims regarding PK in subjects who treated off-site.

6.1 Indication

Self Administration

Subjects had the option to self-administer treatment off-site beginning at Week 208. A total of 419 subjects received all ustekinumab injections on-site, and 144 subjects self-administered at least one treatment off-site. The 144 subjects self-administered ustekinumab off-site as below:

Table 2: Number of subjects with off-site self-administrations from Week 208 through Week 244

Number of off-site injections	Number of subjects (n=144)
One	19 (3.4%)
Two	58 (10.3%)
Three	53 (9.4%)
Four	13 (2.3%)
Five	1 (0.2%)

Source: Attachment 1.10 of 264-Week study report for T08

Of these 144, 75 subjects self-administered treatment off-site at or prior to Week 220. Most subjects self-administered from two to three injections off-site. A total of 31 subjects reverted to administration of treatment at the study site, 28 of whom reverted to on-site treatment for the last injection. Per Attachment 1.9 of the study report for T08, the total number of subjects injecting off-site peaked at Week 220 and progressively and steadily decreased through Week 240 (last study treatment was to have been at Week 244, per the protocol).

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Table 3 Distribution of subjects with first off-site self-administration visit from Week 208 through Week 244; subjects treated with ustekinumab at Week 208 or beyond

Subjects treated with ustekinumab at Week 208 or beyond	563
Subjects with at least 1 off-site self-administered injection	144 (25.6%)
Distribution of subjects by the first off-site self-administered injection	
Week 208	2 (0.4%)
Week 212	11 (2.0%)
Week 216	12 (2.1%)
Week 220	50 (8.9%)
Week 224	32 (5.7%)
Week 228	19 (3.4%)
Week 232	11 (2.0%)
Week 236	6 (1.1%)
Week 240	0 (0.0%)
Week 244	1 (0.2%)

Source: Attachment 1.9 of 264-Week study report for T08

The Medical Officer believes it possible that by the time off-site treatment became an option (at Week 208 of a 264-week trial), study subjects were likely well-habituated to on-site procedures. Also, subjects apparently had to return to the investigation site for study visits on the same schedule irrespective of whether injections were administered on- or off-site. Therefore, the strength of the incentive for subjects to either undertake or continue the new procedures associated with self-administration (e.g. transport of materials, preparation procedures, etc.) is unclear.

For some subjects, self-injection procedures may have been well-honed from medical-supervision, since the protocol allowed for self-injection beginning at Week 12, and off-site treatment only became an option far later in the trial. Nevertheless, some procedures pertaining to off-site treatment may have been completely new even to subjects practiced in self-injection procedures, e.g. transport of the product and attending to all injection procedures independently. The applicant reported no adverse events or errors with product transport or injection procedures for subjects who self-injected off-site.

Evaluation of Self-administration with the LIV

The Medical Officer reviewed the annotated labeling provided with submission of the marketing application (application submission date: December 13, 2007), in which the applicant had proposed self-administration with the LIV. They referenced data in the 52-Week study report for T08 to support the efficacy of self-administration. In T08, the applicant formally assessed the efficacy (and safety) of self-administration with the LIV during the randomized withdrawal portion of the study (at Week 40) by comparing outcomes for subjects who self-administered treatment with outcomes of subjects who had treatment administered by healthcare professionals.

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The applicant referenced data from the 28-Week report from T09 (along with data from T08) to support the safety of self-administration of treatment with the LIV. In T09, the applicant compared adverse events from Week 16 through Week 28 in subjects who self-injected with adverse events in subjects who received treatment from a healthcare professional.

In these formal assessments, per the applicant, 58.8% subjects in the randomized withdrawal portion of T08 and 34.1% of subjects in T09 from Week 16 through Week 28 self-administered study agent (source: Summary of Clinical Safety from the initial submission; Section 5.2.1). However, all subjects self-administered study treatment under medical supervision. No efficacy or safety concerns were identified in the context of supervised self-injection with the LIV. The applicant referenced these same data from T08 and T09 when they again proposed labeling for self-administration in the supplement submitted for the PFS. Comparability of the PFS to the LIV was adequately established in that supplement.

6.1.1 Analysis of Primary Endpoint(s)

The primary endpoint for T08 was the proportion of PASI 75 responders at Week 12. Analyses of data for this endpoint were submitted with the marketing application and were relied on for approval. Outcomes for the primary endpoint are described in the Clinical Studies section of the label.

The applicant performed efficacy analyses which considered off-site treatment. However, the trial was not designed to assess efficacy of off-site treatment; none of these analyses were pre-specified. The applicant did not propose any labeling claims pertaining to efficacy with off-site treatment.

The applicant described that at Week 200 (i.e. prior to allowance for off-site treatment), PASI 75 rates were 81.1% for subjects who would continue on-site treatment and 75.5% for subjects who would elect off-site treatment. At Week 244, PASI 75 responses were 77.9% and 73.6%, respectively.

The applicant concluded that efficacy was maintained with self-administered off-site treatment.

Table 4: PASI 75 response rates at Week 200 and Week 244 in subjects who continued on-site treatment and subjects who administered ustekinumab off-site at Week 208 or beyond in C0743T08

	Subjects had on-site administration of ustekinumab [a]	Subjects who administered ustekinumab off-site [a]
	N=419	N=144
Week 200, before off-site administration	81.1%	75.5%
Week 244, after off-site administration	77.9%	73.6%

a: Placebo crossover subjects are included after crossover to ustekinumab

Source: Attachment 3.24 of 264-Week study report for T08

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7 Review of Safety

Safety Summary

The applicant proposed to update the label with safety data through Year 5 (relying on data submitted as the "5-Year Update"). The new safety data are from the open-label extension phases of the T08 and T09 trials. The new analyses do not change the safety profile as was assessed in the review of data submitted to support S-49. The safety analyses submitted in the S-86 (current supplement) did not reveal any new or worrisome safety signals and are consistent with the information provided in support of S-49. The applicant does not propose comparative or relative safety claims, e.g. statements comparing adverse event rates through year 5 to some previous time point; the new information would replace the current information. The applicant has provided sufficient data to support the proposed updates to subject exposures and event rates in the Clinical Studies Experience section of the label.

The applicant also proposed to update a paragraph in the Clinical Studies Experience section of to add events that were identified as adverse reactions during the original BLA (but not included in the label). The applicant proposes the following revision (proposed new language underscored):

Adverse reactions that occurred at rates less than 1% in the controlled period of STUDIES 1 and 2 through week 12 included: cellulitis, [redacted] (b) (4), herpes zoster, diverticulitis and certain injection site reactions (pain, swelling, pruritus, induration, hemorrhage, bruising, and irritation).

The Medical Officer believes that adding [redacted] (b) (4) to the paragraph would be somewhat redundant to existing information in the label, as [redacted] (b) (4)" are listed as adverse reactions in the existing label. The list of adverse reactions in the label is not intended to be exhaustive; it reads "Adverse reactions that occurred at rates less than 1% in the controlled period of STUDIES 1 and 2 through week 12 *included*…." (emphasis added). The Medical Officer does not believe that listing [redacted] (b) (4)" would add meaningful new information to the label. In the Medical Officer's opinion, lengthening the list, by adding information sufficiently imparted elsewhere, risks obscuring the communication of the following clinically important adverse reactions: cellulitis, herpes zoster, diverticulitis and certain injection site reactions (pain, swelling, pruritus, induration, hemorrhage, bruising, and irritation).

Pertaining to self-administration, no subject experienced an injection site reaction with off-site self-administration. The applicant described no errors or adverse events pertaining to off-site administration or in transport of the product.

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7.1 Methods

7.1.1 Studies/Clinical Studies Used to Evaluate Safety

See 5.1.

7.1.2 Categorization of Adverse Events

The applicant organized adverse events by system-organ class (SOC) and preferred term (PT) using the MedDRA dictionary.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

The applicant pooled data from the four global psoriasis stuides to allow for a larger safety database for estimate of the event rates and detection of possible safety signals.

7.2 Adequacy of Safety Assessments

A total of 3117 subjects were exposed to ustekinumab in the global psoriasis dataset. See Table 4 for the number of subjects exposed per time period. The applicant calculated that the data provided for 8,998 subject-years of follow-up on ustekinumab.

Table 5: Summary of duration of ustekinumab exposure and total ustekinumab dose through the end of the reporting period; subjects treated with ustekinumab in global psoriasis studies (Source: Table 6 of Clinical Overview)

	Ustekinumab		
	45 mg[a]	90 mg[a]	Combined
Subjects treated with ustekinumab in global psoriasis studies	1319	2001	3117
Duration of ustekinumab exposure			
At least 1 year[a]	901 (68.3%)	1136 (56.8%)	1855 (59.5%)
At least 2 years[b]	713 (54.1%)	986 (49.3%)	1653 (53.0%)
At least 3 years[c]	617 (46.8%)	886 (44.3%)	1569 (50.3%)
At least 4 years[d]	566 (42.9%)	746 (37.3%)	1482 (47.5%)
At least 5 years[e]	307 (23.3%)	432 (21.6%)	838 (26.9%)
Avg number of ustekinumab administrations	13.6	12.4	13.7
Median total dose (mg)	540.0	810.0	810.0

[a] The duration between the first and last ustekinumab administration was at least 38 weeks.
[b] The duration between the first and last ustekinumab administration was at least 88 weeks.
[c] The duration between the first and last ustekinumab administration was at least 140 weeks.
[d] The duration between the first and last ustekinumab administration was at least 192 weeks.
[e] The duration between the first and last ustekinumab administration was at least 240 weeks.

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The applicant proposed to update the label as below (proposed deletions marked by strike-through; proposed new language marked by underscore):

The safety data reflect exposure to STELARA® in 3117 psoriasis subjects, including 2414 exposed for at least 6 months, ~~1852~~ 1855 exposed for at least one year,~~1650~~ 1653 exposed for at least two years, ~~1129~~ 1569 exposed for at least three years, ~~and 619~~ 1482 exposed for at least four years and 838 exposed for at least five years.

The proposed updates included changes to the numbers of subjects exposed for at least six months and one year, i.e. submission of the 5-Year Update included proposed revisions to subject numbers from earlier time points. Dr. Kathleen Fritsch, the biostatistical reviewer, explained the derivation of the numbers as follows (also see footnotes to Table 4 for definitions of durations of exposure):

"The subject counts above are nested, that is, each successive count represents the number of subjects from the previous group who remained exposed to treatment in the following time period (e.g. out of the 1482 subjects who were exposed for at least 4 years, 838 remained exposed for at least 5 years). Note that subjects did not need to have continuous treatment. For example, there were three subjects who had treatment withdrawn at Week 40 in Study 08 as part of the protocol and did not have additional ustekinumab exposure until at least Week 160 because they did not meet the retreatment criteria (sufficient loss of response) until that time."

7.3 Major Safety Results

7.3.1 Deaths

A total of 20 deaths were reported in the global psoriasis studies dataset. Four deaths have been reported since the 4-Year update (other deaths have been discussed in previous reviews):

T08:

- Subject (b) (6) (45 mg q12w; dose interval adjusted to q8w): 49 year-old male expired in his sleep (sudden death); past medical history: obesity, sleep apnea (required continuous positive airway pressure (CPAP)); cause of death unknown and presumed cardiovascular.
- Subject (b) (6) (90 mg q12w): 75-year-old male suffered a fatal cervical vertebral fracture from a fall (drug screen positive for ethanol).

One additional death was reported in T08 after the Year 5 database lock: Subject (b) (6) (90 mg q12w) was a 72 year-old male who died from metastatic pancreatic carcinoma approximately one year after diagnosis; disease diagnosed on Study Day 1207.

T09

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- Subject (b) (6) (45 mg q12w; dose adjusted to q8w): 60-year-old male died from complications of metastatic small cell lung cancer; past medical history: tobacco use (was ongoing; 60 pack years)
- Subject (b) (6) (90 mg q12w): 54-year-old man died from complications of adenocarcinoma (unknown primary); past medical history: tobacco use (was ongoing; 40 pack years) event of adenocarcinoma was reported in the 208-Week report

The applicant categorized the causes of the 20 deaths as follows: cardiovascular (n = 5), malignancy-related (n = 5), infection-related (n = 3), and related to other causes e.g. accidental, aspiration, suicide (n = 7). There was no apparent pattern to the categories of death. The applicant calculated the overall incidence of death to be 0.22 per 100 subject-years of follow-up (95% CI: 0.14 to 0.34). Per the applicant, 55.75 deaths would have been expected by CDC estimates. They report the Standardized Mortality Ratio as 0.36.

7.3.2 Nonfatal Serious Adverse Events

In decreasing order of frequency, serious adverse events were most commonly reported in the following system organ classes (SOCs): Cardiac disorders, Infections and infestations, Injury, poisoning and procedural complications, Neoplasms benign, malignant and unspecified (including cysts and polyps), and Gastrointestinal Disorders. In an event-based analysis, serious adverse events reported at a rate of ≥ 0.10 (per review of Table 6 in the Integrated Summary of Safety) were: myocardial infarction (0.24), coronary artery disease (0.21), chest pain (0.19), nephrolithiasis (0.14), cellulitis (0.12), prostate cancer (0.12), angina unstable (0.11), atrial fibrillation (0.11), diverticulitis (0.11), intervertebral disc protrusion (0.11), osteoarthritis (0.11), and renal colic (0.10).

Table 6 Number of treatment-emergent adverse events, serious adverse events, infections, and adverse events leading to discontinuation per hundred subject-years of follow-up for ustekinumab 45 mg and 90 mg combined through the end of the reporting period by time period; subjects treated with ustekinumab in global psoriasis Phase 2 and Phase 3 (Table 6 Summary of Clinical Safety)

	Time Period				
	Year 1 (≤ 48 weeks) Ustekinumab 45 mg and 90 mg Combined	Year 2 (> 48 to ≤ 96 weeks) Ustekinumab 45 mg and 90 mg Combined	Year 3 (> 96 to ≤ 144 weeks) Ustekinumab 45 mg and 90 mg Combined	Year 4 (> 144 to ≤ 192 weeks) Ustekinumab 45 mg and 90 mg Combined	Year 5 (> 192 weeks) Ustekinumab 45 mg and 90 mg Combined
Subjects treated with ustekinumab in global psoriasis Phase 2 and Phase 3[a,b]	3117	2145	1671	1588	1516
Total subject-years of follow-up	2548	1647	1506	1439	1876
Number of adverse events per hundred subject-years of follow-up	382.13	228.91	180.25	164.11	124.90
Number of serious adverse events per hundred subject-years of follow-up	8.36	7.22	5.38	7.51	6.34
Number of infections per hundred subject-years of follow-up	135.50	90.57	70.00	60.68	48.67
Number of discontinuations because of 1 or more adverse events per hundred subjects years of follow-up[c]	3.33	2.76	2.08	2.32	1.24

[a] Global psoriasis studies include Phase 2 C0379T04 and Phase 3 (C0743T08, C0743T09, and C0743T12).
[b] Placebo crossover subjects and etanercept crossover subjects were included in the ustekinumab columns after crossover to ustekinumab. For C0743T09, subjects who were dose escalated from 45 mg to 90 mg were switched to the corresponding column following dose escalation.
[c] Discontinuation analyses were subject-level where subjects discontinued due to 1 or more AEs were counted only once. Therefore, its total subject-years of follow-up is slightly lower than the follow-up displayed.

Rates of serious adverse events showed no clear pattern, but appeared to trend downward through Year 3, with an increase (not progressive) in subsequent time periods. Rates of adverse events, infections and adverse events leading to discontinuation appeared to progressively decrease when considered by annual time periods (i.e. Year 1 through Year 5). However, subject recollection of events that occurred between study visits may have been incomplete because of the length of the intervals between study visits (e.g. 12 weeks) during the long-term extension phase.

7.3.3 Dropouts and/or Discontinuations

Through Year 5, 6.9% of ustekinumab-treated subjects in the global psoriasis studies dataset discontinued study agent due to an adverse event. Adverse events leading to discontinuation were most commonly reported in the Neoplasms benign, malignant and unspecified and Pregnancy, puerperium and perinatal conditions SOCs at 2.3% and 0.8%, respectively. The protocols required discontinuation for any type of malignancy (including skin cancers) until amended in 2008 to allow for no more than two localized basal cell skin cancers that were treated with no evidence of recurrence or residual disease. Subjects who became pregnant were also required to discontinue treatment.

No subjects who self-administered treatment off-site discontinued due to an adverse event.

7.3.4 Significant Adverse Events

The applicant proposed to again update the rates of infections (including serious infections) and malignancies in the Clinical Studies Experience section of the label. These rates were most recently updated with approval of S-49 on May 31, 2012. Approval of S-49 reflected updates to the label with analyses which included new data through three years (Week 152) for T08 and four years (Week 208) for T09. The proposed updates submitted in the current supplement were based on data through completion of both of those trials, i.e. through five years (Week 264) for T08 and T09. The applicant proposed to replace the rates approved in S-49 with rates reflecting the final analyses of the integrated safety database. Dr. Fritsch prepared a table which summarizes and compares the event rates approved under S-49 with those proposed in the supplement under review (S-86):

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Table 7 – Infection and Malignancy Rate Changes due to Completion of Studies 08 and 09 (Source: Table 1 of the statistical review by Dr. Fritsch)

	Up to 4 Years Follow-up (Current Labeling)	Up to 5 Years Follow-up (Proposed Labeling)
Subjects treated	3117	3117
Subjects with 1 or more infections	2192 (70.3%)	2254 (72.3%)
Subjects with 1 or more serious infections	64 (2.1%)	87 (2.8%)
Subjects with NMSC	41 (1.3%)	47 (1.5%)
Subjects with other malignancies	42 (1.3%)	54 (1.7%)
Total subject-years of follow-up - Infections	6791	8998
Infection event rate per subject-years (number of events)		
Infections	0.98 (6673)	0.87 (7800)
Serious Infections	0.01 (75)	0.01 (99)
Total subject-years of follow-up – Malignancies	6758 (All Mal) 6770 (NMSC) 6779 (Oth Mal)	8947 (All Mal) 8965 (NMSC) 8980 (Oth Mal)
Malignancy incidence rate per hundred subject-years (number of subjects)		
Malignant neoplasms	1.23 (83)	1.13 (101)
Non-melanoma skin cancer (NMSC)	0.61 (41)	0.52 (47)
Other malignancies	0.62 (42)	0.60 (54)

Source: Stelara labeling dated 1/25/2013, pg 38 and 43 of the Summary of Clinical Safety, and reviewer analysis.

With the new analyses of the safety data provided by the 5-Year Update, rates of infections and malignancies were essentially stable compared to the analyses in the 4-Year Update. The specific proposed updates are discussed below.

Infections

The applicant proposed to update the discussion of infections in the package insert as below:

In the controlled and non-controlled portions of psoriasis clinical trials (median follow up of ~~2.6~~ 3.2 years), representing ~~6791~~ 8998 subject-years of exposure, ~~70~~ 72.3% of STELARA®-treated subjects reported infections (~~0.98~~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).

In the global psoriasis dataset, 2.8% of subjects reported a serious infection. Per Table 10 of the Integrated Summary of Safety (ISS), serious infections were most commonly reported in the Infection and infestation SOC (2.4%) and the Gastrointestinal disorders SOC (0.3%). Serious infections in all other SOC were reported at ≤ 0.1% (e.g. Respiratory, thoracic and mediastinal disorders). The most commonly reported serious infections were cellulitis (0.3%), diverticulitis (0.3%), and pneumonia (0.2%). Cellulitis and diverticulitis are labeled as adverse reactions for ustekinumab. All other serious infections were reported at a frequency of ≤ 0.1%. In the event based analysis, serious infections were reported at a rate of 1.10 events per 100 subject-years. Serious infections did not appear to increase over time. There was otherwise no apparent pattern to the occurrence of serious infections over time when considered by Year. See Table 8.

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Table 8: Number of serious infections per hundred subject-years of follow-up for ustekinumab 45 mg and 90 mg combined through the end of the reporting period by time period; subjects treated with ustekinumab in global psoriasis Phase 2 and Phase 3 (Source: Table 11 Summary of Clinical Safety)

	Time Period				
	Year 1 (≤ 48 weeks) Ustekinumab 45 mg and 90 mg Combined	Year 2 (> 48 to ≤ 96 weeks) Ustekinumab 45 mg and 90 mg Combined	Year 3 (> 96 to ≤ 144 weeks) Ustekinumab 45 mg and 90 mg Combined	Year 4 (> 144 to ≤ 192 weeks) Ustekinumab 45 mg and 90 mg Combined	Year 5 (> 192 weeks) Ustekinumab 45 mg and 90 mg Combined
Subjects treated with ustekinumab in global psoriasis Phase 2 and Phase 3[a,b]	3117	2145	1671	1588	1516
Total subject-years of follow-up	2548	1647	1506	1439	1876
Number of serious infections	34	17	10	16	22
Event rate per 100 subject-years	1.33	1.03	0.66	1.11	1.17
95% confidence interval[c]	(0.92, 1.86)	(0.60, 1.65)	(0.32, 1.22)	(0.64, 1.81)	(0.73, 1.78)

[a] Global psoriasis studies include Phase 2 C0379T04 and Phase 3 (C0743T08, C0743T09, and C0743T12).
[b] Placebo crossover subjects and etanercept crossover subjects were included in the ustekinumab columns after crossover to ustekinumab. For C0743T09, subjects who were dose escalated from 45 mg to 90 mg were switched to the corresponding column following dose escalation.
[c] Confidence intervals based on an exact method assuming that the observed number of events follows a Poisson distribution.

A total of 72.3% of subjects experienced ≥ one infection. Per Table 8 of the ISS, the most frequently reported infections (at a rate > 5%) were nasopharyngitis (28.6%), upper respiratory tract infection (24.7%), sinusitis (8.8%), influenza (8.8%), bronchitis (8.2%), and gastroenteritis (6.4%). Of subjects who experienced infection, 39% required oral or parenteral antimicrobial treatment. The percentage of subjects who discontinued treatment due to infection was 0.7%. In the event-based analyses, 86.52 infections were reported per 100 subject-years in the global psoriasis database.

There were no cases of active tuberculosis in the global psoriasis studies. One case of asymptomatic reactivation of pulmonary tuberculosis was reported and was discussed in a previous review. One potential opportunistic infection was reported and was also previously discussed: disseminated cutaneous herpes zoster (no apparent visceral involvement).
There were no reports of nontuberculosis mycobacterial infections or salmonellosis. There were no reports of systemic fungal infections.

Malignancies

The applicant proposed to update the discussion of malignancies in the package insert as below:

Malignancies
In the controlled and non-controlled portions of psoriasis clinical trials (median follow up of ~~2.6~~3.2 years, representing ~~6791~~ 8998 subject-years of exposure), 1.~~3~~7% of STELARA®-treated subjects reported malignancies excluding non-melanoma skin cancers (0.~~62~~ 60 per hundred subject-years of follow-up). Non-melanoma skin cancer was reported in 1.35% of STELARA®-treated subjects (0.~~61~~ 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 trials were: prostate, ~~colorectal~~, melanoma ~~in situ~~, 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).

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Malignancies were reported in 101 subjects (3.2%) in the global psoriasis dataset. Of these, 47 subjects (1.5%) reported nonmelanoma skin cancers (NMSCs), and 54 subjects (1.7%) reported other types of malignancies. In the event-based analyses, there were 1.13 malignancies per 100 subject-years of follow-up in the global psoriasis dataset, with 0.52 NMSCs and 0.60 malignancies of other types reported. See Table 9 below.

Table 9: Number of subjects with 1 or more malignancies through the end of the reporting period; subjects treated with ustekinumab in global psoriasis Phase 2 and Phase 3 (Source: Table 13 Summary of Clinical Safety)

	Ustekinumab		
	45 mg	90 mg	Combined
Subjects treated with ustekinumab in global psoriasis Phase 2 and Phase 3[a,b]	1319	2001	3117
Type of malignancy			
Nonmelanoma skin cancer			
Total subject-years of follow-up	3745	5220	8965
Median subject-years of follow-up	2.3	1.9	3.1
Observed number of subjects	24	23	47
Incidence per 100 subject-years	0.64	0.44	0.52
95% confidence interval[c]	(0.41, 0.95)	(0.28, 0.66)	(0.39, 0.70)
Malignancies other than nonmelanoma skin cancer			
Total subject-years of follow-up	3759	5221	8980
Median subject-years of follow-up	2.3	1.8	3.2
Observed number of subjects	22	32	54
Incidence per 100 subject-years	0.59	0.61	0.60
95% confidence interval[c]	(0.37, 0.89)	(0.42, 0.87)	(0.45, 0.78)
All malignancies			
Total subject-years of follow-up	3738	5210	8947
Median subject-years of follow-up	2.3	1.8	3.1
Observed number of subjects	46	55	101
Incidence per 100 subject-years	1.23	1.06	1.13
95% confidence interval[c]	(0.90, 1.64)	(0.80, 1.37)	(0.92, 1.37)

[a] Global psoriasis studies include Phase 2 C0379T04 and Phase 3 (C0743T08, C0743T09, and C0743T12).
[b] Placebo crossover subjects and etanercept crossover subjects were included in the ustekinumab columns after crossover to ustekinumab. For C0743T09, subjects who were dose escalated from 45 mg to 90 mg were switched to the corresponding column following dose escalation.
[c] Confidence intervals based on an exact method assuming that the observed number of subjects with events follows a Poisson distribution.

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Per Table 15 in the ISS (a listing of subjects), the most commonly reported malignancies (4 ≥) in the global psoriasis dataset through five years were: prostate (14 reports), melanoma (6; in situ and invasive), colorectal (5) and breast (4). There were two reports of lymphoma in the global psoriasis dataset. Per Table 10 below, no apparent trend of increase in malignancies was observed over time, with longer term exposures, when the occurrence of malignancies was considered by time period. However, five years may not represent a sufficiently long duration of follow-up to identify an increase in malignancies, given the latency of malignancies.

Table 10 Number of subjects with 1 or more malignancies for ustekinumab 45 mg and 90 mg combined through the end ofthe reporting period by time period; subjects treated with ustekinumab in global psoriasis studies (Source: Table 14 Summary of Clinical Safety)

	Time Period				
	Year 1 (≤ 48 weeks) Ustekinumab 45 mg and 90 mg Combined	Year 2 (> 48 to ≤ 96 weeks) Ustekinumab 45 mg and 90 mg Combined	Year 3 (> 96 to ≤ 144 weeks) Ustekinumab 45 mg and 90 mg Combined	Year 4 (> 144 to ≤ 192 weeks) Ustekinumab 45 mg and 90 mg Combined	Year 5 (> 192 weeks) Ustekinumab 45 mg and 90 mg Combined
Subjects treated with ustekinumab in global psoriasis Phase 2 and Phase 3[a,b]	3117	2145	1671	1588	1516
Type of malignancy					
Nonmelanoma skin cancer					
Total subject-years of follow-up	2540	1644	1503	1432	1864
Median subject-years of follow-up	0.9	0.9	0.9	0.9	1.3
Observed number of subjects	24	8	6	6	3
Incidence per 100 subject-years	0.94	0.49	0.40	0.42	0.16
95% confidence interval[c]	(0.61, 1.41)	(0.21, 0.96)	(0.15, 0.87)	(0.15, 0.91)	(0.03, 0.47)
Malignancies other than nonmelanoma skin cancer					
Total subject-years of follow-up	2547	1643	1503	1435	1871
Median subject-years of follow-up	0.9	0.9	0.9	0.9	1.3
Observed number of subjects	10	16	6	11	11
Incidence per 100 subject-years	0.39	0.97	0.40	0.77	0.59
95% confidence interval[c]	(0.19, 0.72)	(0.56, 1.58)	(0.15, 0.87)	(0.38, 1.37)	(0.29, 1.05)
All malignancies					
Total subject-years of follow-up	2539	1640	1500	1428	1859
Median subject-years of follow-up	0.9	0.9	0.9	0.9	1.3
Observed number of subjects	34	24	12	17	14
Incidence per 100 subject-years	1.34	1.46	0.80	1.19	0.75
95% confidence interval[c]	(0.93, 1.87)	(0.94, 2.18)	(0.41, 1.40)	(0.69, 1.91)	(0.41, 1.26)

[a] Global psoriasis studies include Phase 2 C0379T04 and Phase 3 (C0743T08, C0743T09, and C0743T12).
[b] Placebo crossover subjects and etanercept crossover subjects were included in the ustekinumab columns after crossover to ustekinumab. For C0743T09, subjects who were dose escalated from 45 mg to 90 mg were switched to the corresponding column following dose escalation.
[c] Confidence intervals based on an exact method assuming that the observed number of subjects with events follows a Poisson distribution.

The applicant compared the rates of malignancies in the global psoriasis studies (excluding NMSC) to the expected rates in the general U.S. population using the Surveillance, Epidemiology, and End Results (SEER) database and calculated a standardized incidence ratio (SIR) in ustekinumab subjects of 0.98 (95% CI: 0.74, 1.29). The malignancies specifically listed in the label, i.e. prostate, melanoma, colorectal and breast, were the ones most commonly reported in the global psoriasis dataset, and the applicant calculated the SIRs for these as follows: prostate 1.21 (95% CI: 0.66, 2.04); melanoma (invasive and in situ) 1.42 (95% CI: 0.52, 3.09), colorectal 0.99 (95% CI: 0.32, 2.31) and breast 0.62 (95% CI: 0.17, 1.58).

The observed malignancy rates in the ustekinumab-treated subjects were concluded to be similar to those in the general population. This conclusion remains consistent with the current labeling which states that, “Malignancies other than non-melanoma skin cancer in STELARA®-treated

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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)." The applicant proposed no revisions to this statement.

Dr. Fritsch prepared the following table (Table 11), which compares event rates over time for categories of events impacted by the proposed updates. …

Table 11 – Event Rates by Year of Follow-up for Serious Infections and Malignancies from Studies 04, 08, 09, and 12 (45 mg and 90 mg Doses Combined) Source: Dr. Fritsch Table 3

	Year 1 ≤ 48 Weeks	Year 2 49 – 96 Weeks	Year 3 97 – 144 Weeks	Year 4 145 – 192 Weeks	Year 5 > 192 Weeks
Subjects	3117	2145	1671	1588	1516
Serious Infections					
Subject-years of FU	2548	1647	1506	1439	1876
# Serious infections	34	17	10	16	22
Events per 100 S-Y	1.33	1.03	0.66	1.11	1.17
Cum. evts per 100 S-Y	1.33	1.21	1.07	1.08	1.10
NMSC					
Subject-years of FU	2540	1644	1503	1432	1864
# Subjects w/ events	24	8	6	6	3
Incidence per 100 S-Y	0.94	0.49	0.40	0.42	0.16
Cum. inc. per 100 S-Y	0.94	0.76	0.67	0.62	0.52
Other Malignancies					
Subject-years of FU	2547	1643	1503	1435	1871
# Subjects w/ events	10	16	6	11	11
Incidence per 100 S-Y	0.39	0.97	0.40	0.77	0.59
Cum. inc. per 100 S-Y	0.39	0.62	0.56	0.60	0.60

Source: pg 39 and 45 of the Summary of Clinical Safety.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Unlike the other integrated analyses, the applicant considered pooled data only from T08 and T09 in the analyses of overall adverse events. The average duration of follow-up in the two trials was 215.4 weeks. Through completion of these five-year trials, 94.8% of subjects reported at least one adverse event. Adverse events were most commonly reported in the Infection and infestation SOC with 81.9% of subjects reporting ≥ one adverse event. The most frequently reported adverse events (i.e. ≥ 10%) in this SOC were nasopharyngitis (35.1%), upper respiratory tract infection (30.1%), sinusitis (11.9%), influenza (11.5%), and bronchitis (11.0%). When adverse events were considered per 100 subject-years of follow-up, events were again most frequently reported in the Infection and infestation SOC, and the event rate was 75.99 events per 100 subject-years of follow-up. Per Table 3 of the ISS, SOC in which the rate was ≥ 10 events reported per 100 subject-years were Musculoskeletal and connective tissue disorders (21.52 events per 100 subject-years), Gastrointestinal disorders (14.56), Injury, poisoning and

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procedural complications (13.55), Skin and subcutaneous tissue disorders (12.10), General disorders and administration site conditions (11.45), Nervous system disorders (10.69), and Respiratory, thoracic and mediastinal disorders (10.02).

The applicant analyzed the global psoriasis safety data by year (Years 1, 2, 3, 4, and 5) to assess whether the frequency of adverse events may have correlated with the duration of exposure to ustekinumab. In these analyses, the applicant considered overall adverse events, serious adverse events, infections, and adverse events leading to discontinuation; see Table 6.

7.4.2 Laboratory Findings

The applicant considered only data from T08 and T09 in the pooled analyses of laboratory data. There was no apparent pattern to the occurrence of changes in laboratory values. No new safety signals were identified from analyses of the laboratory data through five years.

Hematology
Markedly abnormal changes in hematology values that occurred on more than one occasion in ≥ 1% or more of subjects included:

- Decreased lymphocytes (percent decrease ≥ 33 and Value <1.0): 55 (2.8%) subjects.
- Elevated eosinophils (percent increase ≥ 100 and Value > 0.8): 28 (1.4%) subjects.

Clinical Chemistry
Markedly abnormal changes in clinical chemistry testing that occurred on more than one occasion in ≥ 1% or more of subjects in the combined ustekinumab group in T08 and T09 included:

- Elevated alanine transaminase (ALT) (percent increase ≥ 100 and Value > 150): 22 (1.1%) subjects.
- Elevated nonfasting glucose (percent increase ≥ 50% and value > 160): 301 (15.3%) subjects.

7.4.3 Immunogenicity

The applicant proposed to update the discussion of immunogenicity in the label as below:

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6.2 Immunogenicity

The presence of ustekinumab in the serum can interfere with the detection of anti-ustekinumab antibodies resulting in inconclusive results due to assay interference. In STUDIES 1 and 2, antibody testing was done at time points when ustekinumab may have been present in the serum. Table 2 summarizes the antibody results from ~~STUDY~~ STUDIES 1 ~~through year 3~~ and ~~STUDY 2~~ through ~~year 4~~Year 5.

Table 2~~.~~: Presence of anti-ustekinumab antibodies in ~~STUDY 1 through Year 3 and STUDY 2~~STUDIES 1 and 2 through Year ~~4~~5.

Antibody Results	STUDY 1 (N=746)	STUDY 2 (N=1202)
Positive	39 (5%)	65 (5%)
Negative	365 (49%)	431 (36%)
Inconclusive	342 (46%)	706 (59%)

Deleted: 124(17%)
Deleted: 150 (12%)
Deleted: 583 (78%)
Deleted: 987 (82%)

The majority of patients who were positive for antibodies to ustekinumab had neutralizing antibodies.

The proposed revisions reflect data only from completion of T08 and T09. The Clinical Pharmacology reviewer, Dr. Jie Wang, concluded that the applicant's proposed updates were acceptable. In subjects positive for anti-ustekinumab antibodies, 64% in T08 had neutralizing antibodies as did 89% in T09. Taken together (i.e. T08 and T09), 79% of subjects ("the majority") were positive for neutralizing antibodies to ustekinumab (per Table 4 in the Summary of Clinical Pharmacology).

The applicant proposed no other clinical pharmacology revisions to the label. However, pertaining to on-site treatment, Dr. Wang found that observed trough concentrations during the extension phase in both studies, for subjects who continued dosing q12 weeks were generally higher than those which are currently described in the label. This was also noted with the PK data reviewed for S-49. Dr. Wang attributed this to "at least two factors": the change in the ustekinumab assay and differences in the study population.

As has previously been the case, the data do not permit an assessment of the impact of immunogenicity on PK or efficacy because subjects who were negative for anti-drug antibodies have undetectable serum concentrations of ustekinumab and most subjects had inconclusive status (as described in the label, ustekinumab in the serum interferes with the assay limiting detection of ADA and making for inconclusive results).

There was no apparent correlation between anti-ustekinumab antibody positivity and injection site reactions. There were no reports of serious injection-site reactions, nor did any subjects discontinue treatment due to an injection-site reaction. No anaphylactic or serum sickness-like reactions to ustekinumab were reported in the global psoriasis dataset (the two reports on anaphylaxis in the database were due to a bee sting and an anesthetic agent).

7.5 Other Safety Explorations

See Section 7.3

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7.6 Additional Submissions

Per agreement at the pre-sBLA meeting, the applicant submitted data from the psoriatic arthritis (PsA) program for the four-month safety update (submit date November 19, 2012). The applicant submitted the PsA data because the psoriasis extension trials were completed, and no additional data would be available from the psoriasis development program during the review cycle for S-86. The applicant had identified three new adverse reactions from review of the safety data from the PsA program: nausea, arthralgia and dental infections. The safety data appear to reveal no new concerns relative to that from the psoriasis program. The following is not intended as a comprehensive review of the safety database for the PsA indication.

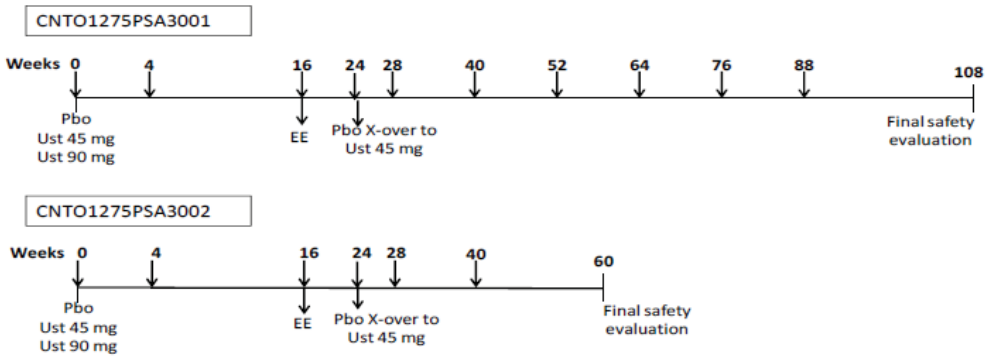
The safety update provided for safety data that were to be included in the Summary of Clinical Safety for the (then) forthcoming sBLA for PsA (See Section 2.2 of this review). Specifically, the applicant submitted pooled safety data from the two ongoing Phase 3 PsA trials, CNTO1275PSA30**01** (**01**; PSUMMIT 1) and CNTO1275PSA30**02** (**02**; PSUMMIT 2) as below:

- safety data are summarized through Week 24 for 01 and 02 and
- through Week 52 for a subset of subjects in 01.

The placebo-controlled period of the trials was through Week 16, and enrollment criteria (criteria for PsA were the same in both trials) for the trials differed slightly:

- 01: PsA ≥ six months prior to first study agent administration and who have active PsA despite current or previous disease modifying anti rheumatic drug (DMARD) or nonsteroidal anti-inflammatory drug (NSAID) therapy
- 02: as above, with 50% to 60% of subjects also previously treated with at least one biologic anti-TNFα agent(s).

Study schemas are as below:



The database in the safety update reflected exposure of 781 subjects to ustekinumab as below:

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- 692 subjects were exposed for ≥6 months.
- 213 subjects were exposed for ≥1 year

Through the placebo-controlled period and consistent with the psoriasis trials, adverse events were most frequently reported in the PsA trials in the following SOCs:

- Infections and infestations (21.4% in the placebo group and 21.3% in the combined ustekinumab group)
- Musculoskeletal and connective tissue disorders (10.4% in the placebo group and 10.1% in the combined ustekinumab group) and
- Gastrointestinal disorders (4.9% in the placebo group and 8.1% in the combined ustekinumab group)

The following adverse events were reported more frequently in ustekinumab-treated subjects: nasopharyngitis, headache, arthralgia, nausea, diarrhea, fatigue, oropharyngeal pain, and back pain.

Nausea occurred at a rate four times higher in the ustekinumab-treated subjects compared to the placebo group (however, no ustekinumab-treated subjects discontinued due to nausea through Week 16). Arthralgia occurred at a rate 2.5 times higher in ustekinumab-treated subjects compared to the placebo group. Dental infections (tooth infection and tooth abscess) occurred more frequently in ustekinumab-treated subjects (1.1%) compared with placebo-treated subjects (0.6%). Based on these observations, the applicant identified nausea, arthralgia and dental infections as three new adverse drug reactions.

Through Week 24 and 52, adverse events continued to be most frequently reported in (in decreasing order of frequency) Infections and infestations, Musculoskeletal and connective tissue disorders and Gastrointestinal disorders SOCs. Through Week 52 (01 only; all subjects received ustekinumab after Week 28), adverse events were reported at the following frequencies: Infections and infestations (39.2%), Musculoskeletal and connective tissue disorders (13.8%), and gastrointestinal disorders (12.1%). The most frequently reported adverse events through Week 52 were nasopharyngitis, upper respiratory tract infection, arthralgia, headache, diarrhea, hypertension, and nausea.

Serious Adverse Events

No deaths were reported.

Through Week 16, serious adverse events were more frequently reported in the placebo group at 2.9% (9 subjects) compared with the ustekinumab group at 1.3% (8 subjects). All serious adverse events were of single reports, i.e. there were no multiple reports of any one type of serious adverse event. There was no apparent pattern to the occurrence of serious adverse events. Only two SOCs had more than one report of a serious adverse event (two reports in each of these SOCs): Gastrointestinal disorders and Renal and urinary disorders.

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Through Week 24, the proportion of subjects with serious adverse events was higher in the placebo group at 3.2% (10 subjects) compared with the ustekinumab group at 1.8% (13 subjects). All serious adverse events were of single reports, i.e. there were no multiple reports of any one type of serious adverse event. There was no apparent pattern in the occurrence of serious adverse events, with no SOC predominating.

Through Week 52, serious adverse events were reported in 4.6% subjects (16 subjects). A dose response was not apparent. The proportion of subjects with serious adverse events was higher in the 45 mg treatment group at 5.8% (7 subjects) compared 2.5% (3 subjects) in the 90mg group.

Infections

Through the placebo-controlled period (Week 16), infections were reported at similar rates in all treatment groups at approximately 21%. The following infections were reported in ≥2% of subjects in any treatment group: nasopharyngitis, upper respiratory tract infection and sinusitis. One serious infection occurred during this period: interstitial lung disease in a subject in the placebo group.

Through Week 24, the proportion of subjects with infections was higher in the active groups: 24.9% in placebo and 27.8% in the ustekinumab treatment groups. The most frequently reported infections through Week 24 were nasopharyngitis (5.2% in placebo, 6.0% in the ustekinumab groups) and upper respiratory tract infection (4.9% in placebo, 6.0% in the ustekinumab groups). This pattern carried through Week 52, where nasopharyngitis and upper respiratory tract infections continued to be the most commonly reported infections.

Four serious infections were reported in ustekinumab-treated subjects through the end of the reporting period (it is unclear whether this would be through Week 24 or through Week 52): cholecystitis, acute cholecystitis, salpingitis and pharyngolaryngeal abscess.

There were no reports of tuberculosis or of opportunistic infections through the end of reporting period.

Malignancies
One malignancy was reported through the placebo-controlled period: squamous cell carcinoma in situ in an area of cleared plaque psoriasis (0-16 weeks) in an ustekinumab-treated subject. No additional malignancies were reported through the end of the reporting period.

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/s/

BRENDA CARR
04/18/2013

JILL A LINDSTROM
04/18/2013
I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125261Orig1s086

CHEMISTRY REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Division of Monoclonal Antibodies
Bethesda, MD 20892
Tel. 301-827-0850

Memorandum of Review

Date: April 1, 2013

To: File for STN: 125261/86, [redacted] (b) (4) and 125261/91
RPM: J. Paul Phillips

From: Laurie Graham
DMA/OBP/OPS/CDER

Through: Patrick Swann, Ph.D.
Deputy Division Director DMA/OBP/OPS/CDER

Subject: STN: 125261/86 [redacted] (b) (4) PAS to update the STELARA prescribing information with safety and efficacy data through 5 years and to include the option for self-administration

Applicant: Janssen Biotech, Inc

Product: STELARA

Action Due Date: May 27, 2013

Review Recommendation: pending IR response

Overview:

The original PAS filed under STN 125261/86 was determined by the Agency to require 4 separate supplements. Specifically, there would need to be 3 user fee supplements (S-86, [redacted] (b) (4) [redacted] (b) (4) associated with labeling changes related to studies C0T74T08, C0743T09, and C0743T26, respectively. In addition, a non-user fee supplement (S-91) would be needed for a literature report and PK information provided for trials C0743T23 and C0743T25. [redacted] (b) (4)

[redacted] (b) (4)

Previously, the presence of neutralizing antibodies (Nab) to Ustekinumab in ADA positive samples was detected using a cell-based assay. Specifically, neutralizing

STN 125261/86, (b) (4) STN 125261/91

(b) (4)

(b) (4) The current submission contains safety and efficacy information from 5 year extensions of the two pivotal studies as well as self-administration data from study C0743T08. The 5 year data assessment included information on neutralizing antibody status. (b) (4) To support this change in the Nab (b) (4)

It is noted that the sponsor is proposing an update to the label to include a statement that "the majority of patients who were positive for antibodies to Ustekinumab had neutralizing antibodies".

(b) (4)

(b) (4) support the modified label that the majority of ADA positive subjects will test positive for neutralizing antibodies.

From a CMC perspective, the PAS is recommended for approval.

<u>The following comments were communicated to the sponsor in the 74-day letter. Following each comment is the sponsor's response, followed by the Agency evaluation of that response</u>:

1. For STN 125261/86, (b) (4) STN 125261/91, submit a categorical exclusion per 21 CFR 25.31.

<u>Sponsor's response:</u> The categorical exclusions were provided.

<u>Reviewer's comment:</u> *The response is acceptable.*

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Reference ID: 3289148

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

/s/

LAURIE J GRAHAM
04/05/2013

PATRICK G SWANN
04/05/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA/Serial Number:	125261 / 86 (b) (4)
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Indication(s):	Psoriasis
Applicant:	Janssen
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1 Executive Summary

The applicant has proposed adding the following statement about [redacted] (b) (4) Stelara is approved for moderate to severe psoriasis and the recommended dosing regimen is injections at Weeks 0 and 4 followed by injections every 12 weeks. The applicant had previously requested [redacted] (b) (4) however the Agency determined that that proposal was not acceptable for labeling. With this supplement, the applicant is proposing [redacted] (b) (4) However, even though the current proposed statement does not [redacted] (b) (4) the general statement still is not supported by any pre-planned analysis from an appropriate study design and the statement is vague and open to reader interpretation. In particular

- [redacted] (b) (4)
- [redacted]
- [redacted]

Therefore, even though the applicant is no longer proposin [redacted] (b) (4) would not be appropriate for labeling, as the claim is not supported by adequate and well-controlled studies and is subject to bias.

With regard to self-injection, the majority of subjects (583/766 or 76%) in Study 08 self-injected at least once, either onsite or offsite. Of the remaining subjects who did not self-inject, 84 (11%) completed the full 5 years of scheduled dosing and 99 (13%) discontinued dosing before the last scheduled dose. The subjects who self-injected did so anywhere from 1 to 29 times. Of the 144 subjects (19%) who self-injected offsite, the median number of times they self-injected offsite was 2 (range 1 to 5 times). Subjects were self-selected for self-administration and offsite administration, and in particular, subjects who administered offsite had to have a lack of previous systemic allergic reactions. Nearly all subjects who self-injected offsite (142/144 or 99%) had previously self-injected onsite. Because of the level of self-selection for self-administration, it is difficult to evaluate whether self-administration on- or offsite impacts safety or efficacy.

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The applicant is proposing to update the infection and malignancy event and incidence rates with the now-complete 5-year follow-up from Studies 08 and 09. Using the additional follow-up from Study 08 (5 years rather than 3 years) and Study 09 (5 years rather than 4 years) leads to a slightly decreased rate for infections and non-melanoma skin cancers (0.98 to 0.87 per subject-year for infections, and 0.61 to 0.52 per hundred subject-years for non-melanoma skin cancers), while the rates for serious infections (0.01 per subject-year both before and after the update) and other malignancies (0.62 to 0.60 per hundred subject-years, before and after, respectively) remained about the same.

Events or incidence per hundred subject-years for serious infections and malignancies were assessed by 48-week intervals ('years') to look for trends of increasing or decreasing rates. The year-to-year variability in the data is large (the largest yearly event rate estimate is about double the smallest yearly estimate in each case); however, the following trends were noted. Serious infections were most common in the first year, with similar estimates in the following years with the exception of the Year 3 estimate, which was lower. The cumulative serious infection event rate was fairly stable over time. Non-melanoma skin cancers were most common in the first year, and the incidence rate decreased over time. The incidence rates for other malignancies were the most variable over time. The lowest incidence rate was observed in the first year; however, the cumulative incidence rate for other malignancies was fairly stable from Year 2 through Year 5. However, because of the observational nature of the long-term follow-up in the safety database and information on subjects who dropped out is not available, it is difficult to interpret any trends in the data beyond the observed subjects.

2 Introduction

2.1 Overview

Stelara (ustekinumab) was approved in September 2009 for the treatment of psoriasis. The Phase 3 development program included two 5-year studies that are now completed. The two studies (08 and 09) had several stages and pre-planned database locks. The initial product labeling at the time of approval included Week 12 efficacy results for both studies and the Week 52 response rates for the subjects in Study 08 who participated in the randomized withdrawal period of the study (responders at Week 28 and 40 who were randomized to either withdraw treatment or continue treatment). The safety database was based on the available data from Studies 08 and 09 (up to 18 months follow-up) and a Phase 2 dose ranging study, Study 04 (up to 36 weeks follow-up).

In August 2011, the applicant submitted a supplement (49) to modify labeling with efficacy and safety findings using data from the 152-week (3-year) database lock for Study 08 and the 208-week (4-year) database lock for Study 09. The applicant proposed to update the Adverse Reactions section of labeling with additional information from the long-term follow-up periods of Studies 08 and 09 as well as from an additional Phase 3 study that had been completed since the original approval (Study 12 – an etanercept-controlled Phase 3 study with up to 64 weeks follow-up). In Supplement 49 the applicant also proposed adding efficacy information to the Clinical Studies section of labeling with

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(b) (4) With the approval of this supplement (May 2012), malignancy and infection rates were updated with the additional data from the clinical trials. However, the applicant's proposed addition to the Clinical Studies section of labeling: (b) (4) was not found to be an acceptable labeling change and is not part of the current labeling.

The applicant has now completed the 5-year follow-up for Studies 08 and 09 and has submitted Supplements 86 (b) (4) to update labeling with efficacy and safety information. Supplement 86 reflects labeling changes based on Study 08 (b) (4) reflects labeling changes based on Study 09. These supplements propose the following labeling modifications:

- Update the malignancy and infection rates with the 5-year follow-up data (Studies 08 and 09)
- Update labeling to allow for self-administration (Study 08)
- Add a statement that (b) (4)
- (b) (4)

This review will evaluate the proposed labeling changes regarding adverse reactions and maintenance of efficacy. This review will briefly comment on self-administration issues, but will not assess the statements regarding (b) (4), as that is beyond the statistical purview. The proposed changes to allow for self-administration (b) (4) The updated malignancy and infection rates rely on information collected in Studies 08 and 09.

2.2 Data Sources

This reviewer evaluated the applicant's clinical study reports, datasets, clinical summaries, and proposed labeling. This submission was submitted in eCTD format and was entirely electronic. The analysis datasets used in this review are archived at \\Cbsap58\m\eCTD_Submissions\STN125261\0212\m5\datasets.

3 Statistical Evaluation

3.1 Data and Analysis Quality

The databases for the studies required minimal data management prior to performing analyses and no requests for additional datasets were made to the applicant.

3.2 Evaluation of Efficacy

3.2.1 Study Design

Studies C0743T08 and C0743T09 are randomized, double-blind studies of 45 mg and 90 mg ustekinumab and placebo in the treatment of psoriasis. Both studies have several

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stages and followed subjects for up to 5 years. The primary timepoint for efficacy evaluation was at the end of the placebo-controlled period at Week 12. At Week 12, subjects randomized to placebo were crossed over to active treatment. At Week 28 non-responders were discontinued. Study 08 evaluated randomized withdrawal among responders, and Study 09 evaluated randomized dose acceleration (every 8 weeks vs. every 12 weeks) among partial responders. After these stages, subjects were followed in an unblinded way on their current regimen for up to 5 years from the start of the study. The primary efficacy endpoint in Studies 08 and 09 was the proportion of subjects with PASI 75 at Week 12. The protocol for Study 08 included three key secondary endpoints

- the proportion of subjects with a PGA score of cleared or minimal at Week 12
- in subjects randomized to placebo or continued every 12 week dosing at Week 40: the time to loss of PASI 75 response based on the data collected through the last subject out for the Week 52 visit (45 mg and 90 mg doses combined versus placebo)
- change in DLQI (Dermatology Life Quality Index) from baseline to Week 12

The protocol for Study 09 included three key secondary endpoints

- the proportion of subjects with a PGA score of cleared or minimal at Week 12
- in subjects randomized to adjusted every 8 week dosing or continued every 12 week dosing at Week 28: the number of visits with PASI 75 response between Week 40 and Week 52 (45 mg and 90 mg doses combined)
- change in DLQI (Dermatology Life Quality Index) from baseline to Week 12

For a more detailed description of the study designs, refer to the statistical review for Supplement 49 (dated 3/30/2012).

The applicant is interested in [redacted] (b) (4). Subjects in Study 09 were allowed to accelerate to every 8 week dosing in the later stages upon agreement of the subject and investigator, therefore the subjects who completed Study 09 are not useful for describing the effects of every 12 week dosing. A portion of subjects in Study 08 were assigned to every 12 week dosing for 5 years, however these subjects had to meet the following criteria

- originally randomized to ustekinumab
- PASI 75 responder at Weeks 28 and 40
- randomized to continue treatment during the randomized withdrawal period (Week 40)
- not drop out of the study

Thus any information on the [redacted] (b) (4).

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3.2.2 Proposed Clinical Studies Section Labeling Changes

In the current submission (Supplement 086) the applicant has proposed adding the following statement to the Clinical Studies section of labeling based on the data from Study 08 which is now completed.

(b) (4)

In the cover letter for this efficacy supplement, the applicant has laid out two reasons for including information (b) (4) in labeling. The applicant's reasons are

- (b) (4)
-

(b) (4) information from the randomized withdrawal period from Study 08 (referred to as Study 1 in labeling) is currently conveyed in the labeling as follows:

> Subjects in 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.

Previously, in Supplement 49 (submitted August 2011) after the Week 152 database lock for Study 08, the applicant had proposed adding the following statement to labeling:

(b) (4)
.

The applicant gave identical reasons for augmenting the Clinical Studies section of labeling in efficacy supplements 49 and 86. This additional statement (b) (4) (b) (4) was not accepted by the Agency following the review of Supplement 49. However, the statement "The median time to loss of PASI 75 response among the subjects randomized to treatment withdrawal was 16 weeks" was added to labeling at that time.

The applicant is no longer proposing to include (b) (4) of the study; however, they are proposing to (b) (4) In general the same reasons as to why (b) (4)

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(b) (4) are not appropriate apply to the more general statement as to the previously proposed (b) (4). These include:

- (b) (4)
-
-

Thus, even though the goal (b) (4) is understandable, it is not possible to make claims about (b) (4) because the studies are not adequately designed to address this issue and the claim is subject to bias. (b) (4) and would be appropriate for labeling. This reviewer does not recommend adding additional statements to labeling regarding (b) (4)

3.2.3 Self-Administration

In this supplement the applicant is requesting labeling language that would specifically permit subjects to self-inject Stelara and remove the language stating that Stelara should only be administered by a healthcare provider. In Study 08 subjects could begin self-injecting at the study site under the supervision of a healthcare provider as early as Week 16. Subjects could begin self-injecting offsite after Amendment 5 (dated March 29, 2010) went into effect. Amendment 5 permitted subjects to self-inject offsite as follows:

> After Amendment 5 is implemented, subjects who have demonstrated that they are capable of self administration, are comfortable with self administration, and have demonstrated a lack of any systemic allergic reaction (including severe or serious injection-site reactions) to previous administrations of ustekinumab, may, at the discretion of the investigator and subject, begin self administration of ustekinumab away from the investigative site. (pg. 39 of c0743t08-appendix-01-264wk.pdf)

The first subject who self-administered offsite did so on April 12, 2010. Subjects self-injected offsite as early as the Week 212 visit, and as late as the Week 244 visit (final dosing visit).

Of the 766 subjects in Study 08, 583 (76%) self-injected at least once (either onsite or away from the site). Of the remaining subjects who did not self-inject, 84 (11%)

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completed the full 5 years of scheduled dosing (last dose between Weeks 232 and 244) and 99 (13%) discontinued dosing before the last scheduled dose. The subjects who self-injected did so anywhere from 1 to 29 times. Of the 144 subjects (19%) who self-injected offsite, the median number of times they self-injected offsite was 2 (range 1 to 5 times).

Subjects were self-selected for self-administration and offsite administration, and in particular, subjects who administered offsite had to have a lack of previous systemic allergic reactions. Nearly all subjects who self-injected offsite (142/144 or 99%) had previously self-injected onsite. Because of the level of self-selection for self-administration, it is difficult to evaluate whether self-administration on- or offsite impacts safety or efficacy.

3.3 Evaluation of Safety

3.3.1 Proposed Adverse Reactions Section Labeling Changes

The applicant has requested updated labeling for the rates of infections, serious infections, and malignancies based on the follow-up in the now-completed Studies 08 and 09. The currently approved labeling states that the safety data reflected in the labeling is based on Stelara exposure in 3117 subjects including 2414 exposed for at least 6 months, 1852 exposed for at least one year, 1650 exposed for at least two years, 1129 exposed for at least three years, and 619 exposed for at least four years. This safety database was derived from the available information from four clinical trials: 36 weeks of safety follow-up from Study 04 (Phase 2 dose-ranging study), the 152-week (3-year) database lock for Study 08, the 208-week (4-year) database lock for Study 09, and 64 weeks of safety follow-up from Study 12 (active- and placebo controlled study). The following is the applicant's proposed changes to the description of the safety database based on the additional years of follow-up from the now-completed Studies 08 and 09.

> The safety data reflect exposure to STELARA® in 3117 psoriasis subjects, including 2414 exposed for at least 6 months, ~~1852~~ 1855 exposed for at least one year, ~~1650~~ 1653 exposed for at least two years, ~~1129~~ 1569 exposed for at least three years, ~~and 619~~ 1482 exposed for at least four years and 838 exposed for at least five years.

For the above subject counts, exposure to ustekinumab is defined as the duration between the first and last ustekinumab administration being at least:

- 14 weeks → 6 months
- 38 weeks → 1 year
- 88 weeks → 2 years
- 140 weeks → 3 years
- 192 weeks → 4 years
- 240 weeks → 5 years

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The subject counts above are nested, that is, each successive count represents the number of subjects from the previous group who remained exposed to treatment in the following time period (e.g. out of the 1482 subjects who were exposed for at least 4 years, 838 remained exposed for at least 5 years). Note that subjects did not need to have continuous treatment. For example, there were three subjects who had treatment withdrawn at Week 40 in Study 08 as part of the protocol and did not have additional ustekinumab exposure until at least Week 160 because they did not meet the retreatment criteria (sufficient loss of response) until that time.

Rates of infections, serious infections, and malignancies are described in labeling using rates per subject-year or per hundred subject-years of follow-up. Using the additional follow-up from Study 08 (5 years rather than 3 years) and Study 09 (5 years rather than 4 years) leads to the following changes in infection and malignancy rates in the updated safety database (Table 1). Event rates for infections are based on the number of separate infections, while the incidence rates for malignancies are based on the number of subjects with malignancies. Because only the first malignancy incidence is counted, the subject-years of follow-up differs slightly for each category. The rate for infections and non-melanoma skin cancers (NMSC) decreased slightly with the additional follow-up, while the rates for serious infections and other malignancies remained about the same.

Table 1 – Infection and Malignancy Rate Changes due to Completion of Studies 08 and 09

	Up to 4 Years Follow-up (Current Labeling)	Up to 5 Years Follow-up (Proposed Labeling)
Subjects treated	3117	3117
Subjects with 1 or more infections	2192 (70.3%)	2254 (72.3%)
Subjects with 1 or more serious infections	64 (2.1%)	87 (2.8%)
Subjects with NMSC	41 (1.3%)	47 (1.5%)
Subjects with other malignancies	42 (1.3%)	54 (1.7%)
Total subject-years of follow-up - Infections	6791	8998
Infection event rate per subject-years (number of events)		
Infections	0.98 (6673)	0.87 (7800)
Serious Infections	0.01 (75)	0.01 (99)
Total subject-years of follow-up - Malignancies	6758 (All Mal) 6770 (NMSC) 6779 (Oth Mal)	8947 (All Mal) 8965 (NMSC) 8980 (Oth Mal)
Malignancy incidence rate per hundred subject-years (number of subjects)		
Malignant neoplasms	1.23 (83)	1.13 (101)
Non-melanoma skin cancer (NMSC)	0.61 (41)	0.52 (47)
Other malignancies	0.62 (42)	0.60 (54)

Source: Stelara labeling dated 1/25/2013, pg 38 and 43 of the Summary of Clinical Safety, and reviewer analysis.

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Like most methods of summarizing data, this method cannot account for events that occur in subjects who do not continue follow-up. If subjects who are likely to develop the events of interest discontinue the study early, increasing the follow-up of the remaining subjects could have a diluting effect on the event rates. In addition, presenting rates per hundred years of follow-up does not allow for the identification of event rates that change over time. Summarizing events by way of subject-years assumes that you can get equivalent information by following a large number of subjects for a short time as by following a small number of subjects for a long time. However, when comparing the event rates from the previous database lock to the current database lock, changes to the event rate per subject-year can indicate whether the events are becoming more or less common in the subjects followed as follow-up time is increased.

To supplement the above analysis, it may be of interest to consider the rates over time. Table 2 presents the numbers of serious infections and malignancies by 48-week intervals ('years'). The year-to-year variability in the data is large (the largest yearly event rate estimate is about double the smallest yearly estimate in each case); however, there are some trends in the observed data. Serious infections were most common in the first year, with similar estimates in the following year with the exception of the Year 3 estimate. The cumulative serious infection event rate was fairly stable over time. Non-melanoma skin cancers (NMSC) were most common in the first year, first appeared at lower (but similar) rates in Years 2 to 4, and were less likely to first appear in Year 5, leading to a decrease in the cumulative incidence rate with each additional year of follow-up. Recall that for NMSC incidence rates are provided, so only the first event is counted, additional NMSC events for that subject are not included. The incidence rates for other malignancies were the most variable over time. The lowest incidence rate was observed in the first year; however, the cumulative incidence rate for other malignancies was fairly stable from Year 2 through Year 5. Note that the 'year' definitions in Table 2 are different from those used to define duration of ustekinumab exposure above.

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Table 2 – Event Rates by Year of Follow-up for Serious Infections and Malignancies from Studies 04, 08, 09, and 12 (45 mg and 90 mg Doses Combined)

	Year 1 ≤ 48 Weeks	Year 2 49 – 96 Weeks	Year 3 97 – 144 Weeks	Year 4 145 – 192 Weeks	Year 5 > 192 Weeks
Subjects	3117	2145	1671	1588	1516
Serious Infections					
Subject-years of FU	2548	1647	1506	1439	1876
# Serious infections	34	17	10	16	22
Events per 100 S-Y	1.33	1.03	0.66	1.11	1.17
Cum. evts per 100 S-Y	1.33	1.21	1.07	1.08	1.10
NMSC					
Subject-years of FU	2540	1644	1503	1432	1864
# Subjects w/ events	24	8	6	6	3
Incidence per 100 S-Y	0.94	0.49	0.40	0.42	0.16
Cum. inc. per 100 S-Y	0.94	0.76	0.67	0.62	0.52
Other Malignancies					
Subject-years of FU	2547	1643	1503	1435	1871
# Subjects w/ events	10	16	6	11	11
Incidence per 100 S-Y	0.39	0.97	0.40	0.77	0.59
Cum. inc. per 100 S-Y	0.39	0.62	0.56	0.60	0.60

Note: FU = follow-up, S-Y = subject-years, Cum. = cumulative
Source: pg 39 and 45 of the Summary of Clinical Safety.

One additional concern with the analysis over time is the different studies may have different patient populations or different methods of data collection, leading to a study effect that might mask time trends. Time trends might be more apparent if the analysis included only subjects in the two studies designed for 5-year follow-up (Studies 08 and 09), rather than including the two shorter-term studies in the analysis. Because subjects from Studies 04 and 12 had a maximum of 36 and 64 weeks of follow-up, respectively, only the event and incidence rates for Years 1 and 2 are affected by the removal of these two studies from the database. Note that this analysis still does not address the issue of whether subjects who drop out or are discontinued would have different outcomes from those who remain in the study until the end. See Table 3. The observed trends in the analysis with only Studies 08 and 09 are similar to those observed in the full database, namely that there is a fair amount of year-to-year variability in the event rates, but that the cumulative event rate for serious infections is fairly constant over time, the incidence rate for NMSC decreases over time, and that the incidence rate for other malignancies was lowest in the first year.

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Table 3 – Event Rates by Year of Follow-up for Serious Infections and Malignancies from Studies 08 and 09 (45 mg and 90 mg Doses Combined)

	Year 1 ≤ 48 Weeks	Year 2 49 – 96 Weeks	Year 3 97 – 144 Weeks	Year 4 145 – 192 Weeks	Year 5 > 192 Weeks
Subjects	1965	1774	1671	1588	1516
Serious Infections					
Subject-years of FU	1754	1584	1506	1439	1876
# Serious infections	17	15	10	16	22
Events per 100 S-Y	0.97	0.95	0.66	1.11	1.17
Cum. evts per 100 S-Y	0.97	0.96	0.87	0.92	0.98
NMSC					
Subject-years of FU	1750	1581	1503	1432	1864
# Subjects w/ events	14	6	6	6	3
Incidence per 100 S-Y	0.80	0.38	0.40	0.42	0.16
Cum. inc. per 100 S-Y	0.80	0.60	0.54	0.51	0.43
Other Malignancies					
Subject-years of FU	1753	1580	1503	1435	1871
# Subjects w/ events	4	16	6	11	11
Incidence per 100 S-Y	0.23	1.01	0.40	0.77	0.59
Cum. inc. per 100 S-Y	0.23	0.60	0.54	0.59	0.59

Note: FU = follow-up, S-Y = subject-years, Cum. = cumulative
Source: Reviewer analysis based on modifications to applicant's programs s_infe_14_f.sas and s_mal_27_d.sas.

The following is the applicant's proposal for updating the event rates for infections and malignancies using the information from the full 5-year clinical trials database as described above. The event rate for serious infections remained the same for the precision used, (0.01 per subject-year), and the other event or incidence rates declined slightly (0.98 to 0.87 per subject-year for infections, 0.62 to 0.60 per hundred subject-years for other malignancies, and 0.61 to 0.52 per hundred subject-years for non-melanoma skin cancers.)

Infections

…

In the controlled and non-controlled portions of psoriasis clinical trials (median follow up of ~~2.6~~3.2 years), representing ~~6791~~ 8998 subject-years of exposure, ~~70~~ 72.3% of STELARA®-treated subjects reported infections (~~0.98~~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 trials (median follow up of ~~2.6~~3.2 years, representing ~~6791~~ 8998 subject-years of exposure), 1.~~3~~7% of STELARA®-treated subjects reported malignancies excluding non-melanoma skin cancers (0.~~62~~60 per hundred subject-years of follow-up). Non-melanoma skin cancer was reported in 1.~~3~~5% of STELARA®-treated subjects

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(0.~~61~~52 per hundred subject-years of follow-up) *[see Warnings and Precautions (5.4)]*.

4 Findings in Special/Subgroup Populations

4.1 Gender, Race, Age, and Geographic Region

Not applicable for this supplement.

4.2 Other Special/Subgroup Populations

Not applicable for this supplement.

5 Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

The applicant has proposed adding the following statement [redacted] (b) (4) that Study 08 has completed its planned 5-year follow-up: [redacted] (b) (4) The applicant had previously requested [redacted] (b) (4) in labeling, however the Agency determined that that proposal was not acceptable. With this supplement, the applicant is proposin [redacted] (b) (4) However, even though the current proposed statement [redacted] (b) (4), the general statement still is not supported by any pre-planned analysis and the statement is vague and open to reader interpretation. In particular

- [redacted] (b) (4)
- [redacted]
- [redacted]

Therefore, even though the applicant is no longer proposing [redacted] (b) (4) would not be appropriate for labeling, as the claim is not supported by adequate and well-controlled studies and is subject to bias.

With regard to self-injection, the majority of subjects (583/766 or 76%) in Study 08 self-injected at least once, either onsite or offsite. Of the remaining subjects who did not self-

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inject, 84 (11%) completed the full 5 years of scheduled dosing and 99 (13%) discontinued dosing before the last scheduled dose. The subjects who self-injected did so anywhere from 1 to 29 times. Of the 144 subjects (19%) who self-injected offsite, the median number of times they self-injected offsite was 2 (range 1 to 5 times). Subjects were self-selected for self-administration and offsite administration, and in particular, subjects who administered offsite had to have a lack of previous systemic allergic reactions. Nearly all subjects who self-injected offsite (142/144 or 99%) had previously self-injected onsite. Because of the level of self-selection for self-administration, it is difficult to evaluate whether self-administration on- or offsite impacts safety or efficacy.

The applicant is proposing to update the infection and malignancy event and incidence rates with the now-complete 5-year follow-up from Studies 08 and 09. Using the additional follow-up from Study 08 (5 years rather than 3 years) and Study 09 (5 years rather than 4 years) leads to a slightly decreased rate for infections and non-melanoma skin cancers (0.98 to 0.87 per subject-year for infections, and 0.61 to 0.52 per hundred subject-years for non-melanoma skin cancers), while the rates for serious infections (0.01 per subject-year both before and after the update) and other malignancies (0.62 to 0.60 per hundred subject-years, before and after, respectively) remained about the same.

Events or incidence per hundred subject-years for serious infections and malignancies were assessed by 48-week intervals ('years') to look for trends of increasing or decreasing rates. The year-to-year variability in the data is large (the largest yearly event rate estimate is about double the smallest yearly estimate in each case); however, the following trends were noted. Serious infections were most common in the first year, with similar estimates in the following years with the exception of the Year 3 estimate, which was lower. The cumulative serious infection event rate was fairly stable over time. The incidence of non-melanoma skin cancers were most common in the first year, and the incidence rate decreased over time. The incidence rates for other malignancies were the most variable over time. The lowest incidence rate was observed in the first year; however, the cumulative incidence rate for other malignancies was fairly stable from Year 2 through Year 5. However, because of the observational nature of the long-term follow-up in the safety database and information on subjects who dropped out is not available, it is difficult to interpret any trends in the data beyond the observed subjects.

5.2 Conclusions and Recommendations

The applicant's proposed labeling addition (b) (4) is not acceptable because the claim is not supported by an adequate and well-controlled study and is subject to bias. No analyses were specified in the protocol for (b) (4) The applicant had previously requested language for labeling describing the (b) (4). Because the previous proposal with language using (b) (4) was not accepted by the Agency, the applicant is now proposing (b) (4) ' However, even general claims need to be supported by adequately pre-specified and well-designed analyses, (b) (4)

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(b) (4)

The applicant is proposing to update the infection and malignancy event and incidence rates with the now-complete 5-year follow-up from Studies 08 and 09. Using the additional follow-up from Study 08 (5 years rather than 3 years) and Study 09 (5 years rather than 4 years) leads to a slightly decreased rate for infections and non-melanoma skin cancers (0.98 to 0.87 per subject-year for infections, and 0.61 to 0.52 per hundred subject-years for non-melanoma skin cancers), while the rates for serious infections (0.01 per subject-year both before and after the update) and other malignancies (0.62 to 0.60 per hundred subject-years, before and after, respectively) remained about the same.

Signatures/Distribution List

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Date: 4/3/2013

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/s/

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04/03/2013

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04/03/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125261Orig1s086

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

Supplemental BLA:	STN 125261/086, (b) (4)
Submission Type:	Efficacy Supplement
Product Name:	STELARA® (ustekinumab)
Submission Date:	07/27/2012
PDUFA Goal Date:	05/27/2013
Indication:	STELARA® is a human IL-12 and -23 antagonist indicated for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.
Dosing Regimen:	STELARA® is administered by subcutaneous injection. For patients weighing ≤100 kg (220 lbs), the recommended dose is 45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks. For patients weighing >100 kg (220 lbs), the recommended dose is 90 mg initially and 4 weeks later, followed by 90 mg every 12 weeks.
Applicant:	Janssen Biotech, Inc.
Clinical Pharmacology Reviewer:	Jie Wang, Ph.D.
Clinical Pharmacology Team Leader:	Yow-Ming Wang Ph.D.
OCP Division:	Division of Clinical Pharmacology 3 (DCP3)
OND Division:	CDER/ODEIII/DDDP

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1. EXECUTIVE SUMMARY

STELARA® (ustekinumab) is a human IgG1κ monoclonal antibody that binds with high affinity and specificity to the p40 protein subunit shared by both the interleukin (IL)-12 and IL-23 cytokines. STELARA® was approved on September 25, 2009 for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. For patients weighing ≤100 kg (220 lbs), the recommended dose is 45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks (q12w). For patients weighing >100 kg (220 lbs), the recommended dose is 90 mg initially and 4 weeks later, followed by 90 mg q12w.

The applicant, Janssen Biotech, Inc., on July 27, 2012, submitted supplemental BLA/086 (b) (4) to update STELARA® USPI with the safety and efficacy data through up to 5 years of treatment based on data from two pivotal clinical trials Study C0743T08 and Study C0743T09, respectively. Additionally, the applicant proposed to update STELARA USPI with information of provisions for self-administration.

1.1. Recommendations

From a Clinical Pharmacology standpoint, the application is acceptable to update STELARA USPI with the safety and efficacy data through up to 5 years of treatment based on clinical data from Studies C0743T08 and C0743T09.

Regarding the provision for self-administration to the STELARA USPI, the submitted data in the current application are not adequate for the assessment of the impact of self-administration on ustekinumab trough PK. This reviewer, therefore, defers the determination to the clinical team based on other assessments such as clinical efficacy/safety data.

1.2. Post-Marketing Commitments

Not applicable.

1.3. Summary of Clinical Pharmacology Findings

1.3.1. Trough serum ustekinumab concentrations in long-term extension period of Study C0743T08 and Study C0743T09

In subjects continued q12w dosing with on-site administration, the mean steady state serum ustekinumab concentrations remained generally stable (from Week 88 to Week 208 in Study C0743T08 and from Week 112 to Week 244 in Study C0743T09) and were approximately dose-proportional. However, the observed trough concentrations were higher than reported in the USPI. The PK findings are consistent with the Clinical Pharmacology assessment of sBLA/049 based on data through Year 3 (Study C0743T08) or Year 4 (Study C0743T09). The higher mean trough concentrations in long-term extension periods were previously found to be attributable to at least two factors, namely, the change of the assay for ustekinumab concentration determination and the differences in study population.

In Study C0743T08, the mean concentrations ranged from 0.51 to 0.65 mcg/mL for 45 mg and from 1.11 to 1.32 mcg/mL for 90 mg, which were higher than those in the current STELARA® USPI by 64.5% to 110% at 45 mg and 73.4% to 106% at 90 mg. In Study C0743T09, the mean concentrations ranged from 0.53 to 0.69 mcg/mL for 45 mg and from 1.07 to 1.30 mcg/mL for 90 mg, which were higher than those in the current STELARA® USPI by 71.0% to 122% at 45 mg and 67.2% to 103% at 90 mg.

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1.3.2. Impact of off-site self-administration on trough serum ustekinumab concentrations in long-term extension period of Study C0743T08 in subjects who received ustekinumab doses q12w

Overall, the submitted data in the current application are not adequate for the assessment of the impact of self-administration on ustekinumab trough PK. The data available for assessment are limited. The assessment duration is between Weeks 208 and 244 where subjects can be given 3 dose administrations of ustekinumab and had about three concentration time points. The number of off-site injections is limited and can vary from 1 to 3 during the study period. By study definition, the off-site group includes subjects who had at least one off-site self-administration given between Week 208 and Week 244. Therefore, the impact of the larger number (e.g., > 3) of off-site injections during a long-term treatment on ustekinumab trough concentrations is unknown.

1.3.3. Immunogenicity of ustekinumab up to Year 5 in long-term extension period of Study C0743T08 and Study C0743T09

In Study C0743T08, the immunogenicity data showed that 5% of subjects had positive anti-drug antibodies (ADA) status, 49% of subjects had negative ADA status and 46% of subjects had inconclusive ADA status through Year 5. In Study C0743T09, the immunogenicity data showed that 5% of subjects had positive ADA status, 36% of subjects had negative ADA status and 59% of subjects had inconclusive ADA status through Year 5.

Among subjects with positive ADA, the majority (64% in Study C0743T08 and 89% in Study C0743T09) were determined to be positive for neutralizing antibodies.

Similar to the Clinical Pharmacology assessment on the sBLA/049 submission, the impact of immunogenicity on PK or efficacy could not be assessed because ADA negative subjects by definition have undetectable ustekinumab concentrations and a majority of subjects had inconclusive ADA status. From the safety standpoint, no clear association was observed between the ADA status and the development of injection site reactions (ISRs) in the 5-year data.

2. QUESTION BASED REVIEW

2.1. What is the relevant regulatory background of the current submission?

STELARA® was approved on September 25, 2009 for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

On August 5, 2011, the applicant submitted sBLA/049 which provided safety data through 4 years and efficacy data through 3 years of the two pivotal studies, i.e., STUDY 1 [C0743T08 or PHOENIX 1] and STUDY 2 [C0743T09 or PHOENIX 2]). The Clinical Pharmacology assessment on the PK and immunogenicity data in the sBLA/049 application was conducted (*DARRTS 04/06/2012*). On May 31, 2012, the sBLA/049 supporting the addition of longer-term safety and efficacy data to the STELARA® USPI was approved. Among other labeling changes, the following statement was removed: (b) (4) (b) (4)

On January 27, 2012, the applicant submitted sBLA/069 which provided the final study report for Study C0743T08 to fulfill Post-marketing Requirement (PMR) No.8. The Clinical Pharmacology assessment on the PMR submission was conducted (*DARRTS 10/26/2012*).

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On June 21, 2012, the applicant submitted sBLA/083 which provided the final study report for Study C0743T09 to fulfill PMR No.9. The Clinical Pharmacology assessment on the PMR submission were conducted (*DARRTS 10/26/2012*).

The applicant, Janssen Biotech, Inc., on July 27, 2012, submitted supplemental BLA/086 (b) (4) (b) (4) to update STELARA® USPI with the safety and efficacy data through up to 5 years of treatment based on data from two pivotal clinical trials Study C0743T08 and Study C0743T09, respectively. In sBLA/086, the applicant also proposed to update STELARA USPI with information of provisions for self-administration based on data from Study C0743T08. On February 15, 2013 as part of the responses to the Agency's information request the applicant submitted additional PK analysis results to support further assessment of whether off-site self-administration impacts ustekinumab PK (sBLA/086-4).

This Clinical Pharmacology review assesses the long-term PK and immunogenicity of ustekinumab in psoriasis patients following chronic dosing for up to 5 years in Study C0743T08 and Study C0743T09. The impact of off-site self-administration on ustekinumab PK was evaluated in subjects who self-administered ustekinumab off-site at least once from Week 208 through Week 244 in Study C0743T08.

2.2. What are the main study design features of Study C0743T08 and Study C0743T09?

Study C0743T08 and Study C0743T09 evaluate the safety and efficacy of SC injections of 2 dose regimens of ustekinumab: 45 mg regimen (45 mg at Week 0 and Week 4 followed by 45 mg q12w maintenance therapy) and 90 mg regimen (90 mg at Week 0 and Week 4 followed by 90 mg q12w maintenance therapy). Both studies include 4 study periods occurring over approximately 5 years: a 12-week placebo-controlled period, a subsequent 16-week placebo crossover and active treatment period, a randomized withdrawal or dose interval adjustment period, and a long-term extension period that began at Week 52 and continued for an additional 4 years.

In Study C0743T08, starting from Week 208, subjects were allowed to self-administer ustekinumab off-site. Per protocol, subjects received three dose administration of ustekinumab from Week 208 through Week 244 and subjects who self-administered at least 1 injection of ustekinumab off-site are categorized as in the off-site administration group, whereas the subjects who continued to receive ustekinumab on-site are categorized as in the on-site administration group.

2.3. Pharmacokinetics

PK data from long-term ustekinumab treatment at 45 mg q12w and 90 mg q12w in Studies C0743T08 and C0743T09 are assessed. Please refer to Clinical Pharmacology review on sBLA/069 (Darrts 10/26/2012) for PK assessment on other dosing regimens.

2.3.1. What were the trough serum ustekinumab concentrations during long-term extension periods of Study C0743T08 and Study C0743T09?

In Study C0743T08, the mean concentrations ranged from 0.51 to 0.65 mcg/mL for 45 mg q12w and from 1.11 to 1.32 mcg/mL for 90 mg q12w during the time period of Week 88 to Week 208 in subjects who had on-site ustekinumab administration. In Study C0743T09, the mean trough ustekinumab serum concentrations ranged from 0.53 to 0.69 mcg/mL for 45 mg q12w and from 1.07 to 1.30 mcg/mL for 90 mg q12w (Table 2.3.1.) during Week 112 through Week 244.

The long-term PK data overall indicated that the mean trough serum ustekinumab concentrations were generally stable and approximately dose-proportionality between 45 mg and 90 mg dose regimens.

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Table 2.3.1. Mean steady state ustekinumab concentrations during long-term extension period of Study C0743T08 and Study C0743T09 in subjects who continued q12w dose regimens. (Data source: *Attachment 2 Pharmacology, 264-Week CSR C0743T08; Attachment 2.1, 264 Week CSR C0743T09.*)

Time (Week)	Ustekinumab trough concentration, mcg/mL (mean ± SD, n=number of subjects)			
	Study C0743T08		Study C0743T09	
	45 mg	90 mg	45 mg	90 mg
88	0.60±0.692 (66)	1.25±1.079 (74)	n/a	n/a
112	0.65±0.683 (67)	1.31±1.168 (73)	0.58±0.458 (188)	1.12±0.836 (246)
136	0.63±0646 (65)	1.29±1.052 (69)	0.53±0.378 (186)	1.07±0.812 (240)
160	0.58±0.628 (64)	1.32±1.226 (71)	0.56±0.451 (177)	1.16±0.888 (228)
184	0.57±0.788 (62)	1.16±1.042 (72)	0.58±0.434 (166)	1.11±0.903 (222)
208	0.51±0.625 (61)	1.11±0.939 (71)	0.58±0.466 (156)	1.07±0.822 (211)
232	0.51±0.851 (56)	1.11±0.974 (70)	0.69±0.634 (144)	1.30±0.933 (196)
244	0.37±0.328 (38)	1.23±1.396 (50)	0.68±0.492 (57)	1.26±1.033 (65)
Current STELARA® USPI labeled steady state concentrations: 0.31 ± 0.33 mcg/mL at 45 mg and 0.64 ± 0.64 mcg/mL at 90 mg				

2.3.2. Did off-site self-administration have impact on the trough ustekinumab concentrations in Study C0743T08?

The submitted PK data in the current application are not adequate for the assessment of the impact of self-administration on ustekinumab trough PK. This reviewer defers the determination to update STELARA USPI with information of provisions for self-administration to the clinical team based on other assessments such as clinical efficacy/safety data.

Among 358 subjects who continued to receive ustekinumab q12w treatment through Week 244 in this study, 87 subjects self-administered at least 1 dose of ustekinumab off-site from Week 208.

Impact of self-administration on trough ustekinumab concentration was evaluated by comparing Week 232 and Week 244 data between subjects in "off-site" group and subjects in "on-site" group. At Week 244 the mean trough ustekinumab concentration appear to be lower in subjects who received ustekinumab dose off-site at least once than in those subjects continuing on-site administrations (Table 2.3.2). Specifically, among subjects receiving 45 mg and 90 mg dose the off-site administration groups had a mean trough concentration of 0.37 mcg/mL and 0.88 mcg/mL, respectively, at Week 244 compared to 0.47 mcg/mL and 1.15 mcg/mL, respectively, in the on-site administration groups. Data from Week 232 showed a similar trend.

Table 2.3.2. Mean trough serum ustekinumab concentrations during long-term extension period of Study C0743T08 by administration locations: on-site *vs* off-site. BW, body weigh; [a] median BW represents the range of body weight from Week 160 through Week 244 in each treatment group. (Data source: *Table 2, Summary of Clinical Pharmacology Studies, sBLA125261/86; Table 2, Page 21-22, Responses to FDA comments, sBLA125261/086-4*)

Time (week)	Ustekinumab Steady State Trough Serum Concentration (mcg/mL, mean ± SD, n=number of subjects)			
	on-site administration		off-site self-administration	
	45 mg	90 mg	45 mg	90 mg
BW[a] (kg)	89.0-92.7	91.6-93.8	84.7-92.4	90.0-100
160	0.59±0.565 n=131	1.23±1.212 n=155	0.66±0.428 n=46	1.12±0.900 n=42
184	0.50±0.610 n=124	1.06±1.022 n=152	0.59±0.487 n=45	0.97±0.824 n=42
208	0.52±0.616 n=124	1.06±1.032 n=147	0.53±0.346 n=46	1.02±0.721 n=41
232	0.52±0.691 n=116	1.07±1.020 n=139	0.42±0.268 n=44	0.97±0.680 n=38
244	0.47±0.380 n=40	1.15±1.349 n=57	0.37±0.283 n=17	0.88±0.514 n=15

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Impact of self-administration on trough ustekinumab concentration was also evaluated by comparing the stability of serum concentrations overtime within subjects in "off-site" group or subjects in "on-site" group. In both 45 mg and 90 mg groups with off-site administration, the mean trough ustekinumab concentrations appear to be decreasing with time from Week 208 through Week 244. Specifically, among subjects receiving 45 mg and 90 mg dose with off-site administrations, the mean trough concentrations were 0.37 mcg/mL and 0.88 mcg/mL, respectively, at Week 244 compared to 0.53 mcg/mL and 1.02 mcg/mL, respectively, at Week 208. However, such a trend towards lower serum concentrations with time was also observed for serum concentrations prior to off-site administration in the same "off-site self-administration" cohort. For example, from Week 160 to Week 208, mean trough concentrations decreased from 0.66 mcg/mL to 0.53 mcg/mL for the 45 mg group and from 1.12 mcg/mL to 1.02 mcg/mL for the 90 mg group (Table 2.3.2). The reasons for the variability of the PK data are unknown.

Additionally, it is unclear if the number of off-site injections has impact on the trough concentrations because three dose administrations were given between Week 208 and Week 244, and the "off-site" group, by study definition, includes subjects who had at least one off-site self-administration. The impact of the larger number (e.g., > 3) of off-site injections during a long-term treatment on ustekinumab trough concentrations is unknown.

2.3.3. Why are the observed ustekinumab trough concentrations during the extension periods higher than the steady state concentrations indicated in the Stelara® USPI?

In Study C0743T08, the observed steady state serum ustekinumab concentrations following q12w dosing, when compared to the mean trough concentrations in the current label (0.31 mcg/mL for 45 mg dose and 0.64 mcg/mL for 90 mg dose), are higher by 64.5% to 110% at 45 mg and 73.4% to 106% at 90 mg with the exception of Week 244 data for 45 mg group. In Study C0743T09, the observed mean trough concentrations from Week 112 through Week 244 in subjects who continued q12w dosing, when compared to those in the current label, are higher by 71.0% to 122% at 45 mg and 67.2% to 103% at 90 mg.

The Clinical Pharmacology review of a previous sBLA/049 determined that the differences between the ustekinumab trough concentrations during the extension periods and those indicated in the current STELARA® USPI are attributable to at least two factors, namely, the change of the assay and the differences in study population. The Clinical Pharmacology review further states the follows:

> *Although, the sponsor has advanced two theories to explain the observed differences in the steady state concentrations of ustekinumab between the new data and the data in the current package insert, we cannot at this time ascertain which (if any) is the correct theory. Even so, the impact of these higher plasma levels for the 45mg group is blunted by the existence of the 90mg group which normally has correspondingly higher levels. As for the 90mg group, the increased levels could represent a safety issue, however, no unusual safety signal was seen in this open label extension studies. Given the data at hand and the confounding assay issue, the sponsor as part of their next efficacy supplement should address this issue through prospectively designed clinical pharmacology studies designed to look at long term plasma concentrations and accumulation of ustekinumab.*
>
> *Given these factors, it is the opinion of the Division of Clinical Pharmacology-3 that the observed differences do not reflect an unknown or unexpected accumulation of drug in a random population. Even so, when new indications or populations are pursued by the sponsor in the future, the opportunity should be taken to conduct prospectively designed clinical pharmacology studies following long term use.*

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2.4. Immunogenicity

2.4.1. What was the incidence rate of anti-ustekinumab antibodies formation up to Year 5 in Study C0743T08 and Study C0743T09?

In Study C0743T08, the immunogenicity results showed that (Table 2.4.1):

- 5% (39/746) of subjects showed positive ADA status through Year 5;
  - 38 of 39 were ADA positive at Week 52 and 1 of 39 became ADA positive between Week 52 and Year 3;
  - between Year 3 and Year 5, no additional subjects became ADA positive;
- 46% of subjects had inconclusive ADA status at Year 5;
- the remaining 49% subjects had negative ADA status.

In Study C0743T09, the immunogenicity results showed that (Table 2.4.1):

- 5% (65/1202) of subjects showed positive ADA status through Year 5;
  - between Week 52 and Year 5, no additional subjects became ADA positive;
- 59% of subjects had inconclusive ADA status at Year 5;
- the remaining 46% subjects had negative ADA status.

However, the immunogenicity positive incidence rates should be interpreted with caution as a large proportion of subjects had inconclusive ADA status because they had detectable serum ustekinumab concentrations which can interfere with the ADA assay.

Table 2.4.1. Incidence rate of anti-ustekinumab antibodies formation in Study C0743T08 and Study C0743T09 through Year 5. Data source: *Week 52 data were provided in the original BLA (125261) application, Year 3 data were provided in the efficacy sBLA (STN125261/049), and Year 5 data were provided in the current sBLA.*

Anti-ustekinumab antibodies	Study C0743T08			Study C0743T09		
	Week 52 (N=743)	Year 3 (N=746)	Year 5 (N=746)	Week 52 (N=1202)	Year 4 (N=1202)	Year 5 (N=1202)
Positive	38 (5%)	39 (5%)	39 (5%)	65 (5%)	65 (5%)	65 (5%)
Negative	351 (47%)	124 (17%)	365 (49%)	193 (16%)	150 (13%)	431 (36%)
Inconclusive	354 (48%)	583 (78%)	342 (46%)	944 (79%)	987 (82%)	706 (59%)

2.4.2. Do the anti-ustekinumab antibodies have neutralizing activity?

Yes, anti-ustekinumab antibodies positive samples were tested in an *in vitro* cell-based assay and results indicate anti-ustekinumab antibodies are neutralizing in nature. The incidence rate of neutralizing antibody was 64% (25/39) and 89% (54/65) among all ADA positive subjects through Year 5 in Study C0743T08 and Study C0743T09, respectively.

2.4.3. What is the impact of immunogenicity on pharmacokinetics, efficacy or safety of ustekinumab?

As indicated in the Clinical Pharmacology review for sBLA/049, the impact of immunogenicity on PK or efficacy could not be assessed mainly because ADA negative subjects by definition have undetectable ustekinumab concentrations and a majority of subjects had inconclusive ADA status. From the safety standpoint, no clear association was observed between the ADA status and the development of ISRs in the 5-year data.

In Study C0743T08, through Year 5, 10.3% ADA positive subjects had 1 or more ISRs, compared to 9.3% in ADA negative subjects and 9.4% in ADA inconclusive subjects. The incidence rate of ISRs was also calculated as the proportion of injections complicated by ISRs. The proportion of ustekinumab injections associated with ISRs was 0.8% in ADA positive subjects, 0.6% in ADA negative subjects, and 0.4% in ADA inconclusive subjects (Table 2.4.3).

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In Study C0743T09, through Year 5, 10.8% ADA positive subjects had 1 or more ISRs, compared to 7.9% in ADA negative subjects and 7.1% in ADA inconclusive subjects. The incidence rate of ISRs was also calculated as the proportion of injections complicated by ISRs. The proportion of ustekinumab injections associated with ISRs was 1.2% in ADA positive subjects, 1.1% in ADA negative subjects, and 0.6% in ADA inconclusive subjects (Table 2.4.3).

Table 2.4.3. Incidence of injection site reactions in Study C0743T08 through Year 5. ISRs, injection site reactions; ADA, anti-drug antibodies. Data source: *Table 22 and Table 23, integrated summary of safety, 5-Year update for Moderate to Severe Psoriasis.*

	Subjects had 1 or more ISRs			Injections associated with ISRs		
	ADA$^+$	ADA$^-$	ADA Inconclusive	ADA$^+$	ADA$^-$	ADA Inconclusive
Study C0743T08	10.3% (4/39)	9.3% (34/365)	9.4% (32/342)	0.8% (5/782)	0.6% (43/6937)	0.4% (24/6607)
Study C0743T09	10.8% (7/65)	7.9% (34/431)	7.1% (50/706)	1.2% (13/1112)	1.1% (94/8768)	0.6% (85/15353)

2.5. What are the bioanalytical methods used to measure ustekinumab concentrations?

Two electrochemiluminescent immunoassays (ECLIA) were used to measure serum ustekinumab concentrations, i.e., ECLIA on [redacted] (b) (4) and ECLIA on [redacted] (b) (4) [redacted] These two assays were validated and have been reviewed in original BLA 125261 or supplemental BLA 125261/049 submission. Assay comparability assessment of the ECLIA on the two platforms using spiked and incurred samples showed that the overall mean result measured by the [redacted] (b) (4) ECLIA was 22.36% higher than those measured by [redacted] (b) (4) ECLIA.

Serum ustekinumab concentrations in samples collected from Week 0 through Week 76 in the Study C0743T08 and from Week 0 through Week 88 in Study C0743T09 were measured using [redacted] (b) (4) ECLIA. [redacted] (b) (4) ECLIA was used to determine serum ustekinumab concentrations in samples collected after Week 76 in Study C0743T08 and after Week 88 in Study C0743T09.

3. LABELING RECOMMENDATIONS

Detailed labeling revisions are summarized as below. The sections in red are the labeling changes proposed by the applicant. The ~~strikethrough text~~ indicates proposed deletion by the applicant. Overall, the labeling update for the 6.2 Immunogenicity section proposed by the applicant is acceptable.

6.2. Immunogenicity

The presence of ustekinumab in the serum can interfere with the detection of anti-ustekinumab antibodies resulting in inconclusive results due to assay interference. In STUDIES 1 and 2, antibody testing was done at time points when ustekinumab may have been present in the serum. Table 2 summarizes the antibody results from ~~STUDY~~ STUDIES 1 ~~through year 3~~ and ~~STUDY~~ 2 through ~~year 4~~ Year 5.

Table 2: Presence of anti-ustekinumab antibodies in ~~STUDY 1 through Year 3 and Study 2 through Year 4~~ STUDIES 1 and 2 through Year 5.

Antibody Results	STUDY 1 (N=746)	STUDY 2 (N=1202)
Positive	39 (5%)	65 (5%)
Negative	~~124 (17%)~~ 365 (49%)	~~150 (12%)~~ 431 (36%)
Inconclusive	~~583 (78%)~~ 342 (46%)	~~987 (12%)~~ 706 (59%)

The majority of patients who were positive for antibodies to ustekinumab had neutralizing antibodies.

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APPENDIX, LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	Anti-Drug Antibodies
CSR	Clinical Study Report
ECLIA	Electrochemiluminescent Immunoassay
IgG	Immunoglobulin G
IL	Interleukin
IR	Information Request
ISRs	Injection Site Reactions
(b) (4)	(b) (4)
Nab	Neutralizing antibody
PK	Pharmacokinetics
q12w	every 12 weeks
SC	subcutaneous
sBLA	supplemental Biological License Application
USPI	US Prescribing Information

Reference ID: 3280818

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/s/

JIE WANG
03/22/2013

YOW-MING C WANG
03/22/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125261Orig1s086

<u>OTHER REVIEW(S)</u>

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

MEMORANDUM:
Review of Requirement for a Risk Evaluation and Mitigation Strategy (REMS)

Date:	July 12, 2013; *Revised July 26, 2013*
Reviewer(s):	Carolyn L. Yancey, M. D., F. A. A. P., Senior Medical Officer, Risk Management Officer, Division of Risk Management (DRISK)
Team Leader:	Kendra Worthy, Pharm. D., Team Leader, DRISK
Division Director:	Claudia Manzo, Pharm. D., DRISK
Drug Name(s):	STELARA (ustekinumab) for subcutaneous injection
Therapeutic Class:	Human Interleukin (IL)-12 and IL-23 Cytokine Antagonists
Dosage and Route:	45 mg/0.5 mL and 90 mg/1.0 mL, in a single-use vial and in a single-use, pre-filled syringe
Application Number:	BLA 125-261/Response to a Memorandum from the Division of Dermatology and Dental Products (dated February 6, 2013 in DARRTS)
PDUFA Date:	Not applicable
Sponsor:	Janssen Biotech, Inc. (Janssen)
OSE RCM #:	2013-467
TSI #:	79

1 INTRODUCTION

This Division of Risk Management (DRISK) review responds to the Division of Dermatology and Dental Products' (DDDP) Memorandum (dated February 6, 2013) requesting that the sponsor of Stelara (ustekinumab) be released from the requirement for a risk evaluation and mitigation strategy (REMS) based on the conclusion that the 18-month and 3-year REMS assessments met the goals of the Stelara REMS.

1.1 BACKGROUND

Ustekinumab is a human interleukin-12 (IL-12) and IL-23 antagonist indicated for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. Ustekinumab liquid in a vial (LIV) is administered by subcutaneous (s.c.) injection based on patient weight[1] and is manufactured in two dosage strengths in a single-use vial and a single-use, pre-filled syringe (PFS).

The Stelara REMS, originally approved on September 25, 2009, includes a Medication Guide, communication plan, and timetable for submission of assessments to ensure that the benefits of Stelara outweigh the potential risks of serious infection, malignancy, and reversible posterior leukoencephalopathy syndrome (RPLS).

To-date, the sponsor of Stelara (Janssen) has not requested that the Agency consider eliminating the requirement for a Stelara REMS. The DDDP requests that the DRISK consider releasing the sponsor of Stelara from the requirement for the REMS based on the following conclusions:

- 18-month and 3-year REMS assessments met the goals of the Stelara REMS
- revised labeling adequately communicates the potential risks associated with Stelara therapy
- no new safety risks were observed in the long-term safety data with Stelara (See Section 1.2, Regulatory History, specifically, comments regarding Supplement 086 and 089)

While no formal policy has been developed within the Center for Drug Evaluation and Research (CDER) to determine when a REMS with a communication plan could be released, the DRISK' best practice allows a sponsor to be released from a requirement for a REMS if the REMS assessments indicate that the goals of the REMS have been met, if the communication activities have been completed, and if the Agency has determined that the REMS is no longer necessary to ensure that the benefits of the product outweigh the risks of the product.

[1] For patients weighing $\leq$100 kg (220 lbs), the recommended Stelara dose is 45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks. For patients weighing > 100 kg (220 lbs), the recommended Stelara dose is 90 mg initially and 4 weeks later, followed by 90 mg every 12 weeks

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1.2 REGULATORY HISTORY

The regulatory history, specific to the Stelara REMS and recent safety information follows:

- September 25, 2009: The Agency approved the original Stelara REMS (see Introduction, in this Memorandum, for the REMS elements)
- December 30, 2009: 1st REMS modification was based on Agency approval of a PFS
- October 20, 2010: 2nd REMS modification was based on Agency approval of labeling revisions regarding allergic reactions and immunotherapy to include angioedema
- March 25, 2011: The sponsor submitted the 18-month REMS assessment. The Agency's conclusions about the 18-month REMS assessment (REMS assessment review written by Therese Cvetkovich, M. D. on June 14, 2011) follow:
  - The 18-month REMS assessment is complete and addresses all issues outlined in the approved REMS assessment plan.
  - Recommendations included the following: "We recommend opening the 90-day discussion period to evaluate whether there are modifications to the Medication Guide that would result in improved patient understanding of the risks of Stelara, which at this time, are theoretical (i.e., the risks of malignancy, serious infections, generally, and of non-tuberculoses mycobacterium and *Salmonella,* specifically) or of uncertain relationship (RPLS) to Stelara.
  - *Note: the REMS modification was approved on May 2, 2012 (see below entry).*
- May 2, 2012: 3rd REMS modification was approved based on the following revisions:
  - Deletion of the second goal related to the Psoriasis Longitudinal Assessment and Registry (PSOLAR) voluntary disease-specific patient registry.
  - Addition of the REMS website landing page as part of the communication plan in the REMS Document. A timeframe for the length of time the website will remain active was added to the Stelara REMS.
  - Removal of the Medication Guide as an element in the REMS. The Medication Guide remains part of approved labeling.
  - Deletion of patient knowledge, attitude and behavior (KAB) surveys and all references to patients from the REMS assessment components based on removal of the Medication Guide as a REMS element.
- July 27, 2012: The sponsor submitted an efficacy Supplement (S-086) proposed to allow for patients to self-administer Stelara. The submission also included an update to the Immunization Section of labeling (5.7 and 12.2), a change in the Adverse Reactions (AR) Section of labeling (6.1 and 6.2) to update patient exposure and the AR rate of infection, malignancy and immunogenicity, all based on data from the clinical Study C-0743T09 PHOENIX-2). (b) (4) No new safety events were reported in the long-term safety data.

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(b) (4)

- September 25, 2012: The sponsor submitted the 3-year REMS assessment report. The Agency's conclusions about the 3-year REMS assessment (REMS assessment review written on November 30, 2012 by Therese Cvetkovich, M. D.) follow:
  - The 3-year REMS assessment is complete and addresses all issues outlined in the approved REMS assessment plan
  - "We concluded that the goal of alerting and warning prescribers of the risks of Stelara is being met."…"We recommend sending the applicant a REMS Complete with Comment letter." The comments communicated to the sponsor in the REMS Complete with Comment letter follow: "In the 3-year Stelara REMS assessment report, you outlined some actions that you intend to undertake to improve prescriber understanding of several risk messages. Please provide for our review the proposed modifications to the (b) (4) and the proposed (b) (4)
- October 3, 2012: The applicant submitted an amendment to their pending supplemental application (S-086) (b) (4)
- October 5, 2012: The Agency completed a 915 Postmarket Review for Stelara. There were no new major safety risks reported with ustekinumab. Self-administration with the PFS and with the LIV (approved in the European Union, Canada, and Australia since 2009) did not demonstrate new potential safety issues from the reported medication error cases with ustekinumab for self-administration, sc injection
- January 24, 2013: (Labeling Supplement 091) The DDDP review, written by Brenda Carr, M. D., supported insertion of new safety information in labeling as follows:
  - (b) (4) squamous cell carcinoma (b) (4) 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. (b) (4)
  - (b) (4) patients, (b) (4) greater than 60 years of age, patients with a medical history of prolonged immunosuppressant therapy (b) (4) those with a history of (b) (4) (PUVA), should be (b) (4) (b) (4)
  - The Medication Guide was revised to align with the above revised labeling per the Patient Labeling Team, Division of Medical Policy Programs (DMPP).

  Note, labeling supplement 091 did not prompt a REMS modification.
- January 31, 2013: The Office of Compliance completed the Stelara REMS Establishment Inspection Report (EIR) and concluded that there were no violations of the statute and no future inspections will be necessary because the REMS is nearly

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complete with the exception of the twice-yearly dissemination of the printed journal information piece in the *Journal of Clinical Oncology and Blood* through 5 years from the date of approval of the original REMS (required dissemination of oncology journal information piece will be completed in 2014).

- February 6, 2013: (Product Correspondence-092) The DDDP completed a Memorandum to the DRISK with the subject, "Release of REMS for BLA 125-261 Stelara (ustekinumab)."
- April 18, 2013: (Supplement 086) The DDDP recommended approval of labeling for self-administration of ustekinumab with the PFS and self-administration with the LIV preparation (based on data submitted in December 2007, Phase 3 clinical trials).
- (b) (4)
- April 19, 2013: (Supplement 099/Labeling) The sponsor submitted a Prior Approval Supplement in response to the Agency's request to update the Postmarketing Experience section of the Stelara package insert to add events of erythrodermic psoriasis and pustular psoriasis (letter dated August 29, 2012). Though the sponsor did not initially agree with the Agency's request, revised labeling includes both of these adverse events in the Postmarketing Experience section of the labeling based on the clinical judgment of the reviewer that there is a causal relationship between ustekinumab and the occurrence of these two events. See Supplement 099 (Labeling) review written by Brenda Carr, M. D., for details supporting causality and the rationale for this revision to the Stelara labeling.
- (b) (4)
- May 21, 2013: The Agency approved S-086; no long-term safety risks were reported.

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

The following materials, listed by the document date, were reviewed to inform the DRISK' recommendation on whether or not the Stelara REMS should be released from the Agency's requirement for a REMS:

- June 14, 2011: The DRISK REMS assessment review (written by Therese Cvetkovich, M. D., Medical Officer)
- November 30, 2012: The DRISK REMS assessment review (written by Therese Cvetkovich, M. D., Medical Officer)

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- February 6, 2013: DDDP Memorandum: Request to release the sponsor of the REMS for BLA 125261 Stelara (ustekinumab) from the requirement for a REMS (written by Brenda Carr, M. D., Medical Officer)

3 RESULTS OF REVIEW

DDDP Memorandum

The DDDP Memorandum (written on January 16, 2013; placed in DARRTS on February 6, 2013) to the DRISK requested that the sponsor of Stelara be released from the requirement for a REMS based on the following rationale:

- No new safety information in the long-term postmarketing safety data
  - Postmarketing safety data did not demonstrate risks of a specific serious infection or a specific malignancy associated with use of ustekinumab. There are no new reported cases of RPLS since approval of Stelara (September 25, 2009). To-date, only a single case of RPLS from the original clinical trials appears in labeling. The DDDP concluded that labeling adequately addresses the risk of RPLS.
- Labeling changes adequately inform providers on the potential risks associated with use of Stelara (serious infection, malignancy, and RPLS).
- The 18-month and 3-year REMS assessments[2] are meeting the goals of the REMS.

The DDDP memorandum states, "as the REMS at each assessment has been found to have met its goals, the medical officer considers releasing the sponsor form the REMS be reasonable and acceptable. The label will continue to serve as a tool for communication of risk and will be updated with new information, including as pertains to serious infections, malignancy and RPLS, as indicated."

Based on the DDDP Memorandum, the DRISK concludes that the DDDP has determined that the Stelara REMS is no longer necessary to ensure that the benefits of Stelara outweigh the risks.

Findings from the Stelara REMS Assessments

The Agency concluded that the Stelara REMS assessments at 18 months (submitted on March 25, 2011) and at 3-years (submitted on September 25, 2012) met the goals of the REMS. In the 3-year REMS assessment, the prescriber survey data demonstrated that prescribers had a high level of knowledge about many of the potential risks with use of Stelara.

Though the Agency concluded the prescriber survey scores were acceptable[3], the sponsor proposed the following non-REMS education materials, specifically, (b) (4) to discuss specific topics in the goals of the Stelara REMS

[2] The 18-month Stelara REMS Assessment (submitted on March 25, 2011) and the 3-year Stelara REMS Assessment (submitted on September 25, 2012) were both determined to be meeting the goals of the REMS.

[3] See the 3-Year REMS Assessment Review by Therese Cvetkovich, M. D. written on November 15, 2012. The REMS Acknowledgement letter was issued by the Agency on December 5, 2012.

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(potential for serious infections, potential for malignancy, and RPLS)" and "an [redacted] (b) (4) for healthcare providers … about the Stelara REMS website location and navigation to the pertinent REMS information. The [redacted] (b) (4) also includes the toll-free number for HCPs to call with questions or to report an adverse event."

Brief description of the sponsor's proposed non-REMS educational materials follow:

[redacted] (b) (4)

REMS Element: Communication Plan Activities

The elements of the Stelara REMS communication plan include the following:

- Dissemination of a *Dear Healthcare Professional letter* and a *Dear Pharmacist letter* has been completed by the sponsor within 60 days of the approval of Stelara
- Dissemination of information about serious infection, malignancy, and RPLS to healthcare providers through certain dermatology, oncology, rheumatology, infectious diseases, and gastroenterology professional journals has been completed except for the oncology journal (see details below).
    1. For display as a panel-poster and distribution as printed material at all dermatology and oncology scientific meetings where the company has a sponsored booth. The sponsor has completed this activity for dermatology; however, the oncology activity is ongoing (through 5 years from initial approval).

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[4] Required Revisions to a Proposed RISK Evaluation and Mitigation Strategy (REMS) Modification for Stelara written on February 28, 2012 by Carolyn L. Yancey, M. D., F.A.A.P., Senior Medical Officer, DRISK

[5] Interim Comments Review for the Proposed Risk Evaluation and Mitigation Strategy (REMS) Modification for Stelara written on December 23, 2011 by Carolyn L. Yancey, M. D., as above.

[6] Risk Evaluation and Mitigation Strategy (REMS) Modification Requirements Based on a REMS Assessment Review written on July 14, 2011 by Carolyn L. Yancey, M. D., as above.

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2. For quarterly presentation as a printed information piece in the *Journal of the American Academy of Dermatology* and the *Archives of Dermatology* for 3 years from initial approval. The sponsor has completed this activity for the two dermatology journals.
3. For quarterly presentation as a printed information piece in the *Journal of Clinical Oncology and Blood* for 5 years from initial approval. This activity is ongoing through 2014.
4. For twice yearly presentation as a printed information piece in *Arthritis and Rheumatism*, the *Journal of Infectious Disease*, and the *American Journal of Gastroenterology*, and *Gastroenterology* for 3 years from initial approval. The sponsor has completed this activity for the rheumatology, infectious diseases, and gastroenterology journal(s).

- The sponsor must maintain the Stelara REMS program website for a period of 5 years from initial approval. This activity is ongoing under the Stelara REMS through 2014.

4 DISCUSSION AND CONCLUSION

While the Stelara REMS appears to be meeting its' goals, the DRISK concludes that the REMS should remain as a requirement for the sponsor through 2014. The original REMS communication plan activities included the requirement that the journal information piece in the *Journal of Clinical Oncology and Blood* for quarterly publication through 5 years from the date of approval of the Stelara REMS (September 25, 2009).[7]

See the **Appendix**, to this Memorandum, for the Safety Requirements Team (SRT) *Checklist: Removing a Communication Plan from a REMS.*

The oncology journal information piece is designated for a longer period of dissemination than the other journal information pieces (designated as quarterly dissemination for 3 years from that date of approval of the Stelara REMS) based on a longer latency period for observation of a malignancy associated with exposure to Stelara.[8] Because the potential risk of malignancy with exposure to Stelara, the DRISK concludes that the communication plan activities, as approved under the current Stelara REMS, should be completed before there is further consideration to release the sponsor from the requirement for the Stelara REMS.

5 RECOMMENDATIONS

The DRISK does not recommend releasing the sponsor, Janssen Biotech, Inc., from the requirement for the Stelara REMS until the communication plan requirements are

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[7] SRT issued a document entitled, "Checklist: Removing a Communication Plan from a REMS" (dated May 18, 2011). The required dissemination activities for the communication plan for the Stelara REMS will not be completed until 2014.

[8] The other journal information pieces in the Stelara REMS are the *Journal of the American Academy of Dermatology* and the *Archives of the Dermatology* (quarterly dissemination for 3 years); *Arthritis and Rheumatism*, the *Journal of Infectious Disease*, the *American Journal of Gastroenterology* and *Gastroenterology* (twice yearly dissemination for 3 years) from the original approval of the Stelara REMS.

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fulfilled in 2014. The DRISK recommends internal discussion of whether or not to release the sponsor from the requirement for the Stelara REMS at the conclusion of the Stelara REMS communication plan activities in 2014.

This internal Memorandum response from the DRISK to the DDDP does not require that a communication be sent to the sponsor from the DDDP.

APPENDIX

Checklist: Removing a Communication Plan from a REMS

Drug Name: _____ Application Number: _____

		Checklist Item	*Notes*
1	☐	All activities for the communication plan are complete and assessed.	
2	☐	The CP has been successfully completed and no further assessments are necessary.	
3	☐	A CP is no longer necessary to ensure that the benefits of the drug outweigh the risks.	
4	☐	The REMS has no ETASU **OR** If the REMS has ETASU, removal of the CP has been discussed with SRT and SWAT.	
5	☐	If necessary, further discussion between OND and OSE confirm none of the following issues exist: 1. Potential modifications to the REMS – other than MG wording revisions – are anticipated in the next 6 months. 2. Emerging safety issues warrant consideration of implementation of other REMS elements besides a MG within the next 6 months.	
6	☐	FDA has received a REMS modification proposal to remove the Communication Plan **OR** FDA has received a proposed REMS modification supplement to modify the REMS (but not remove the CP) and the sponsor has verbally agreed that the CP can be removed from the REMS.	If we have not received a mod proposal, FDA can proactively ask the sponsor to submit a supplement to propose that the CP be removed. If the REMS is a MG and CP REMS, a proposal to remove the MG and CP will effectively constitute a request to eliminate the REMS.

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7	☐	The modification proposal references a new or recent (within the last 18 months) assessment **OR** The modification proposal includes an update on the status of any post-approval studies or clinical trials required as a FDAAA PMR or undertaken to investigate a safety issue.	OND contacts the sponsor if the referred to or submitted assessment is not appropriate.
8	☐	DRISK and/or OND have completed the appropriate review for the referenced assessment.	OND and DRISK together determine the appropriate review for full assessments that are submitted with the mod proposal.
9	☐	Any regulatory actions using the REMS assessment as new safety information (i.e., MG or other safety labeling changes, REMS mods, requiring PMRs) have been completed or will be completed at the same time as the CP is removed from the REMS or the REMS is eliminated.	

If all of the boxes on this checklist can be checked, the communication plan may be removed from the REMS and, if it is a CP-only REMS, the REMS may be eliminated.

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/s/

CAROLYN L YANCEY
07/26/2013
Memorandum to DDDP from DRISK - Not to release requirement for the Stelara REMS

CLAUDIA B MANZO
07/26/2013
concur

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Labeling Review

Date:	March 7, 2013
Reviewer:	Carlos M Mena-Grillasca, RPh, Safety Evaluator Division of Medication Error Prevention and Analysis
Team Leader:	Lubna Merchant, MS, PharmD Division of Medication Error Prevention and Analysis
Associate Director:	Scott Dallas, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Stelara (Ustekinumab) Injection 45 mg/0.5 mL, 90 mg/1 mL
Application Type/Number:	BLA 125261
Submission Number:	S-086
Applicant/sponsor:	Janssen Biotech
OSE RCM #:	2012-2088

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the proposed Instructions for Use for Stelara (Ustekinumab) Injection, BLA 125261/S-086 for areas of vulnerability that could lead to medication errors. In this efficacy supplement the applicant is proposing labeling changes to the Instruction for Use to provide patients with instructions on how to self administer the product. The Division of Dermatology and Dental products requested DMEPA review the changes to the proposed Instructions for Use.

1.1 REGULATORY HISTORY

Stelara (Ustekinumab) Injection was approved on September 25, 2009 for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

1.2 PRODUCT INFORMATION

The following product information is provided in the product's prescribing information.

- Active Ingredient: Ustekinumab
- Indication of Use: Treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.
- Route of Administration: Subcutaneous
- Dosage Form: Injection
- Strength: 45 mg and 90 mg
- Dose and Frequency: Stelara is administered by subcutaneous injection.
    - For patients weighing ≤100 kg (220 lbs), the recommended dose is 45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks.
    - For patients weighing >100 kg (220 lbs), the recommended dose is 90 mg initially and 4 weeks later, followed by 90 mg every 12 weeks.
- How Supplied: 45 mg/0.5 mL in single-use vials and pre-filled syringes
  90 mg/1 mL in single-use vials and pre-filled syringes
- Storage: Refrigerated at 2ºC to 8ºC (36ºF to 46ºF).

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA Adverse Event Reporting System (FAERS) database for Stelara medication error reports. We also reviewed the Stelara Instructions for Use (IFU) submitted by the Applicant and the Stelara IFU reviewed and edited by Patient Labeling.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FDA FAERS using the strategy listed in Table 1.

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Table 1: FAERS Search Strategy	
Date	February 5, 2013 Time limitation from July 3, 2012, date of last AERS search for the 915 NME evaluation for Stelara.
Drug Names	Trade Name: Stelara Active Ingredient: Ustekinumab
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

The FAERS database search identified 33 cases. Appendix D provides listings of all case numbers for the cases identified in the FAERS search. Each case was reviewed for relevancy and duplication. After individual review, 30 cases were not included in the final analysis for the following reasons:

- Dose omission due to other health issues that prevented dosing (n=7), or insurance coverage issues (n=3), or pharmacy 'problem' (n=1), or issue scheduling visit to the doctor's office (n=1), and no causality or contributing factors reported (n=4)
- Wrong frequency of administration due to an adverse event (n=1), off label use (n=1), physician intentionally prescribed an extra dose (n=2), and no causality or contributing factors reported (n=4)
- Overdose due to an order entered twice in the electronic records system (n=1) and physician intentionally prescribing the 90 mg dose (n=1)
- Suspected incorrect storage without additional information (n=1)
- No medication error per additional information reported on follow up (n=1)
- Lack of effect at the recommended dose (n=1)

2.2 Labels and Labeling

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Proposed Instructions for Use submitted by the applicant on September 7, 2012.
- Patient Labeling Review with revisions to the proposed Instructions for Use

2.3 Previously Completed Reviews

DMEPA had previously reviewed medication error cases for Stelara as part of the FDAAA Section 915 NME Post Marketing evaluation, dated October 15, 2012. DMEPA identified no potential safety issues from the reported medication error cases involving Stelara.

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the results of our FAERS search and the risk assessment of the Stelara Instructions for Use labeling.

3.1 MEDICATION ERROR CASES

Following exclusions as described in section 2.1, three Stelara medication error cases remained for our detailed analysis.

- Wrong route of administration errors (n=2). The first is a foreign case that describes a 72 year old male patient that was administered Stelara by the intramusuclar route of administration. The patient experience severe muscle pain and muscle weakness. No causality was provided in the case narrative. The second is a domestic that case describes a 67 year old male patient that was administered Stelara by the intramuscular route of administration. During the course of treatment the patient tested positive for tuberculosis, but it was not active. No causality was provided for the wrong route of administration error.
- Wrong dose error (n=1). This foreign case describes a 46 year old male that received a 90 mg dose instead of his usual 45 mg dose. However, it was not clear from the narrative if this was a dispensing error or a prescribing error. No causality or outcome was reported in this case.

3.2 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESMENT

The applicant is proposing labeling changes to provide instruction for the patient to self administer Stelara at home.

DMEPA reviewed the approved container labels, carton and Prescribing Information (PI) labeling for the USA drug product and found it adequate to mitigate wrong dose and wrong route of administration type of medication errors. We note that the proposed PI, Medication Guide, and Instructions for Use clearly indicate that patients and caregivers must be trained by a healthcare professional prior to self administration at home.

We reviewed the revised Instructions for Use from the Patient Labeling group and noted that the Instructions for Use for the vial dosage form indicate that the needle be prepared (Step 3) prior to preparing the injection site (Step 4). The last instruction during the preparation of the needle indicates "Remove the syringe from the vial. Do not lay the syringe down or allow the needle to touch anything". However, the following instructions for preparing the injection site require that the patient or caregiver clean the skin with antiseptic wipe. The order of these instructions would likely require that patients or caregivers place the prepared syringe on a flat surface in order to prepare the injection site.

DMEPA consulted with the Patient Labeling group and although the final decision was to maintain the order of the steps, they made recommendations to provide patients and caregivers futher handling directions in the Instructions for Use. DMEPA concurrs with their recommendations and they are provided in section 5.1 below.

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4 CONCLUSIONS

DMEPA concludes that the proposed Instructions for Use can be improved to promote the safe use of the product.

5 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this Supplement.

5.1 COMMENTS TO THE REVIEW DIVISION FOR THE REVISED IFU FROM PATIENT LABELING

A. Instructions for Use – Instructions for Injecting Stelara from a vial

1. Step 3: Prepare the Needle. Revise the last bullet after Figure (b) (4) from "Remove the syringe from the vial. Do not lay the syringe down or allow the needle to touch anything" to read "Remove the syringe from the vial. Set the syringe and needle on your work surface without anything touching the needle."
2. Step 5: Inject Stelara. Add a first bullet that reads "Carefully pick up the syringe and needle".

B. Instructions for Use – Instructions for Injecting Stelara (b) (4) a prefilled syringe.

The section titled "Gather the supplies you will need to prepare and give your injection" refers to 1 antiseptic wipe, 1 cotton ball or gauze and 1 Stelara prefilled syringe. However, if the patient is prescribed a 90 mg dose and two 45 mg prefilled syringes are dispensed the patient will need more than one of those items. DMEPA recommends using the same wording from the 'Instruction for Injecting Stelara from a vial', which reads "antiseptic wipes, cotton balls or gauze pads, your prescribed dose of Stelara".

If you have further questions or need clarifications, please contact Janet Anderson, project manager, at 301-796-0675.

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APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

Reference ID: 3272524

Appendix B: Case numbers identified in this review

8646943v1	8889269v2
8659381v3	8900410v3
8675697v2	8911767v1
8711189v2	8916233v3
8713114v1	8919093v3
8721436v1	8932311v1
8725588v1	8935535v2
8726688v1	8935540v3
8731591v2	8949680v2
8734853v1	8953291v2
8737436v1	8966252v1
8738371v1	9005417v1
8739410v1	9019381v1
8748257v1	9028461v1
8809370v1	9046950v1
8809397v5	9046951v1
8845305v1	

Reference ID: 3272524

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/s/

CARLOS M MENA-GRILLASCA
03/07/2013

LUBNA A MERCHANT
03/07/2013

SCOTT M DALLAS
03/07/2013

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: February 12, 2013

To: J. Paul Phillips
Regulatory Project Manager
Division of Dermatology and Dental Products (DDDP)

From: Lynn Panholzer, PharmD
Regulatory Review Officer
Division of Professional Drug Promotion

Susannah K. Hubert, MPH
Regulatory Review Officer
Division of Consumer Drug Promotion

Subject: **BLA 125261/86**
OPDP labeling comments for Stelara (ustekinumab) injection

Background

This consult is in response to DDDP's August 22, 2012, request for OPDP's review of the package insert (PI), medication guide (MG), and instructions for use (IFUs) for Stelara (ustekinumab) injection. OPDP reviewed the substantially complete version of the draft PI sent to OPDP on January 30, 2013, and the draft MG and IFUs previously marked up by the Division of Medical Policy Programs and sent to OPDP on February 8, 2013. Our comment on the PI is included on the attached, marked-up copy of the labeling. We have no comments on the MG or IFUs (attached for reference).

OPDP appreciates the opportunity to provide comments on these materials. If you have any questions or concerns, please contact:

- Lynn Panholzer (PI)
  301-796-0616 or lynn.panholzer@fda.hhs.gov
- Susannah Hubert (MG, IFUs)
  301-796-3245 or susannah.hubert@fda.hhs.gov

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/s/

LYNN M PANHOLZER
02/12/2013

SUSANNAH HUBERT
02/12/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	February 8, 2013
To:	Susan J. Walker, MD Director **Division of Dermatology and Dental Products (DDDP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling Team **Division of Medical Policy Programs**
From:	Latonia M. Ford, RN, BSN, MBA Patient Labeling Reviewer **Division of Medical Policy Programs**
Subject:	DMPP Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	STELARA (ustekinumab)
Dosage Form and Route:	Injection, for subcutaneous use
Application Type/Number:	BLA 125261/S-086 (b) (4)
Applicant:	Janssen Biotech, Inc.

Reference ID: 3257876

1 INTRODUCTION

On July 27, 2012, Janssen Biotech, Inc. submitted Supplemental Biologics License Application (BLA) 125261/S-086 for STELARA (ustekinumab) injection. This submission proposes to update the Prescribing Information (PI) with safety and efficacy data, and to include an option for self-administration. On October 3, 2012 the Applicant submitted an amendment to their pending supplemental application (S-086) in response to an Agency notification (b) (4)

STELARA (ustekinumab) injection was originally approved on September 25, 2009 for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

On August 22, 2012, the Division of Dermatology and Dental Products (DDDP) requested that the Division of Medical Policy Programs (DMPP) review the proposed Medication Guide (MG) and Instructions for Use (IFU) for STELARA (ustekinumab) injection.

This review is written in response to a request by DDDP for DMPP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for STELARA (ustekinumab) injection.

DMPP consulted with the Division of Medication Error Prevention and Analysis (DMEPA) and a separate DMEPA review of the IFUs will be forthcoming.

2 MATERIAL REVIEWED

- Draft STELARA (ustekinumab) injection Medication Guide (MG) and Instructions for Use (IFU) received on October 03, 2012 and received by DMPP on January 30, 2013.
- Draft STELARA (ustekinumab) injection Prescribing Information (PI) received on October 03, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on January 30, 2013.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more

Reference ID: 3257876

accessible for patients with vision loss. We have reformatted the MG and IFUs document using the Verdana font, size 11.

In our review of the MG and IFUs we have:

- ensured that the MG and IFUs are consistent with the Prescribing Information (PI)
- simplified wording and clarified concepts where possible
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and IFUs are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the MG and the IFUs are appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

LATONIA M FORD
02/08/2013

BARBARA A FULLER
02/08/2013

LASHAWN M GRIFFITHS
02/08/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125261Orig1s086

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 009590

MEETING MINUTES

Janssen Research and Development, LLC
Attention: Joseph A. Lallier, MS, MBA, RAC
Associate Director, Global Regulatory Affairs
Welsh & McKean Roads, P.O. Box 776
Spring House, PA 19477

Dear Mr. Lallier:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Stelara® (ustekinumab).

We also refer to the teleconference between representatives of your firm and the FDA on May 23, 2012. The purpose of the meeting was to discuss the submission of a supplemental application for Stelara®, which would propose the option of patient self-administration and longer term clinical data.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Paul Phillips, Regulatory Project Manager at (301) 796-3935.

Sincerely,

{See appended electronic signature page}

Jill Lindstrom, MD
Clinical Team Leader
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-sBLA
Meeting Date and Time:	May 23, 2012; 11:00 a.m. (EDT)
Meeting Location:	Teleconference
Application Number:	IND 009590
Product Name:	Stelara® (ustekinumab)
Indication:	Treatment of moderate to severe psoriasis
Sponsor/Applicant Name:	Janssen Research and Development, LLC
Meeting Chair:	Jill Lindstrom, MD
Meeting Recorder:	J. Paul Phillips

FDA ATTENDEES
Jill Lindstrom, MD, Clinical Team Leader, DDDP
Brenda Carr, MD, Clinical Reviewer, DDDP
Kathleen Fritsch, PhD, Biostatistics Reviewer, DB III
Jie Wang, PhD, Clinical Pharmacology Reviewer, DCP 3
Laurie Graham, MS, Product Quality/CMC Reviewer, DMA
J. Paul Phillips, MS, Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES
Kim Shields, Senior Director, Global Regulatory Leader
Joseph Lallier, Associate Director, Global Regulatory Affairs
Kerry Whitehead, Manager, Global Regulatory Affairs
Philippe Szapary, MD, MSCE, Senior Director, Clinical Research
Yasmine Wasfi, MD, Director, Clinical Research
Yaowei Zhu, PhD, Associate Scientific Director, Clinical Pharmacology
Shu Li, MS, Director, Clinical Biostatistics
Ming-Chun Hsu, PhD, Manager, Clinical Biostatistics

Reference ID: 3138551
Reference ID: 3316566

Purpose of the Meeting:
To discuss the sponsor's plans to submit an efficacy supplement proposing an option for self administration of ustekinumab and to provide efficacy and safety data of treatment with ustekinumab for up to five years.

Question 1:
Does the Agency agree that the proposed analysis of safety and efficacy data from subjects in C0743T08 who self-administered STELARA away from the investigative site would be sufficient to allow the Agency to assess the safety and efficacy of the self-administration of STELARA? If not, what additional data and/or analyses would be required?

Response:
You propose [redacted] (b) (4) These analyses may permit assessment of safety and efficacy of the self-administration of Stelara; however, adequacy of data and analyses is a review issue.

Ensure that the datasets will allow for identification of whether each injection was given by the investigator personnel, by the subject, but supervised, or self-administered off-site.

In the C0743T08 study, if there are additional subjects who developed anti-drug antibodies (ADA) during the study period for self-administration assessment (after Week 208), submit summary of these new ADA events that occurred among subjects whose injections were administered on-site versus subjects who self-administered off-site.

Question 2:
Does the Agency agree with the sponsor's proposal to provide a summary of the efficacy data from C0743T08 and C0743T09 in the Summary of Clinical Efficacy in Module 2.7.3 without the need for a separate Integrated Summary of Efficacy in Module 5.3.5.3?

Response:
This is acceptable.

Question 3:
Does the Agency agree that the proposed efficacy analyses are adequate to allow the Agency to assess the efficacy [redacted] (b) (4) up to 5 years of treatment? If not, what additional analyses would be required?

Response:
Efficacy data should be analyzed as specified in the protocol. Whether specific efficacy results would be appropriate for labeling is a review issue and would depend on factors such as clinical relevance, the presence of adequate controls, and whether the analyses were adequately prespecified.

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Reference ID: 3316566

Question 4:
Does the Agency agree that the proposed safety analyses and proposed data display formats are adequate to allow the Agency to assess the safety of ustekinumab with up to 5 years of treatment? If not, what additional analyses would be required?

Response:
The proposed safety analyses and proposed data display formats as presented in the briefing document will permit an assessment of safety; however, adequacy of data and analyses is a review issue. You propose safety analyses of the pooled dataset from four psoriasis trials: C0379T04, C0743T08, C0743T09, and C0743T12. Your rationale for the pooling strategy is to increase "the precision of the event rate estimates and the ability to detect safety signals." You did not provide draft labeling text in the briefing document (you will propose labeling text for efficacy and safety analyses in the efficacy supplement). Additional analyses may be requested during the review cycle.

Ensure that the safety summaries include adequate assessments over time (e.g. by year) for event counts and rates for non-melanoma skin cancer, other malignancies, infections, and serious infections so that potential rate changes can be identified. Regarding tables such as Attachment 11, also include in these tables columns for the two dosage levels combined, in addition to the doses separately. Provide datasets that will easily allow additional assessments of these events and rates over time.

Question 5:
Does the Agency accept the sponsor's proposal to provide a textual summary of safety analyses in the Summary of Clinical Safety with supporting tables, listings and datasets in the Integrated Summary of Safety, Module 5.3.5.3 (per Option 4 of the April 2009 Guidance titled: "Guidance for Industry Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document")?

Response:
This is acceptable.

Question 6:
Does the Agency agree that it is acceptable to evaluate the immunogenicity of ustekinumab in the C0743T08 and C0743T09 long-term extensions using the current test method in this proposed sBLA, with the understanding that the new test method currently under development as a PMC may necessitate subsequent retesting of all or a subset of the samples collected during the long-term extension period?

Response:
We agree that it is acceptable to evaluate the immunogenicity of ustekinumab using the current test method for the proposed sBLA. We have the following comments and reminders regarding your immunogenicity data submission.

- Use the 3-category classification (i.e., positive, negative, and inconclusive) of anti-drug antibody (ADA) status for reporting of immunogenicity data for study C0743T08 and study

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C0743T09. The analyses of the impact of ADA status on pharmacokinetics, efficacy, and safety should be based on the 3-category classification of ADA status.

- Submit summary of neutralizing antibody to ustekinumab status for study C0743T08 and study C0743T09. In addition, submit an integrated data analysis of neutralizing antibody to ustekinumab status across studies in your "global psoriasis studies dataset" to enable an update to the immunogenicity section of the current Stelara USPI.

Meeting Discussion:
The sponsor agreed to submit neutralizing antibodies status data for studies C0743T04, C0743T08, C0743T09, and C0743T12 to the sBLA for review.

Question 7:
Does the Agency agree with the proposed plan for submission of case narratives and case report forms?

Response:
This is acceptable.

Question 8:
Does the Agency agree with the proposed plan for submission of datasets?

Response:
The proposal to submit efficacy and safety analysis datasets and SDTM datasets for Studies 08, 09, and safety datasets for the four pooled studies is acceptable.

The analysis datasets submitted should be adequate for the Agency to replicate your submitted efficacy and safety analyses (including raw and defined variables, flag variables, treatment codes, etc.) and to conduct related analyses as needed. The datasets should be in SAS transport format and accompanied by adequate documentation (define.pdf).

The analysis safety datasets for the pooled studies should be designed to easily allow additional assessments of targeted safety events and rates over time.

Provide datasets and statistical programs suitable for calculating Poisson confidence intervals for the event/incidence rates in the analysis safety datasets.

Be advised that since 6/23/2011 files associated with Studies 08 and 09 have not been loading with the correct folder/subfolder structure in our eCTD viewer (all files for the two studies are in one place rather than organized into the appropriate subfolders). Other components of your previous supplements are loading correctly. Verify that your eCTD coding is correct with regard to the files for these two studies.

Question 9:
Does the Agency agree that a 4-month safety update will not be required for the proposed sBLA?

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Response:
You will need to submit a 4-month safety update.

Meeting Discussion:
The sponsor proposed to submit pooled safety data from the Phase 3 studies in psoriatic arthritis. The Agency agreed with this approach.

Additional Clinical Pharmacology Comments:
We noted that you have completed a Phase 3 study of ustekinumab in Chinese subjects with moderate to severe psoriasis. It is not clear whether pharmacokinetics (PK) data have been collected in these Chinese subjects and whether race could be a factor affecting ustekinumab exposure. We encourage you to submit the PK analysis report for this Phase 3 study, preferably with analysis datasets, to the IND for our review.

Administrative Comments

1. Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of information submitted to the IND or BLA might identify additional comments or information requests.

2. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).

Prescribing Information

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

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/s/

JILL A LINDSTROM
06/05/2012