HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use STARJEMZA™ safely and effectively. See full prescribing information for STARJEMZA™.

STARJEMZA™ (ustekinumab-hmny) injection, for subcutaneous or intravenous use
Initial U.S. Approval: 2025
STARJEMZA™ (ustekinumab-hmny) is biosimilar* to STELARA® (ustekinumab).

----------INDICATIONS AND USAGE----------
STARJEMZA is a human interleukin-12 and -23 antagonist indicated for the treatment of:
Adult patients with:
- *moderate to severe plaque psoriasis (PsO)* who are candidates for phototherapy or systemic therapy. (1.1)
- *active psoriatic arthritis (PsA)*. (1.2)
- *moderately to severely active Crohn's disease (CD)*. (1.3)
- *moderately to severely active ulcerative colitis.* (1.4)

Pediatric patients 6 years and older with:
- *moderate to severe plaque psoriasis*, who are candidates for phototherapy or systemic therapy. (1.1)
- *active psoriatic arthritis (PsA)*. (1.2)

----------DOSAGE AND ADMINISTRATION----------
Psoriasis Adult Subcutaneous Recommended Dosage (2.1):

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

Psoriasis Pediatric Patients (6 to 17 years old) Subcutaneous Recommended Dosage (2.1): Weight-based dosing is recommended at the initial dose, 4 weeks later, then every 12 weeks thereafter.

Weight Range (kilograms)	Dose
less than 60 kg	0.75 mg/kg
60 kg to 100 kg	45 mg
greater than 100 kg	90 mg

Psoriatic Arthritis Adult Subcutaneous Recommended Dosage (2.2):
- The recommended dosage is 45 mg administered subcutaneously initially and 4 weeks later, followed by 45 mg administered subcutaneously every 12 weeks.
- For patients with co-existent moderate-to-severe plaque psoriasis weighing greater than 100 kg, the recommended dosage is 90 mg administered subcutaneously initially and 4 weeks later, followed by 90 mg administered subcutaneously every 12 weeks.

Psoriatic Arthritis Pediatric (6 to 17 years old) Subcutaneous Recommended Dosage (2.2): Weight-based dosing is recommended at the initial dose, 4 weeks later, then every 12 weeks thereafter.

Weight Range (kilograms)	Dose
less than 60 kg	0.75 mg/kg
60 kg or more	45 mg
greater than 100 kg with co-existent moderate-to-severe plaque psoriasis	90 mg

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

Weight Range (kilograms)	Dose
up to 55 kg	260 mg (2 vials)
greater than 55 kg to 85 kg	390 mg (3 vials)
greater than 85 kg	520 mg (4 vials)

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

----------DOSAGE FORMS AND STRENGTHS----------
Subcutaneous Injection (3)
- Injection: 45 mg/0.5 mL or 90 mg/mL solution in a single-dose prefilled syringe
- Injection: 45 mg/0.5 mL solution in a single-dose vial

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

----------CONTRAINDICATIONS----------
Clinically significant hypersensitivity to ustekinumab products or to any of the excipients in STARJEMZA. (4)

----------WARNINGS AND PRECAUTIONS----------
- Infections: Serious infections have occurred. Avoid starting STARJEMZA during any clinically important active infection. If a serious infection or clinically significant infection develops, discontinue STARJEMZA 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. Consider diagnostic tests for these infections as dictated by clinical circumstances. (5.2)
- Tuberculosis (TB): Evaluate patients for TB prior to initiating treatment with STARJEMZA. Initiate treatment of latent TB before administering STARJEMZA. (5.3)
- Malignancies: Ustekinumab products may increase risk of malignancy. The safety of ustekinumab products in patients with a history of or a known malignancy has not been evaluated. (5.4)
- Hypersensitivity Reactions: If an anaphylactic or other clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue STARJEMZA. (5.5)
- Posterior Reversible Encephalopathy Syndrome (PRES): If PRES is suspected, treat promptly, and discontinue STARJEMZA. (5.6)
- Immunizations: Avoid use of live vaccines in patients during treatment with STARJEMZA. (5.7)
- Noninfectious Pneumonia: Cases of interstitial pneumonia, eosinophilic pneumonia, and cryptogenic organizing pneumonia have been reported during post-approval use of ustekinumab products. If diagnosis is confirmed, discontinue STARJEMZA and institute appropriate treatment. (5.8)

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

To report SUSPECTED ADVERSE REACTIONS, contact Hikma Pharmaceuticals USA Inc. at 1-877-845-0689 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

* Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product. Biosimilarity of STARJEMZA has been demonstrated for the condition(s) of use (e.g., indication(s), dosing regimen(s)), strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information.

Revised: 05/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Plaque Psoriasis (PsO)

STARJEMZA is indicated for the treatment of adults and pediatric patients 6 years of age and older with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

1.2 Psoriatic Arthritis (PsA)

STARJEMZA is indicated for the treatment of adults and pediatric patients 6 years of age and older with active psoriatic arthritis.

1.3 Crohn's Disease (CD)

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

1.4 Ulcerative Colitis

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage in Plaque Psoriasis

Subcutaneous Adult Dosage Regimen

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

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

Subcutaneous Pediatric Dosage Regimen

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

The recommended dose of STARJEMZA for pediatric patients (6-17 years old) with plaque psoriasis based on body weight is shown below (Table 1).

Table 1: Recommended Dose of STARJEMZA for Subcutaneous Injection in Pediatric Patients (6-17 years old) with Plaque Psoriasis

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

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

Table 2: Injection Volumes of STARJEMZA 45 mg/0.5 mL Single-Dose Vials for Pediatric Patients (6-17 years old) With Plaque Psoriasis and Pediatric Patients (6-17 years old) With Psoriatic Arthritis* Weighing Less Than 60 kg

Body Weight (kg) at the time of dosing	Dose (mg)	Volume of injection (mL)
15	11.3	0.12
16	12.0	0.13
17	12.8	0.14
18	13.5	0.15
19	14.3	0.16
20	15.0	0.17
21	15.8	0.17
22	16.5	0.18
23	17.3	0.19
24	18.0	0.20
25	18.8	0.21
26	19.5	0.22
27	20.3	0.22
28	21.0	0.23
29	21.8	0.24
30	22.5	0.25
31	23.3	0.26
32	24	0.27
33	24.8	0.27
34	25.5	0.28
35	26.3	0.29
36	27	0.3
37	27.8	0.31
38	28.5	0.32
39	29.3	0.32
40	30	0.33
41	30.8	0.34
42	31.5	0.35
43	32.3	0.36
44	33	0.37
45	33.8	0.37
46	34.5	0.38
47	35.3	0.39
48	36	0.4
49	36.8	0.41
50	37.5	0.42
51	38.3	0.42
52	39	0.43
53	39.8	0.44
54	40.5	0.45
55	41.3	0.46
56	42	0.46
57	42.8	0.47
58	43.5	0.48
59	44.3	0.49

* Refer to 2.2 Psoriatic Arthritis; Subcutaneous Pediatric Dosage Regimen.

2.2 Recommended Dosage in Psoriatic Arthritis

Subcutaneous Adult Dosage Regimen

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

Subcutaneous Pediatric Dosage Regimen

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

The recommended dose of STARJEMZA for pediatric patients (6 to 17 years old) with psoriatic arthritis, based on body weight, is shown below (Table 3).

Table 3: Recommended Dose of STARJEMZA for Subcutaneous Injection in Pediatric Patients (6 to 17 years old) with Psoriatic Arthritis

Body Weight of Patient at the Time of Dosing	Recommended Dose
less than 60 kg*	0.75 mg/kg
60 kg or more	45 mg
greater than 100 kg with co-existent moderate-to-severe plaque psoriasis	90 mg

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

2.3 Recommended Dosage in Crohn's Disease and Ulcerative Colitis

Intravenous Induction Adult Dosage Regimen

A single intravenous infusion dose of STARJEMZA using the weight-based dosage regimen specified in Table 4 *[see Instructions for dilution of STARJEMZA 130 mg vial for intravenous infusion (2.6)]*.

Table 4: Initial Intravenous Dosage of STARJEMZA

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

Subcutaneous Maintenance Adult Dosage Regimen

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

2.4 General Considerations for Administration

- STARJEMZA is intended for use under the guidance and supervision of a healthcare provider. STARJEMZA should only be administered to patients who will be closely monitored and have regular follow-up visits with a healthcare provider. The appropriate dose should be determined by a healthcare provider using the patient's current weight at the time of dosing. In pediatric patients, it is recommended that STARJEMZA be administered by a healthcare provider. If a healthcare provider determines that it is appropriate, a patient may self-inject or a caregiver may inject STARJEMZA after proper training in subcutaneous injection technique. Instruct patients to follow the directions provided in the Medication Guide *[see Medication Guide]*.

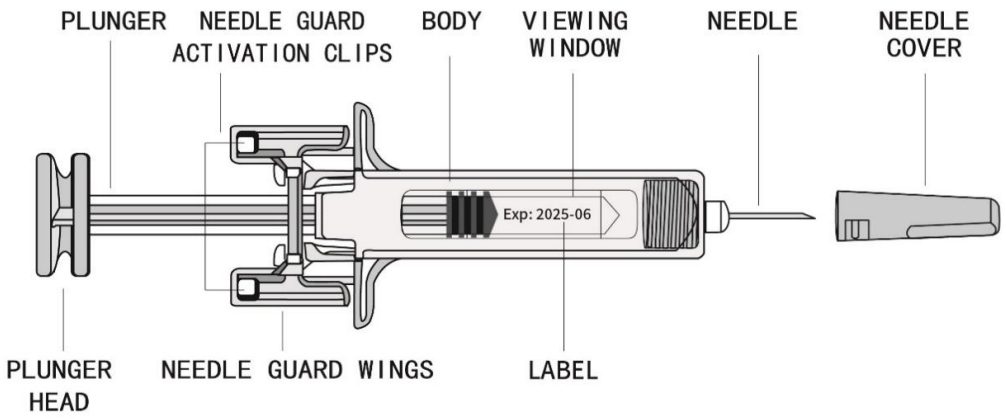
- The needle cover on the prefilled syringe contains dry natural rubber (a derivative of latex). The needle cover should not be handled by persons sensitive to latex.

- It is recommended that each injection be administered at a different anatomic location (such as upper arms, gluteal regions, thighs, or any quadrant of abdomen) than the previous injection, and not into areas where the skin is tender, bruised, erythematous, or indurated. When using the single-dose vial, a 1 mL syringe with a 27 gauge, ½ inch needle is recommended.

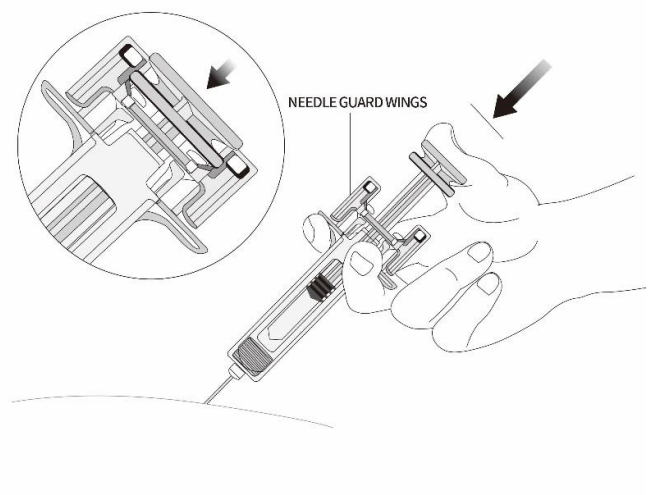
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. STARJEMZA is a clear, colorless to light yellow solution. Do not use STARJEMZA if it is discolored or cloudy, or if other particulate matter is present. STARJEMZA does not contain preservatives; therefore, discard any unused product remaining in the vial and/or syringe.

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

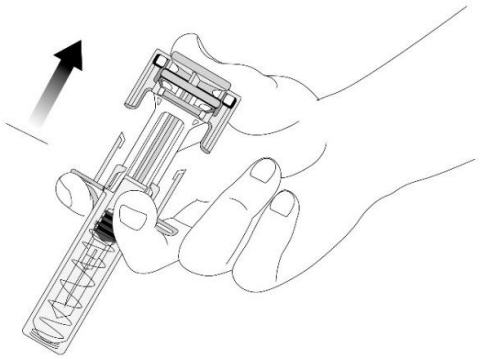
Refer to the diagram below for the provided instructions.



- 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 STARJEMZA subcutaneously as recommended *[see Dosage and Administration (2.1, 2.2, 2.3)]*.
- Inject all of the medication by pushing in the PLUNGER until the PLUNGER HEAD is completely between the needle guard wings. **Injection of the entire prefilled syringe contents is necessary to activate the needle guard**.



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



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

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

STARJEMZA solution for intravenous infusion must be diluted, prepared, and infused by

a healthcare professional using aseptic technique.

1. Calculate the dose and the number of STARJEMZA vials needed based on patient weight (Table 4). Each 26 mL vial of STARJEMZA contains 130 mg of ustekinumab-hmny.

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

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

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

5. Infuse the diluted solution over a period of at least one hour. Once diluted, the infusion should be completely administered within eight hours of the dilution in the infusion bag.

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

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

8. STARJEMZA does not contain preservatives. Each vial is for one-time use in only one patient. Discard any remaining solution. Dispose any unused medicinal product in accordance with local requirements.

Storage

If necessary, the diluted infusion solution may be kept at room temperature up to 25°C (77°F) for up to 7 hours. Storage time at room temperature begins once the diluted solution has been prepared. The infusion should be completed within 8 hours after the dilution in the infusion bag (cumulative time after preparation including the storage and the infusion period). Do not freeze. Discard any unused portion of the infusion solution.

3 DOSAGE FORMS AND STRENGTHS

STARJEMZA™ (ustekinumab-hmny) is a clear, colorless to light yellow solution.

Subcutaneous Injection

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

Intravenous Infusion

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Infections

Ustekinumab products may increase the risk of infections and reactivation of latent infections. Serious bacterial, mycobacterial, fungal, and viral infections were observed in patients receiving ustekinumab products *[see Adverse Reactions (6.1, 6.3)]*.

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

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

Avoid initiating treatment with STARJEMZA in patients with any clinically important active infection until the infection resolves or is adequately treated. Consider the risks and benefits of treatment prior to initiating use of STARJEMZA in patients with a chronic infection or a history of recurrent infection.

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

5.2 Theoretical Risk for Vulnerability to Particular Infections

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

It is not known whether patients with pharmacologic blockade of IL-12/IL-23 from treatment with ustekinumab products may be susceptible to these types of infections. Consider appropriate diagnostic testing, (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 STARJEMZA.

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

5.4 Malignancies

Ustekinumab products are immunosuppressants and may increase the risk of malignancy.

Malignancies were reported among subjects who received ustekinumab in clinical trials *[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 ustekinumab products 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 ustekinumab products who had pre-existing risk factors for developing non-melanoma skin cancer. Monitor all patients receiving STARJEMZA for the appearance of non-melanoma skin cancer. Closely follow patients greater than 60 years of age, those with a medical history of prolonged immunosuppressant therapy and those with a history of PUVA treatment *[see Adverse Reactions (6.1)]*.

5.5 Hypersensitivity Reactions

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

5.6 Posterior Reversible Encephalopathy Syndrome (PRES)

Two cases of posterior reversible encephalopathy syndrome (PRES), also known as Reversible Posterior Leukoencephalopathy Syndrome (RPLS), were reported in clinical trials. Cases have also been reported in postmarketing experience in patients with psoriasis, psoriatic arthritis, and Crohn's disease. Clinical presentation included headaches, seizures, confusion, visual disturbances, and imaging changes consistent with PRES a few days to several months after ustekinumab product initiation. A few cases reported latency of a year or longer. Patients recovered with supportive care following withdrawal of ustekinumab products.

Monitor all patients treated with STARJEMZA for signs and symptoms of PRES. If PRES is suspected, promptly administer appropriate treatment and discontinue STARJEMZA.

5.7 Immunizations

Prior to initiating therapy with STARJEMZA, patients should receive all age-appropriate immunizations as recommended by current immunization guidelines. Patients being treated with STARJEMZA should avoid receiving live vaccines. Avoid administering BCG vaccines during treatment with STARJEMZA 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 STARJEMZA because of the potential risk for shedding from the household contact and transmission to patient.

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

5.8 Noninfectious Pneumonia

Cases of interstitial pneumonia, eosinophilic pneumonia, and cryptogenic organizing pneumonia have been reported during post-approval use of ustekinumab products. Clinical presentations included cough, dyspnea, and interstitial infiltrates following one to three doses. Serious outcomes have included respiratory failure and prolonged hospitalization. Patients improved with

discontinuation of therapy and in certain cases administration of corticosteroids. If diagnosis is confirmed, discontinue STARJEMZA and institute appropriate treatment *[see Postmarketing Experience (6.3)]*.

6 ADVERSE REACTIONS

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

- Infections *[see Warnings and Precautions (5.1)]*
- Malignancies *[see Warnings and Precautions (5.4)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.5)]*
- Posterior Reversible Encephalopathy Syndrome (PRES) *[see Warnings and Precautions (5.6)]*
- Noninfectious Pneumonia *[see Warnings and Precautions (5.8)]*

6.1 Clinical Trials Experience

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

Adult Subjects with Plaque Psoriasis

The safety data reflect exposure to ustekinumab in 3117 adult subjects with plaque psoriasis, 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 5 summarizes the adverse reactions that occurred at a rate of at least 1% with higher rates in the ustekinumab groups during the placebo-controlled period of Ps STUDY 1 and Ps STUDY 2 *[see Clinical Studies (14)]*.

Table 5: Adverse Reactions, Reported by ≥1% of Subjects with Plaque Psoriasis and at Higher Rates in the Ustekinumab groups through Week 12 in Ps STUDY 1 and Ps STUDY 2

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

Adverse reactions that occurred at rates less than 1% in the controlled period of Ps STUDIES 1 and 2 through week 12 included: cellulitis, herpes zoster, diverticulitis, and certain injection site

reactions (pain, swelling, pruritus, induration, hemorrhage, bruising, and irritation).

One case of PRES occurred during adult plaque psoriasis clinical trials *[see Warnings and Precautions (5.6)]*.

Infections

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

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

Malignancies

In the controlled and non-controlled portions of plaque psoriasis clinical trials (median follow-up of 3.2 years, representing 8998 patient-years of exposure), 1.7% of ustekinumab-treated subjects reported malignancies excluding non-melanoma skin cancers (0.60 per hundred patient-years of follow-up). Non-melanoma skin cancer was reported in 1.5% of ustekinumab-treated subjects (0.52 per hundred patient-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 ustekinumab-treated subjects during the controlled and uncontrolled portions of trials 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]

Pediatric Subjects with Plaque Psoriasis

The safety of ustekinumab was assessed in two trials of pediatric subjects with moderate to severe plaque psoriasis. Ps STUDY 3 evaluated safety for up to 60 weeks in 110 pediatric subjects 12 to 17 years old. Ps STUDY 4 evaluated safety for up to 56 weeks in 44 pediatric subjects 6 to 11 years old. The safety profile in pediatric subjects was similar to the safety profile from trials in adults with plaque psoriasis.

Psoriatic Arthritis

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

Crohn’s Disease

The safety of ustekinumab was assessed in 1407 subjects with moderately to severely active

Crohn's disease (Crohn's Disease Activity Index [CDAI] greater than or equal to 220 and less than or equal to 450) in three randomized, double-blind, placebo-controlled, parallel-group, multicenter trials. These 1407 subjects included 40 subjects who received a prior investigational intravenous ustekinumab formulation but were not included in the efficacy analyses. In trials CD-1 and CD-2 there were 470 subjects who received ustekinumab 6 mg/kg as a weight-based single intravenous induction dose and 466 who received placebo *[see Dosage and Administration (2.3)]*. Subjects who were responders in either trial CD-1 or CD-2 were randomized to receive a subcutaneous maintenance regimen of either 90 mg ustekinumab every 8 weeks, or placebo for 44 weeks in trial CD-3. Subjects in these 3 trials may have received other concomitant therapies including aminosalicylates, immunomodulatory agents [azathioprine (AZA), 6-mercaptopurine (6-MP), methotrexate (MTX)], oral corticosteroids (prednisone or budesonide), and/or antibiotics for their Crohn's disease *[see Clinical Studies (14.4)]*.

The overall safety profile of ustekinumab was consistent with the safety profile seen in the adult psoriasis and psoriatic arthritis clinical trials. Common adverse reactions in trials CD-1 and CD-2 and in trial CD-3 are listed in Tables 6 and 7, respectively.

Table 6: Common Adverse Reactions Through Week 8 in Trials CD-1 and CD-2 Occurring in ≥3% of Ustekinumab-Treated Subjects and Higher Than Placebo

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

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

Table 7: Common Adverse Reactions Through Week 44 in Trial CD-3 Occurring in ≥3% of Ustekinumab-Treated Subjects and Higher Than Placebo

	Placebo N=133	**Ustekinumab 90 mg subcutaneous maintenance dose every 8 weeks N=131**
Nasopharyngitis	8%	11%
Injection site erythema	0	5%
Vulvovaginal candidiasis/mycotic infection	1%	5%
Bronchitis	3%	5%
Pruritus	2%	4%
Urinary tract infection	2%	4%
Sinusitis	2%	3%

Infections

In subjects with Crohn's disease, serious or other clinically significant infections included anal abscess, gastroenteritis, and pneumonia. In addition, listeria meningitis and ophthalmic herpes zoster were reported in one patient each *[see Warnings and Precautions (5.1)]*.

Malignancies

With up to one year of treatment in the Crohn's disease clinical trials, 0.2% of ustekinumab-treated subjects (0.36 events per hundred patient-years) and 0.2% of placebo-treated subjects (0.58 events per hundred patient-years) developed non-melanoma skin cancer. Malignancies other

than non-melanoma skin cancers occurred in 0.2% of ustekinumab-treated subjects (0.27 events per hundred patient-years) and in none of the placebo-treated subjects.

Hypersensitivity Reactions Including Anaphylaxis

In CD trials, two subjects reported hypersensitivity reactions following ustekinumab administration. One patient experienced signs and symptoms consistent with anaphylaxis (tightness of the throat, shortness of breath, and flushing) after a single subcutaneous administration (0.1% of subjects receiving subcutaneous ustekinumab). In addition, one subject experienced signs and symptoms consistent with or related to a hypersensitivity reaction (chest discomfort, flushing, urticaria, and increased body temperature) after the initial intravenous ustekinumab dose (0.08% of subjects receiving intravenous ustekinumab). These subjects were treated with oral antihistamines or corticosteroids and in both cases symptoms resolved within an hour.

Ulcerative Colitis

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

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

Infections

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

Malignancies

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

6.2 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of ustekinumab or of other ustekinumab products.

Approximately 6 to 12.4% of subjects treated with ustekinumab in plaque psoriasis and psoriatic arthritis clinical trials developed antibodies to ustekinumab, which were generally low-titer. In

plaque psoriasis clinical trials, antibodies to ustekinumab were associated with reduced or undetectable serum ustekinumab concentrations and reduced efficacy. In plaque psoriasis trials, the majority of subjects who were positive for antibodies to ustekinumab had neutralizing antibodies.

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

6.3 Postmarketing Experience

The following adverse reactions have been reported during post-approval use of ustekinumab products. 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 ustekinumab product exposure.

Immune system disorders: Serious hypersensitivity reactions (including anaphylaxis and angioedema), other hypersensitivity reactions (including rash and urticaria).

Infections and infestations: Lower respiratory tract infection (including opportunistic fungal infections and tuberculosis).

Neurological disorders: Posterior Reversible Encephalopathy Syndrome (PRES).

Respiratory, thoracic, and mediastinal disorders: Interstitial pneumonia, eosinophilic pneumonia, and cryptogenic organizing pneumonia.

Skin reactions: Pustular psoriasis, erythrodermic psoriasis, hypersensitivity vasculitis.

7 DRUG INTERACTIONS

7.1 Concomitant Therapies

In plaque psoriasis trials the safety of ustekinumab products in combination with immunosuppressive agents or phototherapy has not been evaluated. In psoriatic arthritis trials, concomitant MTX use did not appear to influence the safety or efficacy of ustekinumab. In Crohn's disease and ulcerative colitis induction trials, immunomodulators (6-MP, AZA, MTX) were used concomitantly in approximately 30% of subjects and corticosteroids were used concomitantly in approximately 40% and 50% of Crohn's disease and ulcerative colitis subjects, respectively. Use of these concomitant therapies did not appear to influence the overall safety or efficacy of ustekinumab.

7.2 CYP450 Substrates

The formation of CYP450 enzymes can be suppressed by increased levels of certain cytokines (e.g., IL-1, IL-6, TNFα, IFN) during chronic inflammation. Thus, use of ustekinumab products, antagonists of IL-12 and IL-23, could normalize the formation of CYP450 enzymes. Upon initiation or discontinuation of STARJEMZA in patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index, consider monitoring for therapeutic effect or drug concentration and adjust the individual dosage of the CYP substrate as needed. See the prescribing information of specific CYP substrates.

A CYP-mediated drug interaction effect was not observed in subjects with Crohn's disease *[see*

Clinical Pharmacology (12.3)].

7.3 Allergen Immunotherapy

Ustekinumab products have not been evaluated in patients who have undergone allergy immunotherapy. Ustekinumab products 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

Risk Summary

Limited data from observational studies, published case reports, and postmarketing surveillance on the use of ustekinumab products during pregnancy are insufficient to inform a drug associated risk of major birth defects, miscarriage, and other adverse maternal or fetal outcomes. Transport of human IgG antibody across the placenta increases as pregnancy progresses and peaks during the third trimester; therefore, ustekinumab products may be transferred to the developing fetus *[see Clinical Considerations]*. In animal reproductive and developmental toxicity studies, no adverse developmental effects were observed in offspring after administration of ustekinumab to pregnant monkeys at exposures greater than 100 times the maximum recommended human dose (MRHD).

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

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Because ustekinumab products may theoretically interfere with immune response to infections, consider risks and benefits prior to administering live vaccines to infants exposed to STARJEMZA *in utero*. There are insufficient data regarding exposed infant serum levels of ustekinumab products at birth and the duration of persistence of ustekinumab products in infant serum after birth. Although a specific timeframe to delay administration of live attenuated vaccines in infants exposed *in utero* is unknown, consider the risks and benefits of delaying a minimum of 6 months after birth because of the clearance of the product.

Data

Animal Data

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

In a combined embryo-fetal development and pre- and post-natal development toxicity study,

pregnant cynomolgus monkeys were administered subcutaneous doses of ustekinumab twice weekly at exposures greater than 100 times the MRHD from the beginning of organogenesis to Day 33 after delivery. Neonatal deaths occurred in the offspring of one monkey administered ustekinumab at 22.5 mg/kg and one monkey dosed at 45 mg/kg. No ustekinumab-related- effects on functional, morphological, or immunological development were observed in the neonates from birth through six months of age.

8.2 Lactation

Risk Summary

Limited data from published literature suggests that ustekinumab is present in human breast milk. There are no available data on the effects of ustekinumab products on milk production. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed infant to ustekinumab products are unknown. No adverse effects on the breastfed infant causally related to ustekinumab products have been identified in the published literature or postmarketing experience.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for STARJEMZA and any potential adverse effects on the breastfed child from STARJEMZA or from the underlying maternal condition.

8.4 Pediatric Use

Plaque Psoriasis

The safety and effectiveness of STARJEMZA have been established for the treatment of moderate to severe plaque psoriasis in pediatric patients 6 to 17 years of age who are candidates for phototherapy or systemic therapy.

Use of STARJEMZA in pediatric patients 12 to less than 17 years of age is supported by evidence from a multicenter, randomized, 60-week trial (Ps STUDY 3) of ustekinumab that included a 12-week, double-blind, placebo-controlled, parallel group portion, in 110 pediatric subjects 12 years of age and older *[see Adverse Reactions (6.1), Clinical Studies (14.2)]*.

Use of STARJEMZA in pediatric patients 6 to 11 years of age is supported by evidence from an open-label, single-arm, efficacy, safety, and pharmacokinetics trial (Ps STUDY 4) of ustekinumab in 44 subjects *[see Adverse Reactions (6.1), Pharmacokinetics (12.3)]*.

The safety and effectiveness of STARJEMZA have not been established in pediatric patients less than 6 years of age with plaque psoriasis.

Psoriatic Arthritis

The safety and effectiveness of STARJEMZA have been established for treatment of psoriatic arthritis in pediatric patients 6 to 17 years old.

Use of STARJEMZA in these age groups is supported by evidence from adequate and well controlled trials of ustekinumab in adults with psoriasis and PsA, pharmacokinetic data from adult subjects with psoriasis, adult subjects with PsA and pediatric subjects with psoriasis, and safety data of ustekinumab from two clinical trials in 44 pediatric subjects 6 to 11 years old with psoriasis and 110 pediatric subjects 12 to 17 years old with psoriasis. The observed pre-dose (trough) concentrations are generally comparable between adult subjects with psoriasis, adult subjects with PsA and pediatric subjects with psoriasis, and the PK exposure is expected to be comparable between adult and pediatric subjects with PsA *[see Adverse Reactions (6.1), Clinical*

Pharmacology (12.3), and Clinical Studies (14.1, 14.2, 14.3)].

The safety and effectiveness of STARJEMZA have not been established in pediatric patients less than 6 years old with psoriatic arthritis.

Crohn's Disease and Ulcerative Colitis

The safety and effectiveness of STARJEMZA have not been established in pediatric patients with Crohn's disease or ulcerative colitis.

8.5 Geriatric Use

Of the 6709 subjects exposed to ustekinumab, a total of 340 were 65 years of age or older (183 subjects with plaque psoriasis, 65 subjects with psoriatic arthritis, 58 subjects with Crohn's disease, and 34 subjects with ulcerative colitis), and 40 subjects were 75 years of age or older. Clinical trials of ustekinumab did not include sufficient numbers of subjects 65 years of age and older to determine whether they respond differently from younger adult subjects.

10 OVERDOSAGE

Single doses up to 6 mg/kg intravenously have been administered in clinical trials without dose-limiting toxicity. In case of overdosage, monitor the patient for any signs or symptoms of adverse reactions or effects and institute appropriate symptomatic treatment immediately. Consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdose management recommendations.

11 DESCRIPTION

Ustekinumab-hmny, a human IgG1κ monoclonal antibody, is a human interleukin-12 and -23 antagonist. Using DNA recombinant technology, ustekinumab-hmny is produced in a Chinese hamster ovary cell line (CHO-BAT). The manufacturing process contains steps for the clearance of viruses. Ustekinumab-hmny is comprised of 1326 amino acids and has an estimated molecular mass of approximately 145,000 Daltons (the polypeptide part only).

STARJEMZA™ (ustekinumab-hmny) injection is a sterile, preservative-free, clear, colorless to light yellow solution with pH of 5.7-6.3.

STARJEMZA for Subcutaneous Use

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

Each 0.5 mL prefilled syringe or vial delivers 45 mg ustekinumab-hmny, histidine (0.265 mg), L-histidine hydrochloride monohydrate (0.685 mg), polysorbate 80 (0.05 mg), and sucrose (38 mg).

Each 1 mL prefilled syringe delivers 90 mg ustekinumab-hmny, histidine (0.53 mg), L-histidine hydrochloride monohydrate (1.37 mg), polysorbate 80 (0.1 mg), and sucrose (76 mg).

STARJEMZA for Intravenous Infusion

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

Each 26 mL vial delivers 130 mg ustekinumab-hmny, edetate disodium (0.52 mg), histidine (20 mg), L-histidine hydrochloride monohydrate (27 mg), methionine (10.4 mg), polysorbate 80 (10.4 mg), and sucrose (2210 mg).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

Plaque Psoriasis

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

Ulcerative Colitis

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

12.3 Pharmacokinetics

Absorption

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

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

Following the recommended intravenous induction dose, mean ±SD peak serum ustekinumab concentration was 125.2 ± 33.6 mcg/mL in subjects with Crohn's disease, and 129.1 ± 27.6 mcg/mL in subjects with ulcerative colitis. Starting at Week 8, the recommended

subcutaneous maintenance dosing of 90 mg ustekinumab was administered every 8 weeks. Steady state ustekinumab concentration was achieved by the start of the second maintenance dose. There was no apparent accumulation in ustekinumab concentration over time when given subcutaneously every 8 weeks. Mean ±SD steady-state trough concentration was 2.5 ± 2.1 mcg/mL in subjects with Crohn's disease, and 3.3 ± 2.3 mcg/mL in subjects with ulcerative colitis for 90 mg ustekinumab administered every 8 weeks.

Distribution

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

Elimination

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

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

Metabolism

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

Specific Populations

Weight

When given the same dose, subjects with plaque psoriasis or psoriatic arthritis weighing more than 100 kg had lower median serum ustekinumab concentrations compared with those subjects weighing 100 kg or less. The median trough serum concentrations of ustekinumab in subjects of higher weight (greater than 100 kg) in the 90 mg group were comparable to those in subjects of lower weight (100 kg or less) in the 45 mg group.

Age: Geriatric Population

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

Age: Pediatric Population

Following multiple recommended doses of ustekinumab in pediatric subjects 6 to 17 years of age with plaque psoriasis, steady-state serum concentrations of ustekinumab were achieved by Week 28. At Week 28, the mean ±SD steady-state trough serum ustekinumab concentrations were 0.36 ± 0.26 mcg/mL and 0.54 ± 0.43 mcg/mL, respectively, in pediatric subjects 6 to 11 years of

age and pediatric subjects 12 to 17 years of age.

Overall, the observed steady-state ustekinumab trough concentrations in pediatric subjects with plaque psoriasis were within the range of those observed for adult subjects with plaque psoriasis and adult subjects with PsA after administration of ustekinumab.

Drug Interaction Studies

The effects of IL-12 or IL-23 on the regulation of CYP450 enzymes were evaluated in an *in vitro* study using human hepatocytes, which showed that IL-12 and/or IL-23 at levels of 10 ng/mL did not alter human CYP450 enzyme activities (CYP1A2, 2B6, 2C9, 2C19, 2D6, or 3A4).

No clinically significant changes in exposure of caffeine (CYP1A2 substrate), warfarin (CYP2C9 substrate), omeprazole (CYP2C19 substrate), dextromethorphan (CYP2D6 substrate), or midazolam (CYP3A substrate) were observed when used concomitantly with ustekinumab at the approved recommended dosage in subjects with Crohn's disease *[see Drug Interactions (7.2)]*.

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

No effects on fertility were observed in male cynomolgus monkeys that were administered ustekinumab at subcutaneous doses up to 45 mg/kg twice weekly (45 times the MRHD on a mg/kg basis) prior to and during the mating period. However, fertility and pregnancy outcomes were not evaluated in mated females.

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

13.2 Animal Toxicology and/or Pharmacology

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

14 CLINICAL STUDIES

14.1 Adult Plaque Psoriasis

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

Ps STUDY 1 enrolled 766 subjects and Ps STUDY 2 enrolled 1230 subjects. The trials had the same design through Week 28. In both trials, subjects were randomized in equal proportion to placebo, 45 mg or 90 mg of ustekinumab. Subjects randomized to ustekinumab 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 ustekinumab (either 45 mg or 90 mg) at Weeks 12 and 16.

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

In both trials, 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.

Clinical Response

The results of Ps STUDY 1 and Ps STUDY 2 are presented in Table 8 below.

Table 8: Clinical Outcomes at Week 12 in Adults with Plaque Psoriasis in Ps STUDY 1 and Ps STUDY 2

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

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

In subjects who weighed 100 kg or less, response rates were comparable with both the 45 mg and 90 mg doses; however, in subjects who weighed greater than 100 kg, higher response rates were seen with 90 mg dosing compared with 45 mg dosing (Table 9 below).

Table 9: Clinical Outcomes by Weight at Week 12 in Adults with Plaque Psoriasis in Ps STUDY 1 and Ps STUDY 2

	Ps STUDY 1			Ps STUDY 2		
		Ustekinumab			Ustekinumab	
	Placebo	45 mg	90 mg	Placebo	45 mg	90 mg
Subjects randomized	**255**	**255**	**256**	**410**	**409**	**411**
PASI 75 response*						

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

* Subjects were dosed with trial medication at Weeks 0 and 4.

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

14.2 Pediatric Plaque Psoriasis

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

Subjects were randomized to receive placebo (n = 37), the recommended dose of ustekinumab (n = 36), or one-half the recommended dose of ustekinumab (n = 37) by subcutaneous injection at Weeks 0 and 4 followed by dosing every 12 weeks (q12w). The recommended dose of ustekinumab was 0.75 mg/kg for subjects weighing less than 60 kg, 45 mg for subjects weighing 60 kg to 100 kg, and 90 mg for subjects weighing greater than 100 kg. At Week 12, subjects who received placebo were crossed over to receive ustekinumab at the recommended dose or one-half the recommended dose.

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

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

Clinical Response

The efficacy results at Week 12 for Ps STUDY 3 are presented in Table 10.

Table 10: Efficacy Results at Week 12 in Pediatric Subjects 12 to 17 years with Plaque Psoriasis in Ps STUDY 3

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

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

14.3 Psoriatic Arthritis

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

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

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

Clinical Response

In both trials, a greater proportion of subjects achieved ACR 20, ACR 50 and PASI 75 response in the ustekinumab 45 mg and 90 mg groups compared to placebo at Week 24 (see Table 11). ACR 70 responses were also higher in the ustekinumab 45 mg and 90 mg groups, although the difference was only numerical (p=NS) in STUDY 2. Responses were consistent in subjects treated with ustekinumab alone or in combination with methotrexate. Responses were similar in subjects regardless of prior TNFα exposure.

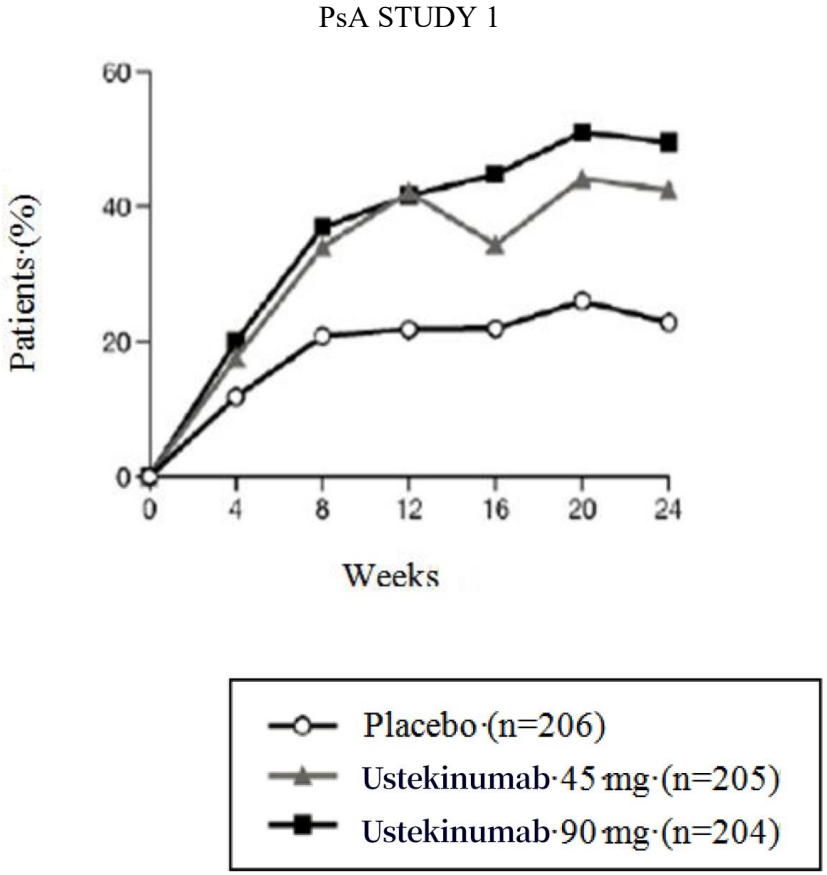
Table 11: ACR 20, ACR 50, ACR 70 and PASI 75 responses in PsA STUDY 1 and PsA STUDY 2 at Week 24

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

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

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

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



The results of the components of the ACR response criteria are shown in Table 12.

Table 12: Mean change from baseline in ACR components at Week 24

	PsA STUDY 1		
		Ustekinumab	
	Placebo (N = 206)	45 mg (N = 205)	90 mg (N = 204)
Number of swollen joints[a]			
Baseline	15	12	13
Mean Change at Week 24	-3	-5	-6
Number of tender joints[b]			
Baseline	25	22	23
Mean Change at Week 24	-4	-8	-9
Subject's assessment of pain[c]			
Baseline	6.1	6.2	6.6
Mean Change at Week 24	-0.5	-2.0	-2.6
Subject global assessment[c]			
Baseline	6.1	6.3	6.4
Mean Change at Week 24	-0.5	-2.0	-2.5
Physician global assessment[c]			
Baseline	5.8	5.7	6.1

Mean Change at Week 24	-1.4	-2.6	-3.1
Disability index (HAQ)[d]			
Baseline	1.2	1.2	1.2
Mean Change at Week 24	-0.1	-0.3	-0.4
CRP (mg/dL)[e]			
Baseline	1.6	1.7	1.8
Mean Change at Week 24	0.01	-0.5	-0.8

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

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

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

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

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

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

Physical Function

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

14.4 Crohn's Disease

Ustekinumab was evaluated in three randomized, double-blind, placebo-controlled clinical trials in adult subjects with moderately to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] score of 220 to 450). There were two 8-week intravenous induction trials (CD-1 and CD-2) followed by a 44-week subcutaneous randomized withdrawal maintenance trial (CD-3) representing 52 weeks of therapy. Subjects in CD-1 had failed or were intolerant to treatment with one or more TNF blockers, while subjects in CD-2 had failed or were intolerant to treatment with immunomodulators or corticosteroids, but never failed treatment with a TNF blocker.

Trials CD-1 and CD-2

In trials CD-1 and CD-2, 1409 subjects were randomized, of whom 1368 (CD-1, n=741; CD-2, n=627) were included in the final efficacy analysis. Induction of clinical response (defined as a reduction in CDAI score of greater than or equal to 100 points or CDAI score of less than 150) at Week 6 and clinical remission (defined as a CDAI score of less than 150) at Week 8 were evaluated. In both trials, subjects were randomized to receive a single intravenous administration of ustekinumab at either approximately 6 mg/kg, placebo (see Table 4), or 130 mg (a lower dose than recommended).

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

In trial CD-2, subjects had failed or were intolerant to prior treatment with corticosteroids (81% of

subjects), at least one immunomodulator (6-MP, AZA, MTX; 68% of subjects), or both (49% of subjects). Additionally, 69% never received a TNF blocker and 31% previously received but had not failed a TNF blocker. At baseline, and throughout the trial, approximately 39% of the subjects were receiving corticosteroids and 35% of the subjects were receiving immunomodulators (AZA, 6-MP, MTX). The median baseline CDAI score was 286 in the ustekinumab and 290 in the placebo group.

In these induction trials, a greater proportion of subjects treated with ustekinumab (at the recommended dose of approximately 6 mg/kg dose) achieved clinical response at Week 6 and clinical remission at Week 8 compared to placebo (see Table 13 for clinical response and remission rates). Clinical response and remission were significant as early as Week 3 in ustekinumab-treated subjects and continued to improve through Week 8.

Table 13: Induction of Clinical Response and Remission in CD-1[*] and CD-2[**]

	CD-1 n = 741			CD-2 n = 627		
	Placebo N = 247	**Ustekinumab[†] N = 249**	**Treatment difference and 95% CI**	**Placebo N = 209**	**Ustekinumab[†] N = 209**	**Treatment difference and 95% CI**
Clinical Response (100 point), Week 6	53 (21%)	84 (34%)[a]	12% (4%, 20%)	60 (29%)	116 (56%)[b]	27% (18%, 36%)
Clinical Remission, Week 8	18 (7%)	52 (21%)[b]	14% (8%, 20%)	41 (20%)	84 (40%)[b]	21% (12%, 29%)
Clinical Response (100 point), Week 8	50 (20%)	94 (38%)[b]	18% (10%, 25%)	67 (32%)	121 (58%)[b]	26% (17%, 35%)
70 Point Response, Week 6	75 (30%)	109 (44%)[a]	13% (5%, 22%)	81 (39%)	135 (65%)[b]	26% (17%, 35%)
70 Point Response, Week 3	67 (27%)	101 (41%)[a]	13% (5%, 22%)	66 (32%)	106 (51%)[b]	19% (10%, 28%)

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

[*] Patient population consisted of subjects who failed or were intolerant to TNF blocker therapy

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

[†] Infusion dose of ustekinumab using the weight-based dosage regimen specified in Table 4.

[a] $0.001 \leq p < 0.01$

[b] $p < 0.001$

Trial CD-3

The maintenance trial (CD-3) evaluated 388 subjects who achieved clinical response (≥100 point reduction in CDAI score) at Week 8 with either induction dose of ustekinumab in trials CD-1 or CD-2. Subjects were randomized to receive a subcutaneous maintenance regimen of either 90 mg ustekinumab every 8 weeks or placebo for 44 weeks (see Table 14).

Table 14: Clinical Response and Remission in CD-3 (Week 44; 52 weeks from initiation of the induction dose)

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

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

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

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

† Subjects who achieved clinical response to ustekinumab at the end of the induction trial.

[a] $p < 0.01$

[b] $0.01 \leq p < 0.05$

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

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

At Week 0 of trial CD-3, 46/72 (64%) ustekinumab-treated subjects who had previously failed immunomodulator therapy or corticosteroids (but not TNF blockers) were in clinical remission and 45/72 (63%) of these subjects were in clinical remission at Week 44. In the placebo arm, 50/70 (71%) of these subjects were in clinical remission at Week 0 while 31/70 (44%) were in remission at Week 44. In the subset of these subjects who were also naïve to TNF blockers, 34/52 (65%) of ustekinumab-treated subjects were in clinical remission at Week 44 as compared to 25/51 (49%) in the placebo arm.

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

14.5 Ulcerative Colitis

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

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

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

Trial UC-1

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

The primary endpoint was clinical remission at Week 8. Clinical remission with a definition of: Mayo stool frequency subscore of 0 or 1, Mayo rectal bleeding subscore of 0 (no rectal bleeding), and Mayo endoscopy subscore of 0 or 1 (Mayo endoscopy subscore of 0 defined as normal or inactive disease and Mayo subscore of 1 defined as presence of erythema, decreased vascular pattern and no friability) is provided in Table 15.

The secondary endpoints were clinical response, endoscopic improvement, and histologic-endoscopic mucosal improvement. Clinical response with a definition of (≥ 2 points and ≥ 30% decrease in modified Mayo score, defined as 3-component Mayo score without the Physician's Global Assessment, with either a decrease from baseline in the rectal bleeding subscore ≥1 or a rectal bleeding subscore of 0 or 1), endoscopic improvement with a definition of Mayo endoscopy subscore of 0 or 1, and histologic-endoscopic mucosal improvement with a definition of combined endoscopic improvement and histologic improvement of the colon tissue [neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue] are provided in Table 15.

In UC-1, a significantly greater proportion of subjects treated with ustekinumab (at the recommended dose of approximately 6 mg/kg dose) were in clinical remission and response and achieved endoscopic improvement and histologic-endoscopic mucosal improvement compared to placebo (see Table 15).

Table 15: Proportion of Subjects Meeting Efficacy Endpoints at Week 8 in UC-1

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

† Infusion dose of ustekinumab using the weight-based dosage regimen specified in Table 4.

ǂ An additional 7 subjects on placebo and 9 subjects on ustekinumab (6 mg/kg) had been exposed to, but had not failed, biologics.

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

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

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

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

[a] Adjusted treatment difference (97.5% CI)

[b] $p < 0.001$

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

Rectal Bleeding and Stool Frequency Subscores

Decreases in rectal bleeding and stool frequency subscores were observed as early as Week 2 in ustekinumab-treated subjects.

Trial UC-2

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

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

Results of the primary and secondary endpoints at Week 44 in subjects treated with ustekinumab at the recommended dosage (90 mg every 8 weeks) compared to the placebo are shown in Table 16.

Table 16: Efficacy Endpoints of Maintenance at Week 44 in UC-2 (52 Weeks from Initiation of the Induction Dose)

Endpoint	**Placebo* N = 175†**		**90 mg Ustekinumab every 8 weeks N = 176**		**Treatment difference and 95% CI**
	N	**%**	**N**	**%**	
Clinical Remission**	**46**	**26%**	**79**	**45%**	19% (9%, 28%) [a]
Bio-naïveǂ	30/84	36%	39/79	49%	
Prior biologic failure	16/88	18%	37/91	41%	
Maintenance of Clinical	**84**	**48%**	**130**	**74%**	26%

Response at Week 44†					(16%, 36%) [a]
Bio-naïve‡	49/84	58%	62/79	78%	
Prior biologic failure	35/88	40%	64/91	70%	
Endoscopic Improvement§	**47**	**27%**	**83**	**47%**	20% (11%, 30%) [a]
Bio-naïve‡	29/84	35%	42/79	53%	
Prior biologic failure	18/88	20%	38/91	42%	
Corticosteroid-free Clinical Remission‡	**45**	**26%**	**76**	**43%**	17% (8%, 27%) a
Bio-naïve‡	30/84	36%	38/79	48%	
Prior biologic failure	15/88	17%	35/91	38%	
Maintenance of Clinical Remission at Week 44 in subjects who achieved clinical remission 8 weeks after induction	**18/50**	**36%**	**27/41**	**66%**	31% (12%, 50%) b
Bio-naïve‡	12/27	44%	14/20	70%	
Prior biologic failure	6/23	26%	12/18	67%	

‡ An additional 3 subjects on placebo and 6 subjects on ustekinumab had been exposed to, but had not failed, biologics.

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

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

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

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

‡ Corticosteroid-free clinical remission was defined as subjects in clinical remission and not receiving corticosteroids at Week 44.

a p =<0.001

b p=0.004

Other Endpoints

Week 16 Responders to Ustekinumab Induction

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

Histologic-Endoscopic Mucosal Improvement at Week 44

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

Endoscopic Normalization

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

15 REFERENCES

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

16 HOW SUPPLIED/STORAGE AND HANDLING

STARJEMZA™ (ustekinumab-hmny) injection is a sterile, preservative-free, clear, colorless to light yellow solution. It is supplied as individually packaged, single-dose prefilled syringes or single-dose vials.

For Subcutaneous Use

Prefilled Syringes

- 45 mg/0.5 mL (NDC 0143-9168-01)
- 90 mg/mL (NDC 0143-9170-01)

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

Single-dose Vial

- 45 mg/0.5 mL (NDC 0143-9169-01)

For Intravenous Infusion

Single-dose Vial

- 130 mg/26 mL (5 mg/mL) (NDC 0143-9171-01)

Storage and Stability

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

If needed, individual prefilled syringe may be stored at room temperature up to 30°C (86°F) for a maximum single period of up to 30 days in the original carton to protect from light. Record the date when the prefilled syringe is first removed from the refrigerator on the carton in the space provided. Discard the prefilled syringe if not used within 30 days at room temperature storage. An individual 45 mg vial may be stored at room temperature, up to 25°C (77°F), out of the original carton for up to 8 hours. After filling STARJEMZA into the syringe with attached needle, the filled syringe with needle can be stored at up to 25°C (77°F) for up to 4 hours before injection. Once the prefilled syringe or the 45 mg vial has been stored at room temperature, do not return it to the refrigerator. Do not use STARJEMZA after the expiration date on the carton or on the prefilled syringe or on the 45 mg vial.

17 PATIENT COUNSELING INFORMATION

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

Infections

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

Malignancies

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

Hypersensitivity Reactions

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

Posterior Reversible Encephalopathy Syndrome (PRES)

Inform patients to immediately contact their healthcare provider if they experience signs and symptoms of PRES (which may include headache, seizures, confusion, or visual disturbances) *[see Warnings and Precautions (5.6)]*.

Immunizations

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

Administration

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

Manufactured by:
Bio-Thera Solutions, Ltd.
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Guangzhou, Guangdong, China 511356

Distributed by:
Hikma Pharmaceuticals USA Inc.
Berkeley Heights, NJ 07922

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