

## PRODUCT MONOGRAPH

Pr **STELARA™\***

ustekinumab Injection

Sterile Solution

45 mg/0.5 mL  
90 mg/1.0 mL<sup>†</sup>

Selective Immunomodulating Agent

STELARA™ (ustekinumab) should be used only by physicians who have sufficient knowledge of plaque psoriasis and who have fully familiarized themselves with the efficacy/safety profile of the drug.

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**PART I: HEALTH PROFESSIONAL INFORMATION**

**SUMMARY PRODUCT INFORMATION**

| <b>Route of Administration</b> | <b>Dosage Form / Strength</b>  | <b>Clinically Relevant Nonmedicinal Ingredients</b>  |
|--------------------------------|--|--|
| Subcutaneous Injection         | Sterile solution in single-use pre-filled syringe:<br>45 mg / 0.5 mL,<br>90 mg/1.0 mL <sup>†</sup> | None<br><i>For a complete listing see Dosage Forms, Composition and Packaging section.</i> |

<sup>†</sup>90mg/1.0 mL not available in Canada

**DESCRIPTION**

STELARA™ (ustekinumab) is a fully human IgG1κ monoclonal antibody with an approximate molecular weight of 148,600 daltons. STELARA™ (ustekinumab) is produced by a recombinant cell line cultured by continuous perfusion and is purified by a series of steps that includes measures to inactivate and remove viruses.

STELARA™ does not contain preservatives. STELARA™ contains 90 mg ustekinumab per mL.

STELARA™ is supplied as a single-use, sterile solution in a glass syringe with a fixed 27G, half-inch needle and needle cover. The needle cover is manufactured using a dry natural rubber (a derivative of latex) (see **WARNINGS AND PRECAUTIONS, Hypersensitivity Reactions**). The syringe is fitted with a passive safety guard.

## INDICATIONS AND CLINICAL USE

STELARA™ (ustekinumab) is indicated in adult patients for the treatment of chronic moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

## CONTRAINDICATIONS

- Patients with known hypersensitivity to STELARA™ or any of its components.
- Patients with severe infections such as sepsis, tuberculosis and opportunistic infections (see **WARNINGS AND PRECAUTIONS, Infections**).

## WARNINGS AND PRECAUTIONS

### **Carcinogenesis and Mutagenesis**

STELARA™ (ustekinumab) is a selective immunomodulator. Immunomodulating agents have the potential to increase the risk of malignancy. Some patients who received ustekinumab in clinical studies developed malignancies (see **ADVERSE REACTIONS**). In the controlled and non-controlled portions of psoriasis clinical studies, the incidence of malignancies excluding nonmelanoma skin cancers was 0.36 per 100 patient-years of follow-up for ustekinumab-treated patients (8 patients in 2249 patient-years of follow-up) and included breast, colon, head and neck, kidney, prostate, and thyroid cancers. The rate of malignancies reported in ustekinumab-treated patients was comparable to the rate expected in the general population (standardized incidence ratio = 0.68 [95% confidence interval: 0.29, 1.34]. The incidence of nonmelanoma skin cancer was 0.80 per 100 patient-years of follow-up for ustekinumab-treated patients (18 patients in 2245 patient-years of follow-up).

STELARA™ (ustekinumab) has not been studied in patients with a history of malignancy. Caution should be exercised when considering the use of STELARA™ in patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy.

### **Hepatic/Biliary/Pancreas**

Specific studies have not been conducted in patients with hepatic insufficiency.

### **Hypersensitivity Reactions**

In post-marketing experience, serious allergic reactions, including angioedema and possible anaphylaxis, have been reported. If an anaphylactic or other serious allergic reaction occurs, administration of STELARA™ (ustekinumab) should be discontinued immediately and appropriate therapy instituted (see **ADVERSE REACTIONS**).

The needle cover on the pre-filled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex.

## **Immune**

### **Immunization**

It is recommended that live viral or bacterial vaccines not be given concurrently with STELARA™ (ustekinumab). No data are available on the secondary transmission of infection by live vaccines in patients receiving STELARA™. Caution is advised when administering some live vaccines to household contacts of patients receiving STELARA™ because of the potential risk for shedding from the household contact and transmission to the patient. Patients receiving STELARA™ may receive concurrent inactivated or non-live vaccinations (see **DRUG INTERACTIONS**).

### **Immunosuppression**

The safety and efficacy of STELARA™ (ustekinumab) in combination with immunosuppressive agents or phototherapy have not been evaluated. Caution should be exercised when considering concomitant use of immunosuppressive agents and STELARA™.

### **Immunotherapy**

STELARA™ (ustekinumab) has not been evaluated in patients who have undergone allergy immunotherapy. STELARA™ may affect allergy immunotherapy. Caution should be exercised in patients receiving or who have received allergy immunotherapy particularly for anaphylaxis.

## **Infections**

STELARA™ (ustekinumab) is a selective immunomodulator and may have the potential to increase the risk of infections and reactivate latent infections.

In clinical studies, serious bacterial, fungal, and viral infections have been observed infrequently in patients receiving ustekinumab. STELARA™ (ustekinumab) should not be given to patients with an existing clinically important, active infection. Caution should be exercised when considering the use of STELARA™ in patients with a chronic infection or a history of recurrent infection.

Prior to initiating treatment with STELARA™ (ustekinumab), patients should be evaluated for tuberculosis infection. STELARA™ should not be given to patients with active tuberculosis. Treatment of latent tuberculosis infection should be initiated prior to administering STELARA™. Anti-tuberculosis therapy should also be considered 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. In clinical studies, patients with latent tuberculosis who were concurrently treated with isoniazid did not develop tuberculosis. Patients receiving STELARA™ should be monitored closely for signs and symptoms of active tuberculosis during and after treatment.

Patients should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur. If a patient develops a serious infection, they should be closely monitored and STELARA™ (ustekinumab) should not be administered until the infection resolves (see **ADVERSE REACTIONS**).

## **Neurologic**

### **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 and a half years, presented with headache, seizures and confusion in the setting of alcohol abuse. 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, acute hypertension, cytotoxic agents, immunosuppressive therapy and alcohol abuse. Fatal outcomes have been reported.

If RPLS is suspected, STELARA™ should be discontinued and appropriate treatment administered.

## **Renal**

Specific studies have not been conducted in patients with renal insufficiency.

## **Special Populations**

**Pregnant Women:** There is no evidence from animal studies of teratogenicity, birth defects or developmental delays at dose levels up to approximately 45-fold higher than the highest equivalent dose intended to be administered to psoriasis patients (see **TOXICOLOGY, Reproductive Toxicology**). However, animal reproductive and developmental studies are not always predictive of human response.

It is not known whether STELARA™ (ustekinumab) can cause fetal harm when administered to a pregnant woman or whether it can affect reproductive capacity. While it is known that human IgG antibodies, like ustekinumab, cross the placenta, no adequate and well-controlled studies have been conducted to evaluate if ustekinumab can cross the human placenta in pregnant women. In developmental toxicity studies in monkeys, ustekinumab was detected in fetal serum following repeated dosing of pregnant monkeys during the period of organogenesis. Although ustekinumab crossed the monkey placenta there was no evidence of teratogenicity in these studies. STELARA™ should be given to a pregnant woman only if the benefit clearly outweighs the risk.

**Nursing Women:** Ustekinumab is excreted in the milk of lactating monkeys administered ustekinumab. It is not known if ustekinumab is absorbed systemically after ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because of the potential for adverse reactions in nursing infants from ustekinumab, a decision should be made whether to discontinue nursing or to discontinue the drug.

**Pediatrics (< 18 years of age):** Specific studies of STELARA™ (ustekinumab) in pediatric patients have not been conducted.

**Geriatrics (> 65 years of age):** No major age-related differences in clearance or volume of distribution were observed in clinical studies. While the experience in the elderly is limited, no overall differences in efficacy or safety in patients age 65 and older [N=131] who received ustekinumab were observed compared with younger patients.

## **ADVERSE REACTIONS**

### **Adverse Drug Reaction Overview**

The following serious adverse reactions were reported:

- Serious Infections
- Malignancies

The most common adverse reactions (>10%) in controlled and uncontrolled portions of the psoriasis clinical studies with STELARA™ (ustekinumab) were nasopharyngitis and upper respiratory tract infection. Most were considered to be mild and did not necessitate drug discontinuation.

### **Clinical Trial Adverse Drug Reactions**

*Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

The safety data described below reflect exposure to STELARA™ (ustekinumab) in 3 placebo-controlled studies of 2266 patients, including 1970 exposed for at least 6 months, 1285 exposed for at least 1 year and 373 for at least 18 months.

Table 1.1 summarizes the adverse drug reactions that occurred at a rate of at least 1% and at a higher rate by preferred term in the STELARA™ (ustekinumab) group during the placebo-controlled period of the Phase 3 studies (PHOENIX 1 and PHOENIX 2).

**Table 1.1 Adverse drug reactions reported by  $\geq 1\%$  of patients through Week 12 in PHOENIX 1 and 2**

|                                   | Placebo   | STELARA™ (ustekinumab) |           |
|-----------------------------------|-----------|------------------------|-----------|
|                                   |           | 45 mg                  | 90 mg     |
| Patients treated                  | 665       | 664                    | 666       |
| Nasopharyngitis                   | 51 (7.7%) | 56 (8.4%)              | 49 (7.4%) |
| Upper respiratory tract infection | 30 (4.5%) | 36 (5.4%)              | 28 (4.2%) |
| Headache                          | 23 (3.5%) | 33 (5.0%)              | 32 (4.8%) |
| Fatigue                           | 14 (2.1%) | 18 (2.7%)              | 17 (2.6%) |
| Diarrhea                          | 12 (1.8%) | 13 (2.0%)              | 13 (2.0%) |
| Back pain                         | 8 (1.2%)  | 9 (1.4%)               | 14 (2.1%) |
| Dizziness                         | 8 (1.2%)  | 8 (1.2%)               | 14 (2.1%) |
| Pharyngolaryngeal pain            | 7 (1.1%)  | 9 (1.4%)               | 12 (1.8%) |
| Pruritus                          | 9 (1.4%)  | 10 (1.5%)              | 9 (1.4%)  |
| Injection site erythema           | 3 (0.5%)  | 6 (0.9%)               | 13 (2.0%) |
| Myalgia                           | 4 (0.6%)  | 7 (1.1%)               | 8 (1.2%)  |
| Depression                        | 3 (0.5%)  | 8 (1.2%)               | 4 (0.6%)  |

Table 1.2 present the rates at which the STELARA™ ADRs occurred in treatment groups in the ACCEPT trial.

**Table 1.2 Adverse drug reactions reported by  $\geq 1\%$  of patients through Week 12 in ACCEPT**

|                                   | ENBREL<br>(etanercept) | STELARA™ (ustekinumab) |            |
|-----------------------------------|------------------------|------------------------|------------|
|                                   |                        | 45 mg                  | 90 mg      |
| Patients treated                  | 347                    | 209                    | 347        |
| Nasopharyngitis                   | 29 (8.4%)              | 21 (10.0%)             | 34 (9.8%)  |
| Upper respiratory tract infection | 20 (5.8%)              | 13 (6.2%)              | 22 (6.3%)  |
| Headache                          | 38 (11.0%)             | 31 (14.8%)             | 41 (11.8%) |
| Fatigue                           | 13 (3.7%)              | 8 (3.8%)               | 19 (5.5%)  |
| Diarrhea                          | 9 (2.6%)               | 8 (3.8%)               | 9 (2.6%)   |
| Back pain                         | 7 (2.0%)               | 14 (6.7%)              | 15 (4.3%)  |
| Dizziness                         | 8 (2.3%)               | 3 (1.4%)               | 6 (1.7%)   |
| Pharyngolaryngeal pain            | 14 (4.0%)              | 5 (2.4%)               | 14 (4.0%)  |
| Pruritus                          | 14 (4.0%)              | 12 (5.7%)              | 16 (4.6%)  |
| Injection site erythema           | 51 (14.7%)             | 2 (1.0%)               | 2 (0.6%)   |
| Myalgia                           | 7 (2.0%)               | 3 (1.4%)               | 7 (2.0%)   |

### **Infections:**

In placebo-controlled studies of psoriasis patients, the rates of infection or serious infection were similar between ustekinumab-treated patients and those treated with placebo. In the placebo-controlled period of clinical studies of psoriasis patients, the rate of infection was 1.39 per patient-year of follow-up in ustekinumab-treated patients, and 1.21 per patient-year of follow-up in placebo-treated patients. Serious infections occurred in 0.01 per patient-year of follow-up in ustekinumab-treated patients (5 serious infections in 407 patient-years of follow-up) and 0.02 per patient-year of follow-up in placebo-treated patients (3 serious infections in 177 patient-years of follow-up) (see **WARNINGS AND PRECAUTIONS**).

In the controlled and non-controlled portions of placebo-controlled psoriasis clinical studies, the rate of infection was 1.24 per patient-year of follow-up in ustekinumab-treated patients. The incidence of serious infections was 0.01 per patient-year of follow-up in ustekinumab-treated patients (24 serious infections in 2251 patient-years of follow-up) and included cellulitis, diverticulitis, osteomyelitis, viral infections, gastroenteritis, pneumonia, and urinary tract infections.

### **Malignancies:**

In the placebo-controlled period of the psoriasis clinical studies, the incidence of non-melanoma skin cancer was 0.74 per 100 patient-years of follow-up for ustekinumab-treated patients (3 patients in 406 patient-years of follow-up) compared with 1.13 per 100 patient-years of follow-up for placebo-treated patients (2 patient in 176 patient-years of follow-up) during the placebo-controlled periods. In a Phase 3 clinical trial (ACCEPT) comparing ustekinumab and etanercept for the treatment of moderate to severe plaque psoriasis, 209 patients received ustekinumab 45mg, 347 patients received ustekinumab 90 mg, and 347 patients received etanercept. Through Week 12, three (0.5%) subjects in the ustekinumab groups had a non-melanoma skin cancer detected in areas of psoriasis that had cleared with treatment. No skin cancers were observed in the etanercept group but due to the short treatment period, the possible pre-existing malignancies and the differences in efficacy (see **CLINICAL TRIALS** section), the clinical relevance has not been established.

The incidence of malignancies excluding non-melanoma skin cancer was 0.25 per 100 patient-years of follow-up for ustekinumab-treated patients (1 patient in 406 patient-years of follow-up) compared with 0.57 per 100 patient-years of follow-up for placebo-treated patients (1 patient in 177 patient-years of follow-up) during the placebo-controlled periods. In the ACCEPT trial, through Week 12, one subject (0.2%) with a familial history of breast cancer was diagnosed with breast cancer versus no malignancies in the etanercept group.

In the controlled and non-controlled portions of the placebo-controlled psoriasis clinical trials, the incidence of malignancies excluding non-melanoma skin cancers was 0.36 per 100 patient-years of follow-up for ustekinumab-treated patients (8 patients in 2249 patient-years of follow-up) and included breast, colon, head and neck, kidney, prostate, and thyroid cancers. The rate of malignancies reported in ustekinumab-treated patients was comparable to the rate expected in the general population (standardized incidence ratio = 0.68 [95% confidence interval: 0.29, 1.34]).

The incidence of non-melanoma skin cancer was 0.80 per 100 patient-years of follow-up for ustekinumab-treated patients (18 patients in 2245 patient-years of follow-up).

### **Hypersensitivity Reactions:**

In clinical studies of ustekinumab, rash and urticaria have each been observed in <2% of patients.

### **Immunogenicity:**

Approximately 5% of patients treated with ustekinumab developed antibodies to ustekinumab, which were generally low-titer. No apparent correlation of antibody development to injection site reactions was seen. Patients positive for antibodies to ustekinumab exhibited median serum levels of ustekinumab that were consistently lower than those in patients negative or undetectable for antibodies to ustekinumab and tended to have lower efficacy; however, antibody positivity does not preclude a clinical response.

### **Less Common Clinical Trial Adverse Drug Reactions (<1%)**

The following adverse drug reactions occurred at rates less than 1% during the psoriasis clinical trials:

**Infections and infestations:** cellulitis

**General disorders and administration site conditions:** injection site reactions (including pain, swelling, pruritus, induration, hemorrhage, bruising and irritation)

### **Abnormal Hematologic and Clinical Chemistry Findings**

During the placebo-controlled period of the Phase 2 and Phase 3 studies (through week 12), an increase in non-fasting blood glucose levels was observed, as follows: Subjects with any abnormal value: 49 (6.7%) placebo vs. 83 (5.3%) in the combined ustekinumab group; Subjects with > 1 abnormal value: 9 (1.2%) placebo vs 35 (2.2%) in the combined ustekinumab group. The clinical significance of these changes in glucose is unknown. No such increase in fasting blood glucose levels was observed in the same subjects.

### **Post-Market Adverse Drug Reactions**

**Immune system disorders:** Common - Hypersensitivity reactions (including rash, urticaria)  
Rare - Serious allergic reactions (including angioedema)

## **DRUG INTERACTIONS**

### **Overview**

Specific drug interaction studies have not been conducted with STELARA™ (ustekinumab).

In population pharmacokinetic analysis, the effect of the most frequently used concomitant medications in patients with psoriasis (including paracetamol/acetaminophen, ibuprofen, acetylsalicylic acid, metformin, atorvastatin, naproxen, levothyroxine, hydrochlorothiazide, and influenza vaccine) on pharmacokinetics of ustekinumab was explored and none of the concomitant medications exerted significant impact. The pharmacokinetics of ustekinumab was not impacted by the prior use of methotrexate, cyclosporine, or other biological therapeutics for the treatment of psoriasis.

### **Drug-Drug Interactions**

#### **Live Vaccines**

Live vaccines should not be given concurrently with STELARA™ (ustekinumab) (see **WARNINGS AND PRECAUTIONS**).

#### **Immunosuppressants**

The safety and efficacy of STELARA™ (ustekinumab) in combination with immunosuppressive agents or phototherapy have not been evaluated (see **WARNINGS AND PRECAUTIONS**).

### **Drug-Food Interactions**

Interactions with food have not been established.

### **Drug-Herb Interactions**

Interactions with herbal products have not been established.

### **Drug-Laboratory Interactions**

Interactions with laboratory tests have not been established.

### **Drug-Lifestyle Interactions**

The pharmacokinetics of ustekinumab were not impacted by the use of tobacco or alcohol.

## **DOSAGE AND ADMINISTRATION**

STELARA™ (ustekinumab) is administered by subcutaneous injection.

## **Dosing Considerations**

STELARA™ (ustekinumab) is intended for use under the guidance and supervision of a physician. A patient may self-inject with STELARA™ (ustekinumab) if a physician determines that it is appropriate after proper training in subcutaneous injection technique.

Prior to subcutaneous administration, visually inspect the solution for particulate matter and discoloration. The product is colourless to light yellow and may contain a few small translucent or white particles of protein. This appearance is not unusual for proteinaceous solutions. The product should not be used if solution is discolored or cloudy, or if other particulate matter is present. STELARA™ (ustekinumab) does not contain preservatives; therefore, any unused product remaining in the syringe should not be used.

The needle cover on the pre-filled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex.

Patients should be instructed to inject the full amount of STELARA™ (ustekinumab) according to the directions provided in the CONSUMER INFORMATION Section (see ***Product Monograph, Part III: CONSUMER INFORMATION Section***).

## **Recommended Dose and Dosage Adjustment**

The recommended dose of STELARA™ (ustekinumab) is 45 mg administered at Weeks 0 and 4, then every 12 weeks thereafter. Alternatively, 90 mg may be used in patients with a body weight greater than 100 kg.

In patients weighing >100 kg, both 45 mg and 90 mg were shown to be efficacious. However, 90 mg was efficacious in a higher percentage of these patients than the 45 mg dose.

For patients who inadequately respond to dosing every 12 weeks, consideration may be given to treating as often as every 8 weeks.

Consideration should be given to discontinuing treatment in patients who have shown no response up to 12 weeks of treatment.

## **Re-treatment**

Re-treatment with a dosing regimen of Weeks 0 and 4 followed by 12 week dosing after interruption of therapy has been shown to be safe and effective. (see **CLINICAL TRIALS, Study Results, Efficacy of retreatment**).

## OVERDOSAGE

Single doses up to 4.5 mg/kg intravenously have been administered in clinical studies without dose limiting toxicity. In case of overdose, 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 (see **DETAILED PHARMACOLOGY, TOXICOLOGY**).

For management of a suspected drug overdose, contact your regional Poison Control Centre.

## ACTION AND CLINICAL PHARMACOLOGY

### **Mechanism of Action**

STELARA™ (ustekinumab) is a fully human IgG1 $\kappa$  monoclonal antibody, a first-in-class agent that binds with high affinity and specificity to the p40 protein subunit of the human cytokines interleukin IL-12 and IL-23. STELARA™ inhibits the bioactivity of human IL-12 and IL-23 by preventing these cytokines from binding to their IL-12R $\beta$ 1 receptor protein expressed on the surface of immune cells. STELARA™ cannot bind to IL-12 or IL-23 that is pre-bound to IL-12R $\beta$ 1 cell surface receptors. Thus, STELARA™ is not likely to contribute to complement or antibody-mediated cytotoxicity of the receptor-bearing cell.

IL-12 and IL-23 are heterodimeric cytokines secreted by activated antigen-presenting cells, such as macrophages and dendritic cells. IL-12 and IL-23 participate in immune function by contributing to NK cell activation and CD4<sup>+</sup> T-cell differentiation and activation. However, abnormal regulation of IL-12 and IL-23 has been associated with immune-mediated diseases, such as psoriasis. STELARA™ (ustekinumab) prevents IL-12 and IL-23 contributions to immune cell activation, such as intracellular signaling and cytokine secretion. Thus, STELARA™ is believed to interrupt signalling and cytokine cascades that are central to psoriasis pathology.

### **Pharmacodynamics**

Treatment with ustekinumab resulted in significant improvement in histological measures of psoriasis including epidermal hyperplasia and cell proliferation. These results are consistent with the clinical efficacy observed. STELARA™ (ustekinumab) had no apparent effect on the percentages of circulating immune cell populations including memory and naive T-cell subsets or circulating cytokine levels.

Treatment with ustekinumab resulted in a decrease in the gene expression of its molecular targets IL-12 and IL-23 as shown by analyses of mRNA obtained from lesional skin biopsies of psoriatic patients at baseline and up to two weeks post-treatment. In addition, ustekinumab down-regulated the gene expression of inflammatory cytokines and chemokines such as MCP-1, TNF-alpha, IP-10 and IL-8 in lesional skin biopsies. These results are consistent with the significant clinical benefit observed with ustekinumab treatment.

Clinical response (improvement in PASI) appeared to be related to serum ustekinumab levels. Patients with psoriasis with higher clinical responses as measured by PASI response had higher median serum concentrations of ustekinumab than those with lower clinical responses. Overall, the proportion of patients with psoriasis who achieved PASI 75 response increased with increasing serum levels of ustekinumab. The proportion of patients who achieved PASI 75 response at Week 28 increased with increasing serum ustekinumab trough levels at Week 28.

### **Pharmacokinetics**

The median pharmacokinetic parameters of ustekinumab following a single SC administration in adult patients with psoriasis are shown in Table 1.3. The pharmacokinetic parameters of ustekinumab (CL/F,  $V_z/F$ , and  $t_{1/2}$ ) were generally comparable between 45 mg and 90 mg subcutaneous doses.

| Dose                    | 45 mg |                        |                         | 90 mg |                        |                         |
|-------------------------|-------|------------------------|-------------------------|-------|------------------------|-------------------------|
|                         | N     | Median (Range)         | Mean ( $\pm$ SD)        | N     | Median (Range)         | Mean ( $\pm$ SD)        |
| $C_{max}$ ( $\mu$ g/mL) | 22    | 2.4<br>(1.0, 5.4)      | 2.7<br>( $\pm$ 1.2)     | 24    | 5.3<br>(1.2, 12.3)     | 6.1<br>( $\pm$ 3.6)     |
| $t_{max}$ (day)         | 22    | 13.5<br>(1.9, 58.2)    | 15.3<br>( $\pm$ 13.5)   | 24    | 7.0<br>(2.9, 27.1)     | 9.9<br>( $\pm$ 7.4)     |
| AUC ( $\mu$ g·day/mL)   | 18    | 84.9<br>(31.2, 1261.9) | 196.7<br>( $\pm$ 298.2) | 21    | 226.9<br>(57.1, 755.5) | 274.9<br>( $\pm$ 206.5) |
| $t_{1/2}$ (day)         | 18    | 19.8<br>(5.0, 353.6)   | 45.6<br>( $\pm$ 80.2)   | 21    | 21.2<br>(13.6, 85.8)   | 26.7<br>( $\pm$ 19.3)   |
| CL/F (mL/day/kg)        | 18    | 5.3<br>(0.2, 12.9)     | 5.8<br>( $\pm$ 3.5)     | 21    | 4.5<br>(1.5, 14.9)     | 5.7<br>( $\pm$ 3.6)     |
| $V_z/F$ (mL/kg)         | 18    | 154.2<br>(32.6, 280.5) | 160.5<br>( $\pm$ 64.5)  | 21    | 160.5<br>(37.3, 354.1) | 178.7<br>( $\pm$ 85.2)  |

Source data: C0379T04 CSR

**Absorption:** The median time to reach the maximum serum concentration ( $t_{max}$ ) was 8.5 days after a single 90 mg subcutaneous administration in healthy subjects (n = 30). The median  $t_{max}$  values of ustekinumab following a single subcutaneous administration of either 45 mg or 90 mg in patients with psoriasis were comparable to that observed in healthy subjects.

The absolute bioavailability (F) of ustekinumab following a single subcutaneous administration was estimated to be 57.2% in patients with psoriasis (n = 17).

**Distribution:** The median apparent volume of distribution during the terminal phase ( $V_z/F$ ) following a single subcutaneous administration to patients with psoriasis ranged from 76 to 161 mL/kg (n = 4 to 21).

**Metabolism:** The exact metabolic pathway for ustekinumab is unknown.

**Excretion:** The median apparent clearance (CL/F) following a single subcutaneous administration to patients with psoriasis ranged from 2.7 to 5.3 mL/day/kg. The median half-life ( $t_{1/2}$ ) of ustekinumab was approximately 3 weeks in patients with psoriasis, ranging from 15 to 32 days across all psoriasis studies (n = 4 to 21).

**Dose Linearity:** The systemic exposure of ustekinumab ( $C_{max}$  and AUC) increased in a linear manner following a single subcutaneous administration at doses ranging from approximately 24 mg to 240 mg in patients with psoriasis.

**Single Dose vs. Multiple Doses:** Serum concentration-time profiles of ustekinumab were generally predictable after single or multiple subcutaneous dose administrations on the basis of a one-compartment model. Steady-state serum concentrations of ustekinumab were achieved by Week 28 after initial subcutaneous doses at Weeks 0 and 4 followed by doses every 12 weeks. The median steady-state trough concentration ranged from 0.21 µg/mL to 0.26 µg/mL (45 mg; n = 242 to 390) and from 0.47 µg/mL to 0.49 µg/mL (90 mg; n = 236 to 386). There was no apparent accumulation in serum ustekinumab concentration over time when given subcutaneously every 12 weeks.

#### **Impact of Weight on Pharmacokinetics:**

Serum ustekinumab concentrations were affected by patient weight. When given the same dose, patients of higher weight (> 100 kg) had lower median serum ustekinumab concentrations compared with those in patients of lower weight ( $\leq$  100 kg). However, across doses, the median trough serum concentrations of ustekinumab in patients with higher weight (> 100 kg) in the 90 mg group were comparable to those in patients with lower weight ( $\leq$  100 kg) in the 45 mg group.

Of the demographic factors (e.g., gender, race, age, body size), baseline patient physical or biochemical characteristics, or medical or medication history, or concomitant medications evaluated in a population pharmacokinetic analysis, only body weight, diabetes comorbidity, and positive immune response to ustekinumab were found to be important covariates affecting the systemic exposure to ustekinumab in patients with moderate to severe psoriasis. Clinical relevance of the effects of these important covariates, however, needs to be evaluated concurrently with clinical efficacy and safety data.

The effect of the most frequently used concomitant medications in patients with psoriasis (including paracetamol/acetaminophen, ibuprofen, acetylsalicylic acid, metformin, atorvastatin, naproxen, levothyroxine, hydrochlorothiazide, and influenza vaccine) on pharmacokinetics of ustekinumab was explored and none of the concomitant medications exerted significant impact. The pharmacokinetics of ustekinumab was not impacted by the prior use of methotrexate, cyclosporine, or other biological therapeutics for the treatment of psoriasis.

#### **Special Populations and Conditions**

**Pediatrics (< 18 years of age):** Specific studies of STELARA™ (ustekinumab) in pediatric patients have not been conducted.

**Geriatrics (> 65 years of age):** No specific studies have been conducted in elderly patients.

**Gender, Race and Genetic Polymorphism:** The apparent clearance of ustekinumab was not impacted by sex, age, or race.

**Hepatic Insufficiency:** No pharmacokinetic data are available in patients with impaired hepatic function.

**Renal Insufficiency:** No pharmacokinetic data are available in patients with renal insufficiency.

## **STORAGE AND STABILITY**

STELARA™ (ustekinumab) must be refrigerated at 2 to 8°C and protected from light. Keep the product in the original carton to protect from light until the time of use. Do not freeze. Do not shake.

## **SPECIAL HANDLING INSTRUCTIONS**

Following administration of STELARA™ (ustekinumab), the syringe should be disposed of in a puncture-resistant container for syringes and needles. Patients or caregivers should be instructed in the technique as well as proper syringe and needle disposal, and not to reuse these items.

## **DOSAGE FORMS, COMPOSITION AND PACKAGING**

STELARA™ (ustekinumab) is supplied as a single-use, sterile solution in a Type 1 glass syringe with a fixed 27G, half-inch needle and needle cover. The needle cover is manufactured using a dry natural rubber (a derivative of latex) (see **WARNINGS AND PRECAUTIONS, Hypersensitivity Reactions**). The syringe is fitted with a passive safety guard.

Each mL of STELARA™ (ustekinumab) contains 90 mg of ustekinumab.

STELARA™ (ustekinumab) contains the following inactive ingredients: sucrose, L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, and water for injection.

STELARA™ (ustekinumab) does not contain preservatives.

There are two strengths of STELARA™ (ustekinumab) available: 45 mg of ustekinumab in 0.5 mL and 90 mg of ustekinumab in 1.0 mL<sup>†</sup>

STELARA™ is available in the following packaging presentation:

- 1 single-use pre-filled syringe

<sup>†</sup>90mg/1.0 mL not available in Canada

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

|                                       |   |
|---------------------------------------|---|
| Proper name:                          | STELARA™  |
| Chemical name:                        | Ustekinumab   |
| Molecular formula and molecular mass: | Ustekinumab is a fully human IgG1κ mAb, with an approximate molecular weight of 148,600 daltons.              |
| Physicochemical properties:           | STELARA™ solution is clear to slightly opalescent, colourless to light yellow with a pH of approximately 6.0. |

#### Product Characteristics

STELARA™ (ustekinumab) is supplied as a single-use, sterile solution in a Type 1 glass syringe with a fixed 27G, half-inch needle and needle cover. The needle cover is manufactured using a dry natural rubber (a derivative of latex) (see **WARNINGS AND PRECAUTIONS, Hypersensitivity Reactions**). The syringe is fitted with a passive safety guard.

STELARA™ (ustekinumab) is supplied as 2 dosage presentations at 45 mg in 0.5 mL volume or at 90 mg in 1 mL volume<sup>†</sup>. Each 1 mL of STELARA™ (ustekinumab) liquid contains 90 mg ustekinumab. No preservatives are present.

#### Viral Inactivation

STELARA™ (ustekinumab) is produced by a recombinant cell line cultured by continuous perfusion and is purified by a series of steps that includes measures to inactivate and remove viruses.

### CLINICAL TRIALS

The safety and efficacy of ustekinumab was assessed in two multicentre, randomized, double-blind, placebo-controlled studies (PHOENIX 1 and PHOENIX 2) in patients 18 years of age and older with chronic (>6 months) plaque psoriasis who had a minimum body surface area (BSA) involvement of 10%, and Psoriasis Area and Severity Index (PASI) score  $\geq 12$  and who were candidates for phototherapy or systemic therapy. Patients with guttate, erythrodermic, or pustular psoriasis were excluded from the studies. No concomitant anti-psoriatic therapies were allowed during the study with the exception of low-potency topical corticosteroids on the face

<sup>†</sup>90mg/1.0 mL not available in Canada

and groin after Week 12. A total of 1996 patients were enrolled in the two studies. The safety and efficacy of ustekinumab beyond 3 years have not been established.

In addition, a multicenter, randomized, active-controlled study (ACCEPT) compared the safety and efficacy of ustekinumab and etanercept in patients 18 years of age and older with chronic (>6 months) plaque psoriasis who had a minimum BSA involvement of 10%, PASI score  $\geq 12$ , Physician Global Assessment (PGA) score  $\geq 3$ , who were candidates for phototherapy or systemic therapy, and who had had an inadequate response to, intolerance to, or contraindication to cyclosporine, methotrexate, or PUVA therapy. A total of 903 patients were enrolled in the study.

### Study demographics and trial design

Baseline disease characteristics across PHOENIX 1 and 2 were similar (Table 2.1 and Table 2.2). In both studies, patients in all treatment groups had a median baseline PASI score ranging from 17 to 18. Approximately two-thirds of all patients 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 patients had a history of psoriatic arthritis. Similar disease characteristics were also seen in the ACCEPT trial (Table 2.1 and Table 2.2).

**Table 2.1: Summary of patient demographics for PHOENIX 1, PHOENIX 2 and ACCEPT**

| Study #              | Trial design                                | Dosage, route of administration and duration  | Study subjects (n=number) | Mean age (Range) | Gender             |
|----------------------|---|---|---------------------------|------------------|--------------------|
| C0743T08 (PHOENIX 1) | Double-Blind Placebo-Controlled             | Fixed doses:<br>Placebo (N = 255)<br>Placebo → 45 mg SC regimen <sup>a</sup> (N = 123)<br>Placebo → 90 mg SC regimen <sup>a</sup> (N = 120)<br>45 mg SC Weeks 0, 4 then q12w (N = 255)<br>90 mg SC Weeks 0, 4 then q12w (N = 256) | N=766                     | 45.3 (19,76)     | M=531<br>F=235     |
| C0743T09 (PHOENIX 2) | Double-Blind Placebo-Controlled             | Fixed doses:<br>Placebo (N = 410)-Placebo → 45 mg SC regimen <sup>a</sup> (N = 197)<br>Placebo → 90 mg SC regimen <sup>a</sup> (N = 195)<br>45 mg SC Weeks 0, 4 then q12w (N = 409)<br>90 mg SC Weeks 0, 4 then q12w (N = 411)    | N=1230                    | 46.2 (18, 86)    | M=840<br>F=390     |
| C0743T12 (ACCEPT)    | Assessor-Blind Active-Comparator Controlled | Fixed doses:<br>Etanercept 50 mg (N=347) twice weekly through Week 12<br>Ustekinumab 45 mg (N=209) at Week 0 and 4<br>Ustekinumab 90 mg (N=347) at Week 0 and 4   | N= 903                    | 45.0 (18, 81)    | M = 613<br>F = 290 |

<sup>a</sup> The placebo groups crossed over to receive ustekinumab (45 mg or 90 mg) at Weeks 12 and 16 then q12w

**Table 2.2: Baseline Disease Characteristics in PHOENIX 1, PHOENIX 2 and ACCEPT**

|   | PHOENIX 1 |             | PHOENIX 2 |             | ACCEPT     |             |
|---|-----------|-------------|-----------|-------------|------------|-------------|
|   | Placebo   | Ustekinumab | Placebo   | Ustekinumab | Etanercept | Ustekinumab |
| Patients randomized at Week 0   | N=255     | N=511       | N=410     | N=820       | N=347      | N=556       |
| Median BSA  | 22.0      | 21.0        | 20.0      | 21.0        | 19.0       | 20.0        |
| BSA $\geq$ 20%  | 145 (57%) | 276 (54%)   | 217 (53%) | 445 (54%)   | 169 (49%)  | 289 (52%)   |
| Median PASI   | 17.80     | 17.4        | 16.90     | 17.60       | 16.8       | 17.1        |
| PASI $\geq$ 20  | 91 (36%)  | 169 (33%)   | 133 (32%) | 300 (37%)   | 102 (29%)  | 205 (37%)   |
| PGA of marked or severe   | 112 (44%) | 223 (44%)   | 160 (39%) | 328 (40%)   | 148 (43%)  | 242 (44%)   |
| History of psoriatic arthritis  | 90 (35%)  | 168 (33%)   | 105 (26%) | 200 (24%)   | 95 (27%)   | 157 (28%)   |
| Prior phototherapy  | 150 (59%) | 342 (67%)   | 276 (67%) | 553 (67%)   | 224 (65%)  | 368 (66%)   |
| Prior conventional systemic therapy excluding biologics <sup>a</sup>  | 142 (56%) | 282 (55%)   | 241 (59%) | 447 (55%)   | 199(57%)   | 311 (56%)   |
| Prior conventional systemic or biologic therapy <sup>a</sup>  | 189 (74%) | 364 (71%)   | 287 (70%) | 536 (65%)   | 218(63%)   | 337 (61%)   |
| Failed to respond to, had contraindication for, or intolerant to $\geq$ 1 conventional therapy <sup>a</sup>   | 139 (55%) | 270 (53%)   | 254 (62%) | 490 (60%)   | 347 (100%) | 555 (100%)  |
| Failed to respond to, had contraindication for, or intolerant to $\geq$ 3 conventional therapies <sup>a</sup> | 30 (12%)  | 54 (11%)    | 66 (16%)  | 134 (16%)   | 52 (15%)   | 78 (14%)    |

<sup>a</sup> In PHOENIX 1 and 2, conventional systemic agents include acitretin, PUVA, methotrexate, and cyclosporine. In ACCEPT, conventional systemic agents included PUVA, methotrexate, and cyclosporine. All patients were required to be etanercept naïve at baseline in ACCEPT, but in PHOENIX 1 and 2 patients may have previously received etanercept.

PHOENIX 1 evaluated the safety and efficacy of ustekinumab versus placebo in 766 patients with plaque psoriasis. Patients were randomized in equal proportion to placebo, 45 mg or 90 mg of ustekinumab. Patients randomized to ustekinumab received 45 mg or 90 mg doses at Weeks 0 and 4 followed by the same dose every 12 weeks. Patients 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 followed by the same dose every 12 weeks. To evaluate the efficacy of every 12-week dosing, patients who were PASI 75 responders at both Weeks 28 and 40 were re-randomized to either continue dosing of ustekinumab every 12 weeks or to placebo (i.e., withdrawal of therapy). Patients withdrawn from ustekinumab at Week 40 reinitiated ustekinumab at their original dosing regimen when they experienced at least a 50% loss of their PASI improvement obtained at Week 40. Patients were followed for at least 76 weeks.

PHOENIX 2 evaluated the safety and efficacy of ustekinumab versus placebo in 1230 patients with plaque psoriasis. This study design was identical to PHOENIX 1 through Week 28.

#### Dose Adjustment (every 8 weeks)

At Week 28, PHOENIX 1 patients who were nonresponders (<PASI 50 response) discontinued treatment and patients who were partial responders ( $\geq$  PASI 50 response and <PASI 75 response) were adjusted to every-8-week dosing. PASI 75 responders at Week 28 who became partial responders or nonresponders at Week 40 were adjusted to every-8-week dosing.

In PHOENIX 2, patients who were partial responders at Week 28 were re-randomized to either continue every 12 weeks dosing of ustekinumab or to switch to every 8 weeks dosing.

All patients were followed for up to 76 weeks in PHOENIX 1 and up to 52 weeks in PHOENIX 2 following first administration of study treatment.

In both studies, the primary endpoint was the proportion of patients who achieved a reduction in score of at least 75% from baseline at Week 12 by the PASI (PASI 75). Patients achieving  $\geq$  90% improvement in PASI from baseline (PASI 90) were considered PASI 90 responders and patients with  $\geq$  50% improvement in PASI from baseline (PASI 50) were considered PASI 50 responders. Another key efficacy assessment was the Physician's Global Assessment (PGA), 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.

The Dermatology Life Quality Index (DLQI), a dermatology-specific quality of life instrument designed to assess the impact of the disease on a patient's quality of life, was assessed in both PHOENIX 1 and PHOENIX 2. Other efficacy assessments included the Nail Psoriasis Severity Index (NAPSI), a physician-assessed score that measures the severity of nail involvement (PHOENIX 1); the Itch Visual Analog Scale (VAS), used to assess the severity of itch at the time of the assessment (PHOENIX 1); the Hospital Anxiety and Depression Scale (HADS), a self-rating tool developed to evaluate psychological measures in patients with physical ailments (PHOENIX 2); and the Work Limitations Questionnaire (WLQ), a 25-item, self-administered questionnaire that was used to measure the impact of chronic health conditions on job performance and work productivity among employed populations (PHOENIX 2).

The ACCEPT trial compared the efficacy of ustekinumab to etanercept and evaluated the safety of ustekinumab and etanercept in moderate to severe psoriasis patients. The active-controlled portion of the study was from Week 0 to Week 12, during which the efficacy and safety of etanercept and 2 dose levels of ustekinumab were evaluated. This trial was powered to test the superiority of each dose level to etanercept and the primary endpoint was the proportion of patients who achieved a PASI 75 at week 12.

### **Study results**

The results of PHOENIX 1 and PHOENIX 2 for key psoriasis clinical outcomes are presented in Table 2.3.

#### ***Efficacy at the Primary Endpoint, PHOENIX 1 and PHOENIX 2***

The onset of action with ustekinumab was rapid and improvement was seen within 2 weeks of the first dose. In both the PHOENIX 1 and PHOENIX 2 studies, a significantly greater proportion of patients randomized to treatment with ustekinumab were PASI 75 responders compared with placebo at Week 12 (Table 2.3). In the PHOENIX 1 study, 67% and 66% of patients receiving ustekinumab 45 mg and 90 mg, respectively, achieved a PASI 75 response at Week 12 compared with 3% of patients receiving placebo. In the PHOENIX 2 study, 67% and 76% of patients receiving ustekinumab 45 mg and 90 mg, respectively, achieved a PASI 75 response at Week 12 compared with 4% of patients receiving placebo.

All 3 components of the PASI (plaque thickness/induration, erythema, and scaling) contributed comparably to the improvement in PASI.

The efficacy of ustekinumab was significantly superior ( $p < 0.001$ ) to placebo across all subgroups defined by baseline demographics, clinical disease characteristics (including patients with a history of psoriatic arthritis) and prior medication usage. While pharmacokinetic modelling suggested a trend towards higher CL/F in patients with diabetes, a consistent effect on efficacy was not observed.

**Table 2.3: Clinical Outcomes - PHOENIX 1 and PHOENIX 2**

|  | PHOENIX 1 |             |           | PHOENIX 2 |             |           |
|--|-----------|-------------|-----------|-----------|-------------|-----------|
|  | Placebo   | Ustekinumab |           | Placebo   | Ustekinumab |           |
|  |           | 45 mg       | 90 mg     |           | 45 mg       | 90 mg     |
| <b>Week 12</b>                               |           |             |           |           |             |           |
| Patients randomized                          | 255       | 255         | 256       | 410       | 409         | 411       |
| <b>PASI response</b>                         |           |             |           |           |             |           |
| PASI 50 response <sup>a</sup>                | 26 (10%)  | 213 (84%)   | 220 (86%) | 41 (10%)  | 342 (84%)   | 367 (89%) |
| PASI 75 response <sup>a</sup>                | 8 (3%)    | 171 (67%)   | 170 (66%) | 15 (4%)   | 273 (67%)   | 311 (76%) |
| PASI 90 response <sup>a</sup>                | 5 (2%)    | 106 (42%)   | 94 (37%)  | 3 (1%)    | 173 (42%)   | 209 (51%) |
| PASI 100 response <sup>a</sup>               | 0 (0%)    | 33 (13%)    | 28 (11%)  | 0 (0%)    | 74 (18%)    | 75 (18%)  |
| <b>PGA of Cleared or Minimal<sup>a</sup></b> |           |             |           |           |             |           |
|  | 10 (4%)   | 151 (59%)   | 156 (61%) | 18 (4%)   | 277 (68%)   | 300 (73%) |
| <b>Week 28</b>                               |           |             |           |           |             |           |
| Patients evaluated                           | --        | 250         | 243       | --        | 397         | 400       |
| <b>PASI response</b>                         |           |             |           |           |             |           |
| PASI 50 response                             | --        | 228 (91%)   | 234 (96%) | --        | 369 (93%)   | 380 (95%) |
| PASI 75 response                             | --        | 178 (71%)   | 191 (79%) | --        | 276 (70%)   | 314 (79%) |
| PASI 90 response                             | --        | 123 (49%)   | 135 (56%) | --        | 178 (45%)   | 217 (54%) |
| PASI 100 response                            | --        | 52 (21%)    | 71(29 %)  | --        | 74(19%)     | 118 (30%) |
| <b>PGA of Cleared or Minimal</b>             |           |             |           |           |             |           |
|  | --        | 146 (58%)   | 160 (66%) | --        | 241(61%)    | 279 (70%) |

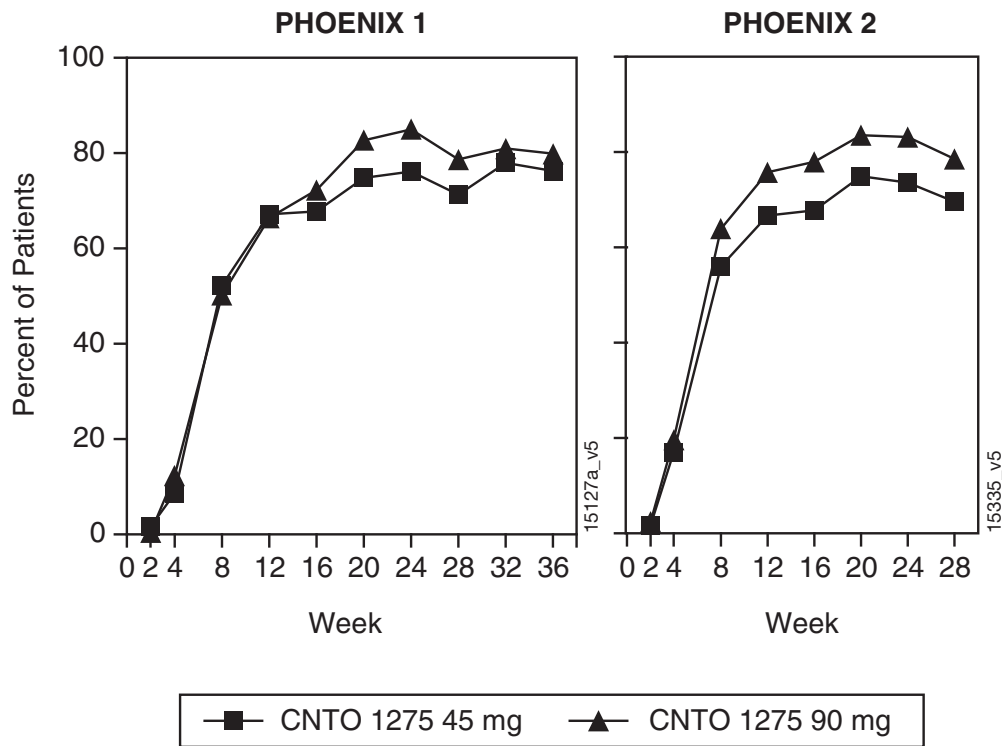
<sup>a</sup>  $p < 0.001$  for 45 mg or 90 mg comparison with placebo.

### Other efficacy measures at Week 12

In both PHOENIX 1 and PHOENIX 2, compared with placebo, significantly greater proportions of patients randomized to 45 mg or 90 mg ustekinumab achieved a cleared or minimal PGA score, and significantly greater proportions of patients randomized to 45 mg or 90 mg ustekinumab were PASI 50, PASI 90 and PASI 100 responders at Week 12 (Table 2.3). In the PHOENIX 1 study, 60% and 62% of the patients treated with 45 mg and 90 mg ustekinumab, respectively, achieved PGA scores of cleared or minimal compared with 4% of placebo-treated patients. In PHOENIX 2, 68% and 73% of patients receiving 45 mg or 90 mg ustekinumab, respectively, had cleared or minimal PGA scores compared with 5% of the placebo patients. In PHOENIX 1, PASI 90 was achieved by 42% and 37% of the patients treated with 45 mg and 90 mg ustekinumab, respectively, compared with 2% of placebo-treated patients. In addition, a significantly higher proportion of subjects treated with either 45 mg (13%) or 90 mg (11%) achieved a PASI of 0 (i.e., PASI 100 response) compared with the placebo group (0.0%;  $p < 0.001$ ). In PHOENIX 2, the percentage of patients achieving PASI 100 and PASI 90 was 18% and 42%, respectively, in the 45 mg ustekinumab group, and 18% and 51%, respectively, in the 90 mg ustekinumab group versus 1% in the placebo group. The percentage of patients achieving PASI 50 in PHOENIX 1 was 84% and 86% in the 45 mg and 90 mg ustekinumab groups, respectively, compared with 10% in the placebo group. Similarly, 84% of patients treated with 45 mg ustekinumab, 89% of patients treated with 90 mg ustekinumab and 10% of patients treated with placebo reached PASI 50 in PHOENIX 2 (Table 2.3).

### Response over time

In PHOENIX 1, significantly greater proportions of ustekinumab-treated patients had PASI 50 responses (9% and 10% for the 45 mg and 90 mg groups, respectively) compared with placebo (2%) by Week 2 ( $p < 0.001$ ). Significantly greater proportions of patients treated with ustekinumab achieved PASI 75 responses (9% and 12% for the 45 mg and 90 mg ustekinumab groups, respectively) compared with placebo (0.4%) by Week 4 ( $p < 0.001$ ). Maximum response was generally achieved by Week 24 in the 45 mg and 90 mg ustekinumab treatment groups, and response rates were generally sustained through Week 36 (Figure 2.1). In PHOENIX 1, PASI 75 rates at Week 24 were 76% for the 45 mg group, and 85% for the 90 mg group. Higher response rates were observed in patients receiving ustekinumab 90 mg than in those receiving ustekinumab 45 mg by Week 16 and these higher response rates were sustained through Week 36 (Figure 1). Similar results were observed in the PHOENIX 2 study through Week 28.



**Figure 2.1: PASI 75 response over time in PHOENIX 1 and 2**

In prespecified analyses of efficacy by body weight in PHOENIX 1 and PHOENIX 2, no consistent pattern of dose response was seen in patients  $\leq 100$  kg. In patients who weighed  $>100$  kg, higher PASI 75 response rates were seen with 90 mg dosing compared with 45 mg dosing, and a higher proportion of patients receiving 90 mg dosing had PGA scores of cleared or minimal compared with patients receiving 45 mg dosing (Table 2.4).

**Table 2.4: Clinical Outcomes by Weight – PHOENIX 1 and PHOENIX 2**

| <b>Week 12</b>                      |                    |                    |              |                    |                    |              |
|-------------------------------------|--------------------|--------------------|--------------|--------------------|--------------------|--------------|
|                                     | <b>PHOENIX 1</b>   |                    |              | <b>PHOENIX 2</b>   |                    |              |
|                                     | <b>Placebo</b>     | <b>Ustekinumab</b> |              | <b>Placebo</b>     | <b>Ustekinumab</b> |              |
|                                     |                    | <b>45 mg</b>       | <b>90 mg</b> |                    | <b>45 mg</b>       | <b>90 mg</b> |
| Patients randomized at Week 0       | 255                | 255                | 256          | 410                | 409                | 411          |
| PASI 75 response by weight          |                    |                    |              |                    |                    |              |
| ≤ 100 kg                            |                    |                    |              |                    |                    |              |
| N                                   | 166                | 168                | 164          | 290                | 297                | 289          |
| PASI 75 response                    | 6 (4%)             | 124 (74%)          | 107 (65%)    | 12 (4%)            | 218 (73%)          | 225 (78%)    |
| >100 kg                             |                    |                    |              |                    |                    |              |
| N                                   | 89                 | 87                 | 92           | 120                | 112                | 121          |
| PASI 75 response                    | 2 (2%)             | 47 (54%)           | 63 (68%)     | 3 (3%)             | 55 (49%)           | 86 (71%)     |
| PGA of Cleared or Minimal by weight |                    |                    |              |                    |                    |              |
| ≤ 100 kg                            |                    |                    |              |                    |                    |              |
| N                                   | 166                | 168                | 164          | 290                | 297                | 289          |
| PGA response                        | 7 (4%)             | 110 (65%)          | 104 (63%)    | 16 (6%)            | 219 (74%)          | 217 (75%)    |
| >100 kg                             |                    |                    |              |                    |                    |              |
| N                                   | 89                 | 87                 | 92           | 120                | 112                | 121          |
| PGA response                        | 3 (3%)             | 44 (51%)           | 54 (59%)     | 4 (3%)             | 59 (53%)           | 85 (70%)     |
| <b>Week 28</b>                      |                    |                    |              |                    |                    |              |
|                                     | <b>PHOENIX 1</b>   |                    |              | <b>PHOENIX 2</b>   |                    |              |
|                                     | <b>Ustekinumab</b> |                    |              | <b>Ustekinumab</b> |                    |              |
|                                     | <b>45 mg</b>       | <b>90 mg</b>       |              | <b>45 mg</b>       | <b>90 mg</b>       |              |
| N                                   | 250                | 243                |              | 397                | 400                |              |
| PASI 75 response by weight          |                    |                    |              |                    |                    |              |
| ≤ 100 kg                            |                    |                    |              |                    |                    |              |
| N                                   | 164                | 153                |              | 287                | 280                |              |
| PASI 75 response                    | 130 (79%)          | 124 (81%)          |              | 217 (76%)          | 226 (81%)          |              |
| >100 kg                             |                    |                    |              |                    |                    |              |
| N                                   | 86                 | 90                 |              | 110                | 119                |              |
| PASI 75 response                    | 48 (56%)           | 67 (74%)           |              | 59 (54%)           | 88 (74%)           |              |
| PGA of Cleared or Minimal by weight |                    |                    |              |                    |                    |              |
| ≤ 100 kg                            |                    |                    |              |                    |                    |              |
| N                                   | 164                | 153                |              | 287                | 280                |              |
| PGA response                        | 107 (65%)          | 107 (70%)          |              | 194 (68%)          | 208 (74%)          |              |
| >100 kg                             |                    |                    |              |                    |                    |              |
| N                                   | 86                 | 90                 |              | 110                | 119                |              |
| PGA response                        | 40 (47%)           | 54 (60%)           |              | 49 (45%)           | 71 (60%)           |              |

### Therapeutic benefit of long-term continuous use

At Week 40 in PHOENIX 1, among patients who were PASI 75 responders at both weeks 28 and 40, 162 patients were re-randomized to receive ustekinumab at 45 mg and 90 mg given every 12 weeks (maintenance treatment) and 160 were re-randomized to receive placebo (treatment withdrawal). Maintenance of PASI 75 was significantly superior with continuous maintenance treatment compared with treatment withdrawal ( $p < 0.001$ ) through at least 1.5 years of follow-up. Similar results were seen with each dose of ustekinumab.

At Week 52, 89% of patients re-randomized to maintenance treatment were PASI 75 responders compared with 63% of patients re-randomized to placebo (treatment withdrawal) ( $p < 0.001$ ) (Table 2.5). At Week 76, 84% of patients re-randomized to maintenance treatment were PASI 75 responders compared with 19% of patients re-randomized to placebo (treatment withdrawal) ( $p < 0.001$ ). Through Week 76, the proportion of subjects in the combined maintenance treatment group who were PASI 50 responders remained consistently at greater than 95%. By contrast, the proportion of PASI 50 responders in the combined withdrawal group progressively decreased over time such that by Weeks 52 and 76, only 50% and 31% remained as PASI 50 responders respectively. Among patients withdrawn from treatment, the rates of loss of the various PASI responses (PASI 50, 75, 90) were generally comparable in all groups regardless of dose. No rebound of psoriasis occurred in patients who were randomized to treatment withdrawal.

**Table 2.5: Summary of PASI response from Week 40 through Week 76 in subjects randomized at Week 40 in PHOENIX 1**

|                                | Ustekinumab |            | Ustekinumab |            | Ustekinumab |             |
|--------------------------------|-------------|------------|-------------|------------|-------------|-------------|
|                                | 45 mg       |            | 90 mg       |            | Combined    |             |
|                                | Placebo     | q12 wks    | Placebo     | q12 wks    | Placebo     | q12 wks     |
| Patients randomized at Week 40 | 73          | 77         | 87          | 85         | 160         | 162         |
| Week 52 N                      | 73          | 77         | 86          | 85         | 159         | 162         |
| ≥90% improvement               | 27 (37.0%)  | 45 (58.4%) | 33 (38.4%)  | 60 (70.6%) | 60 (37.7%)  | 105 (64.8%) |
| ≥75% improvement               | 47 (64%)    | 67 (87.0%) | 53 (61.6%)  | 77 (90.6%) | 100 (62.9%) | 144 (88.9%) |
| ≥50% improvement               | 63 (86%)    | 75 (97.4%) | 71 (82.6%)  | 83 (97.6%) | 134 (84.3%) | 158 (97.5%) |
| Week 76 N                      | 71          | 77         | 85          | 82         | 156         | 159         |
| ≥90% improvement               | 5 (7.0%)    | 38 (49.4%) | 4 (4.7%)    | 52 (63.4%) | 9 (5.8%)    | 90 (56.6%)  |
| ≥75% improvement               | 14 (19.7%)  | 63 (81.8%) | 15 (17.6%)  | 71 (86.6%) | 29 (18.6%)  | 134 (84.3%) |
| ≥50% improvement               | 22 (31.0%)  | 74 (96.1%) | 27 (31.8%)  | 79 (96.3%) | 49 (31.4%)  | 153 (96.2%) |

### Efficacy of retreatment

In PHOENIX 1, after randomized withdrawal from therapy at week 40, patients reinitiated their original ustekinumab treatment regimen after a loss of  $\geq 50\%$  of PASI improvement. Retreatment with ustekinumab resulted in 71% of evaluated patients regaining PASI 75 response within 8 weeks after reinitiating therapy and 85% of evaluated patients regaining PASI 75 response within 12 weeks after reinitiating therapy.

### Dosing interval adjustment

In PHOENIX 1, Week 28 and Week 40 partial responders and Week 40 nonresponders were adjusted from every-12-week to every-8-week dosing. Approximately 40%-50% of Week 28 partial responders to every-12-week dosing achieved PASI 75 response after adjustment to every-8-week dosing and this proportion of PASI 75 responders was maintained through Week

52. A similar proportion of patients who were PASI 75 responders at Week 28 and subsequently became partial responders or nonresponders at Week 40 achieved PASI 75 response following a dosing interval adjustment to every 8 weeks.

In PHOENIX 2, among patients initially randomized to 90 mg dosing who were partial responders at Week 28, dosing adjustment to every 8 weeks resulted in consistently superior efficacy as compared with continued every 12 weeks dosing: Partial responders randomized to 90 mg every 8 weeks achieved PASI 75 response at more visits between Weeks 40 and 52 than partial responders randomized to continue 90 mg every 12 weeks ( $p = 0.014$ ), and a higher proportion of subjects achieved a PASI 75 response at Week 52 (68.8% with every 8 weeks dosing versus 33.3% with every 12 weeks dosing;  $p = 0.004$ ). Among patients initially randomized to 45 mg dosing who were partial responders at Week 28, response rates were not higher among patients in whom dosing was adjusted to every 8 weeks compared with patients who continued every 12 weeks dosing.

### *Quality of life*

In PHOENIX 1 and 2, the mean baseline DLQI scores ranged from 11 to 12. In PHOENIX 1, the mean baseline SF-36 Physical Component ranged from 47-49 and the mean baseline SF-36 Mental Component was approximately 50. Quality of life improved significantly in patients randomized to 45 mg or 90 mg ustekinumab compared with patients randomized to placebo as evaluated by DLQI in PHOENIX 1 and 2 and SF-36 in PHOENIX 1. Quality of life improvements were significant as early as 2 weeks in patients treated with ustekinumab ( $p < 0.001$ ) and these improvements were maintained over time with continued dosing.

In PHOENIX 1, 65% and 71% of patients treated with 45 mg and 90 mg of ustekinumab, respectively, showed a clinically meaningful reduction (5 or more points) in DLQI from baseline at week 12 compared to 18% in placebo group ( $p < 0.001$  for both groups compared with placebo). Furthermore, 33% and 34% of patients treated with 45 mg and 90 mg of ustekinumab, respectively, showed a DLQI score of 0 compared to 1% in the placebo group ( $p < 0.001$  for both groups compared with placebo), indicating no impairment in QOL from disease or treatment in these patients. In PHOENIX 2, 72% and 77% of patients treated with 45 mg and 90 mg of ustekinumab, respectively, showed a clinically meaningful reduction (5 or more points) in DLQI from baseline at Week 12 compared to 21% in placebo group ( $p < 0.001$  for both groups compared with placebo). In addition, 37% and 39% of patients treated with 45 mg and 90 mg of ustekinumab, respectively, showed a DLQI score of 0 compared to 1% in the placebo group ( $p < 0.001$  for both groups compared with placebo).

In PHOENIX 1, the median baseline NAPSI score for nail psoriasis was 4.0 and the median number of fingernails involved with psoriasis was 8.0. Nail psoriasis improved significantly in patients randomized to 45 mg or 90 mg ustekinumab compared with patients randomized to placebo when measured by the NAPSI score ( $p \leq 0.001$ ). Improvements in physical and mental component summary scores of the SF-36 and in the Itch Visual Analogue Scale (VAS) were also significant in each ustekinumab treatment group compared with placebo ( $p < 0.001$ ). In PHOENIX 2, the Hospital Anxiety and Depression Scale (HADS) and Work Limitations Questionnaire (WLQ) were also significantly improved in each ustekinumab treatment group compared with placebo ( $p < 0.001$ ).

### ACCEPT

Significantly greater proportions of subjects treated with ustekinumab 45 mg (67%; p = 0.012) or 90 mg (74%; p < 0.001) were PASI 75 responders at Week 12 compared with the etanercept group (56.8%). PASI 90 response was observed in 36% and 45 % of patients in the ustekinumab 45 mg and 90 mg groups, respectively, compared with 23% of patients receiving etanercept (p<0.001 for each comparison versus etanercept). PASI 100 response was observed in 12% and 21% of patients in the ustekinumab 45 mg and 90 mg groups, respectively, compared to 6% of patients receiving etanercept (Table 2.6). In addition, a greater proportion of patients in the ustekinumab 45 mg and 90 mg treatment groups achieved a PGA score of “cleared” or “minimal” (65 % and 71 %, respectively) compared with patients in the etanercept treatment group (49 %) (p<0.001 for each comparison versus etanercept).

**Table 2.6 Clinical outcomes at Week 12: ACCEPT**

|  | ACCEPT                            |                                    |                        |
|--|-----------------------------------|------------------------------------|------------------------|
|  | Etanercept<br>(50mg twice a week) | Ustekinumab (at week 0 and week 4) |                        |
|  |                                   | 45 mg                              | 90 mg                  |
| Patients randomized                          | 347                               | 209                                | 347                    |
| <b>PASI response</b>                         |                                   |                                    |                        |
| PASI 50 response                             | 286 (82%)                         | 181 (87%)                          | 320 (92%) <sup>a</sup> |
| PASI 75 response                             | 197 (57%)                         | 141 (67%) <sup>b</sup>             | 256 (74%) <sup>a</sup> |
| PASI 90 response                             | 80 (23%)                          | 76 (36%) <sup>a</sup>              | 155 (45%) <sup>a</sup> |
| PASI 100 response                            | 22 (6%)                           | 25 (12%) <sup>c</sup>              | 74 (21%) <sup>a</sup>  |
| <b>PGA of Cleared or Minimal<sup>a</sup></b> | 170 (49%)                         | 136 (65%) <sup>a</sup>             | 245 (71%) <sup>a</sup> |
| <b>PASI 75 RESPONSE BY WEIGHT</b>            |                                   |                                    |                        |
| ≤100 kg                                      |                                   |                                    |                        |
| N  | 251                               | 151                                | 244                    |
| PASI 75 response                             | 154 (61%)                         | 109 (72%)                          | 189 (77%)              |
| >100 kg                                      |                                   |                                    |                        |
| N  | 96                                | 58                                 | 103                    |
| PASI 75 response                             | 43 (45%)                          | 32 (55%)                           | 67 (65%)               |
| <b>PGA OF CLEARED OR MINIMAL BY WEIGHT</b>   |                                   |                                    |                        |
| ≤100 kg                                      |                                   |                                    |                        |
| N  | 251                               | 151                                | 244                    |
| PGA response                                 | 131 (52%)                         | 110 (73%)                          | 185 (76%)              |
| >100 kg                                      |                                   |                                    |                        |
| N  | 96                                | 58                                 | 103                    |
| PGA response                                 | 39 (41%)                          | 26 (45%)                           | 60 (58%)               |

<sup>a</sup> p < 0.001 for ustekinumab 45 mg or 90 mg comparison with etanercept.

<sup>b</sup> p = 0.012 for ustekinumab 45 mg comparison with etanercept.

<sup>c</sup> p = 0.020 for ustekinumab 45 mg comparison with etanercept.

Greater proportions of subjects in the ustekinumab 45 mg and 90 mg groups achieved PASI 75 responses when compared with subjects in the etanercept group regardless of a subject's previous psoriasis medication history.

## DETAILED PHARMACOLOGY

### TOXICOLOGY

The toxicity of ustekinumab was specifically evaluated in a number of nonclinical studies. An overview of these toxicity studies is provided in Table 2.7.

#### General Toxicity Studies

In repeated-dose toxicity studies in cynomolgus monkeys, ustekinumab was well tolerated following IV doses up to 45 mg/kg/week for up to 1 month and following twice-weekly SC doses up to 45 mg/kg for 6 months. There were no ustekinumab-related findings in the immunotoxicity and cardiovascular safety pharmacology evaluations. In histopathology evaluations there were no preneoplastic changes observed. No evidence of ustekinumab-related local intolerance was observed in examinations of subcutaneous injection sites in a local tolerance study and in the chronic subcutaneous toxicity study.

The 45 mg/kg dose is approximately 45-fold higher than the highest equivalent dose intended to be administered to psoriasis patients (based on administration of a 90 mg SC dose to a 90 kg patient) and the average  $C_{max}$  value observed following the last SC 45 mg/kg dose in the 6-month chronic toxicity study in cynomolgus monkeys was approximately 118-fold higher than the median  $C_{max}$  value of ustekinumab observed following 4 weekly 90 mg SC doses in psoriasis patients.

#### Reproductive Toxicology

Three developmental toxicity studies were conducted in cynomolgus monkeys. No ustekinumab-related maternal toxicity, abortions, still-births, embryotoxicity, developmental delays, malformations or birth defects were observed at doses up to 45 mg/kg following weekly or twice weekly administration of ustekinumab via the IV or SC routes, respectively. In neonates born from pregnant monkeys treated with ustekinumab, no adverse effects on growth or functional development were observed and no deficits were observed in immunotoxicity evaluations. In a male fertility study in cynomolgus monkeys, no ustekinumab-related effects on mating behaviour, sperm parameters, or serum concentrations of male hormones were observed following twice weekly subcutaneous administration of ustekinumab at doses up to 45 mg/kg.

A female fertility toxicity study was conducted in mice using an analogous antibody that binds to and inhibits IL-12 and IL-23 activity in mice. Twice weekly subcutaneous administration of the anti-mouse IL-12/23 antibody was well tolerated at doses up to 50 mg/kg and no adverse effects on female fertility parameters were observed.

**Table 2.7: Non-Clinical Toxicology Studies with ustekinumab**

| Study  | Species/ Strain       | Route    | Duration of Dosing   | Doses (mg/kg)              | Results   |
|--|-----------------------|----------|--|----------------------------|---|
| <b>Repeat-Dose Toxicity</b>                    |                       |          |  |                            |   |
| Subchronic toxicity                            | Monkey/<br>Cynomolgus | IV       | 1 month  | 9, 45 weekly               | No treatment-related signs of toxicity.   |
| Subchronic toxicity                            | Monkey/<br>Cynomolgus | IV       | 1 month  | 9, 45 weekly               | No treatment-related signs of toxicity.   |
| Chronic toxicity                               | Monkey/<br>Cynomolgus | SC       | 6 months   | 22.5, 45 twice weekly      | No treatment-related signs of toxicity. No preneoplastic changes observed on histopathology.  |
| <b>Reproductive and Developmental Toxicity</b> |                       |          |  |                            |   |
| Embryofetal Development                        | Monkey/<br>Cynomolgus | IV       | Pregnant females: gestation day 20 to gestation day 50                                   | 9, 45 weekly               | No maternal or fetal abnormalities were observed.   |
| Embryofetal Development                        | Monkey/<br>Cynomolgus | SC       | Pregnant females: gestation day 20 – gestation day 51                                    | 22.5, 45 twice weekly      | A statistically significant increase in maternal 17 $\beta$ -estradiol levels relative to the control group was observed on days 80 and 100 of gestation in the 22.5 and 45 mg/kg groups. However, foetal 17 $\beta$ -estradiol levels were not affected, and there were no other treatment-related maternal or foetal abnormalities observed at either dose level. |
| Male fertility                                 | Monkey/<br>Cynomolgus | SC       | Males: 13 weeks  | 22.5, 45 twice weekly      | No changes in fertility parameters observed.  |
| Female fertility                               | Mouse/Crl CD-1        | SC       | beginning 15 days before cohabitation and continuing through day 7 of presumed gestation | 25, 50 twice weekly        | No maternal or fetal abnormalities were observed.   |
| Embryofetal and pre- and postnatal development | Monkey/<br>Cynomolgus | SC       | Pregnant females: gestation day 20 – postpartum day 30                                   | 22.5, 45 twice weekly      | No effects on pregnancy or delivery; or morphological, functional and immunological developmental parameters of offspring. Ustekinumab was detected in the milk of lactating monkeys.   |
| <b>Local Tolerance</b>                         |                       |          |  |                            |   |
| Pharmacokinetics and injection site irritation | Monkey/<br>Cynomolgus | SC       | 18 days  | 45 twice weekly            | Minimal signs of local irritation at injection sites were observed, with no associated histopathologic findings.  |
| <b>Other Toxicity Studies</b>                  |                       |          |  |                            |   |
| Tissue cross-reactivity                        | Human Tissues         | In vitro |  | 1.13, 11.3, 113, 225 mg/mL | No binding to nontarget normal human tissues.   |
| Tissue cross-reactivity                        | Human Tissues         | In vitro |  | 1.13, 11.3, 113, 225 mg/mL | No binding to nontarget normal human tissues  |
| Asthma model                                   | Monkey/<br>Cynomolgus | IV       | Single dose  | 9, 45                      | No exacerbation of pulmonary function or cellular responses.  |
| Asthma model                                   | Monkey/<br>Cynomolgus | IV       | 1 week   | 45                         | No exacerbation of pulmonary function or cellular responses.  |

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## PART III: CONSUMER INFORMATION

Pr **STELARA™\***  
ustekinumab Injection

This leaflet is part III of a three-part "Product Monograph" published when STELARA™ was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about STELARA™. Contact your doctor or pharmacist if you have any questions about the drug.

### ABOUT THIS MEDICATION

#### **What the medication is used for:**

STELARA™ is a prescription medicine that is approved for adults with moderate to severe plaque psoriasis that is chronic (doesn't go away).

#### **What it does:**

STELARA™ blocks the action of two proteins in your body called interleukin 12 (IL-12) and interleukin 23 (IL-23). In people with psoriasis, their immune system may attack parts of their body like the skin and nails and that attack uses IL-12 and IL-23. Ustekinumab can block the IL-12 and IL-23 from causing the immune system to attack the skin and nails.

#### **When it should not be used:**

- after the expiration date on the label;
- if the seal is broken;
- if the liquid is discoloured, cloudy or you can see other particulate matter floating in it;
- if you know or think that it may have been exposed to extreme temperatures (such as accidentally frozen or heated);
- if you have had an allergic reaction to STELARA™, or any of the other ingredients in STELARA™. See below for a complete list of ingredients in STELARA™.
- if you have a serious infection such as tuberculosis, infections caused by bacteria or fungi, and bacterial infections that have spread throughout the body (sepsis).

You should not receive a live vaccine while taking STELARA™.

Always keep medicine out of the reach of children.

#### **What the medicinal ingredient is:**

ustekinumab

#### **What the important nonmedicinal ingredients are:**

sucrose, L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80 and water for injection. No preservatives are present.

#### **What dosage forms it comes in:**

Single-use pre-filled syringe: 45 mg/0.5 mL, 90 mg/1.0 mL †

### WARNINGS AND PRECAUTIONS

Your doctor will assess your health before each treatment.

BEFORE you use STELARA™ talk to your doctor or pharmacist if you:

- have any kind of infection even if it is very minor.
- have an infection that won't go away or a history of infection that keeps coming back.
- have had TB (tuberculosis), or if you have recently been near anyone who might have TB.
- have or have had any type of cancer.
- have recently received or are scheduled to receive a vaccine. Tell your doctor if anyone in your house needs a vaccine. The viruses in some vaccines can spread to people with a weakened immune system, and can cause serious problems.
- are receiving an "allergy shot"
- are pregnant, planning to become pregnant, or breastfeeding.

If you develop headache, vision problems, seizures or change in mental status (for example, confusion) contact your doctor immediately.

The needle cover on the pre-filled syringe contains dry natural rubber (a form of latex). This may cause allergic reactions in people who are sensitive to latex. Tell your doctor if you have ever had an allergic reaction to latex and developed any allergic reaction to STELARA™ injection.

STELARA™ should only be used during a pregnancy if needed. Women who are breastfeeding should talk to their doctor about whether or not to use STELARA™.

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

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

†90mg/1.0 mL not available in Canada

## INTERACTIONS WITH THIS MEDICATION

STELARA™ may change the way the body responds to live vaccines.

STELARA™ may interact with other medications that decrease the activity of the immune system.

If you have questions ask your health care provider.

## PROPER USE OF THIS MEDICATION

- STELARA™ is given by injection under the skin.
- STELARA™ is intended for use under the guidance and supervision of your doctor. If your doctor determines that it is appropriate, you may be able to administer STELARA™ to yourself, after proper training in injection technique (see the “Instructions for injecting STELARA™ under the skin yourself”.)

### Usual dose:

Your doctor will determine the right dose of STELARA™ for you and how often you should receive it. Make sure to discuss with your doctor when you will receive injections and to come in for all your scheduled follow-up appointments.

### Overdose:

Call your doctor if you accidentally inject STELARA™ more frequently than instructed.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

### Missed Dose:

If you miss a dose and your psoriasis has not recurred, make the next injection as soon as you remember. Do not double up the injection. If you miss a dose and your psoriasis recurs, call your doctor before taking another injection.

## Instructions for injecting STELARA™ under the skin yourself:

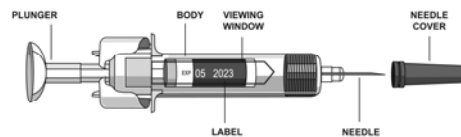
At the start of your therapy, STELARA™ may be injected by your healthcare provider. However, your doctor may decide that it is right for you or your caregiver to learn how to inject STELARA™ under the skin (subcutaneously) yourself. If you would like to self-inject STELARA™, you must be trained by a healthcare professional. If you have not been trained, please contact your healthcare provider to schedule a training session. Call your healthcare provider if you have any questions about giving yourself an injection. STELARA™ is not to be mixed with other liquids for injection.

## INSTRUCTIONS FOR INJECTING STELARA™ USING A PRE-FILLED SYRINGE

To reduce the risk of accidental needle sticks to users, each pre-filled syringe is equipped with a needle guard that is automatically activated to cover the needle after complete delivery of the syringe content.

Do not shake STELARA™ at any time. Prolonged vigorous shaking may damage the product. If the product has been shaken vigorously, don't use it.

### 1: PREPARING FOR PRE-FILLED SYRINGE USE



#### **Take the Syringe out of the Refrigerator**

If your dose amount is 90 mg and you receive two 45 mg packages, you need to give a second injection right after the first. Choose a different site for the second injection.

#### **Check Expiration Date**

Open the box and remove the pre-filled syringe. Check the expiration date on the pre-filled syringe and the label of the box. If the expiration date has passed, don't use it.

#### **Assemble Additional Supplies**

Assemble the additional supplies you will need for your injection. These include an antiseptic wipe, a cotton ball or gauze, and a sharps container for syringe disposal.

#### **Check Solution in Syringe**

Hold the pre-filled syringe with the covered needle pointing upward. Make sure the syringe is not damaged. Look at the solution or liquid in the syringe to make sure that it is clear to slightly opalescent and colorless to slightly yellow. DO NOT use if it is frozen, discolored, cloudy or contains particles and contact your healthcare provider for assistance.

**DO NOT** remove the needle cover from the pre-filled syringe.

**DO NOT** pull back on the plunger head at any time.

### 2: CHOOSING AND PREPARING THE INJECTION SITE

#### **Choose the Injection Site\***

Good sites are the top of the thigh and around the tummy (abdomen) but about 2 inches away from the belly button (navel). Avoid, if possible, skin involved with psoriasis. If your caregiver is giving you the injection, they may use the upper arms or buttocks as well.

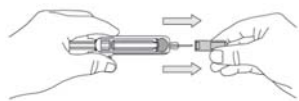


\*Areas in gray are recommended injection sites.

#### **Prepare the Injection Site**

Thoroughly wash your hands with soap and warm water. Wipe the injection site with an antiseptic wipe. DO NOT touch this area again before giving the injection.

### 3: INJECTING THE MEDICATION



#### Remove the Needle Cover

When you are ready to inject, pick up the pre-filled syringe, hold the body of the syringe with one hand and pull the needle cover straight off. Throw the needle cover into the trash. You may notice a small air bubble in the pre-filled syringe. You do not need to remove the air bubble. You may also see a drop of liquid at the end of the needle – this is normal. Do not touch the needle or allow it to touch any surface.

Note: The needle cover should NOT be removed until you are ready to inject the dose. Do not use syringe if it is dropped without the needle cover in place. If you drop the syringe without the needle cover in place, please contact your healthcare provider for assistance.

#### Inject the Medication

Gently pinch the cleaned skin between your thumb and index finger. Don't squeeze it.



Push the syringe needle into the pinched skin.

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 pinched.

When the plunger meets the end of the syringe barrel, and all of the medication has been injected, release the pinched skin and gently remove the needle. Following complete injection, the needle guard will automatically extend over the needle and lock as you take your hand off the plunger.



### 4: AFTER THE INJECTION

Press an antiseptic wipe over the injection site for a few seconds after the injection.

#### Dispose of the Empty Syringe

Immediately dispose of the empty syringe into the sharps container. For your safety and health and for the safety of others, needles and syringes **must NEVER** be re-used. Dispose of sharps container according to your local regulations.

#### Use a Cotton Ball or Gauze

There may be a small amount of blood or liquid at the injection site, which is normal. You can press a cotton ball or gauze over the injection site and hold for 10 seconds. Do not rub the injection site. You may cover the injection site with a small adhesive bandage, if necessary.

### SIDE EFFECTS AND WHAT TO DO ABOUT THEM

STELARA™ is a medicine that may decrease the activity of your immune system. It can increase your chances of getting serious side effects including:

#### Serious Infections

- STELARA™ may lower your ability to fight infections. Some infections could become serious and lead to hospitalization. If you have an infection, tell your healthcare provider before you start using STELARA™. If you get an infection, have any sign of an infection such as fever, feel very tired, cough, flu-like symptoms, or have any open cuts or sores, tell your healthcare provider right away.
- Your doctor will examine you for tuberculosis (TB) and perform a test to see if you have TB. 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™.

#### Cancers

- Many drugs such as STELARA™ that may decrease the activity of the immune system, may increase the risk of cancer. Tell your doctor if you notice any unusual changes to your skin or health status while receiving STELARA™ treatment.

Other serious side effects may occur including allergic reactions. Signs of a serious allergic reaction may include a skin rash, a swollen face, lips, mouth, or throat or wheezing, dizziness, trouble swallowing or breathing. Tell your doctor or get emergency medical help right away if you think you are having an allergic reaction.

The most common side effects of STELARA™ are:

- Upper respiratory infections such as sinus infection and sore throat

Uncommon side effects include cellulitis, a type of infection of the skin.

*This is not a complete list of side effects. For any unexpected*

effects while taking STELARA™, contact your doctor or pharmacist.

## HOW TO STORE IT

If you are using STELARA™ at home, it is important to store the product in your refrigerator although not in the freezer compartment. STELARA™ should not be frozen. Keep the product in the original carton to protect from light until the time of use.

## **REPORTING SUSPECTED SIDE EFFECTS**

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program  
Health Canada  
Postal Locator 0701D  
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect).

*NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.*

## MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:

<http://www.janssen.ca>

or by contacting the sponsor, Janssen Inc.

at: 1-800-567-3331

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