เอกสารกำกับยาภาษาอังกฤษสำหรับแพทย์

PRODUCT NAME

STELARA®, STELARA® 130 MG (ustekinumab)

DOSAGE FORMS AND STRENGTHS

Ustekinumab is a fully human IgG1κ monoclonal antibody with an approximate molecular weight of 148600 daltons. 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 is available in the following presentations:

Solution for injection for subcutaneous administration

Pre-filled Syringe

- 45 mg / 0.5 mL
- 90 mg / 1.0 mL

Single-use Vial

- 45 mg / 0.5 mL
- 90 mg / 1.0 mL

Solution for intravenous infusion

Single-use Vial

- 130 mg / 26 mL

For excipients, see *List of Excipients.*

CLINICAL INFORMATION

Indications

Plaque Psoriasis

Adults

STELARA is indicated for:

- treatment of psoriasis

- improving health related quality of life

in adults with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

Psoriatic Arthritis (PsA):

STELARA, alone or in combination with methotrexate (MTX), is indicated for:

- reducing signs and symptoms
- improving physical function
- inhibiting the progression of structural damage
- improving enthesitis
- improving psoriasis
- improving health-related quality of life

in adults with active psoriatic arthritis.

Crohn's Disease

STELARA is indicated for:

- inducing and maintaining clinical response
- inducing and maintaining clinical remission
- eliminating corticosteroid use
- inducing endoscopic healing
- improving health-related quality of life

in adults with moderately to severely active Crohn's Disease who:

- have failed or were intolerant to immunomodulators or corticosteroids or
- were corticosteroid dependent or
- have failed or were intolerant to one or more anti-TNF treatment.

Dosage and Administration

Dosage – (Adults)

Plaque Psoriasis

For the treatment of plaque psoriasis, STELARA is administered by subcutaneous injection. The recommended dose of STELARA 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.

Dose Adjustment

For patients who inadequately respond to 45 mg every 12 weeks, consideration may be given to treating with 90 mg every 12 weeks. For patients who inadequately respond to dosing every 12 weeks, a 90 mg dose every 8 weeks may be considered.

Re-treatment

Re-treatment with a dosing regimen of Weeks 0 and 4 after interruption of therapy has been shown to be safe and effective.

Psoriatic Arthritis

For the treatment of psoriatic arthritis, STELARA is administered by subcutaneous injection. The recommended dose of STELARA 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.

Crohn's Disease

In patients with Crohn's disease, the recommended treatment regimen is a single intravenous (IV) tiered dose of STELARA based on body weight (Table 1), followed by 90 mg subcutaneous dosing 8 weeks later, then every 8 weeks thereafter (see *Instructions for Use, Handling and Disposal*).

Table 1: Initial IV dosing of STELARA[a]

Body Weight of Patient at the time of dosing	Dose	Number of 130 mg STELARA Vials
≤ 55 kg	260 mg	2
> 55 kg to ≤ 85 kg	390 mg	3
> 85 kg	520 mg	4

[a] Recommended dose (approximately 6 mg/kg)

For some patients, a single IV dose based on body weight (Table 1) followed by 90 mg subcutaneous dosing 8 weeks later, then every 12 weeks thereafter may be acceptable. Patients who inadequately respond to 90 mg subcutaneous dosing every 12 weeks may benefit from an increase in dosing frequency to every 8 weeks. (see *Clinical Studies*)

Immunomodulators and/or corticosteroids may be continued during treatment with STELARA. In patients who have responded to treatment with STELARA corticosteroids may be reduced or discontinued in accordance with standard of care.

If therapy is interrupted, resumption of treatment with subcutaneous dosing every 8 weeks is safe and effective.

General Consideration for Administration

Subcutaneous administration

STELARA is intended for use under the guidance and supervision of a physician. A patient may self-inject with STELARA if a physician determines that it is appropriate and with medical

follow-up as necessary, after proper training in subcutaneous injection technique and disposal (see *Instructions for Use, Handling and Disposal*).

Comprehensive instructions for the subcutaneous administration of STELARA are given in the "Core Patient Package Insert (CPPI)". Patients should be instructed to inject the prescribed amount of STELARA according to the directions provided in the patient information leaflet. 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.

Intravenous infusion (Crohn's Disease)

STELARA 130 mg vial is for IV infusion only. Intravenous infusion of STELARA should be administered by qualified health care professionals (For preparation, see *Instructions for Use, Handling and Disposal*).

Special populations

Pediatrics

Studies of STELARA in pediatric patients below 12 years of age have not been conducted.

Elderly

Of the 5884 patients exposed to STELARA, a total of 310 were 65 years or older (183 patients with psoriasis, 69 patients with psoriatic arthritis and 58 with Crohn's disease). No major age-related differences in clearance or volume of distribution were observed in clinical studies. Although no differences in safety or efficacy were observed between older and younger patients, the number of patients aged 65 and over is not sufficient to determine whether they respond differently from younger patients.

Renal impairment

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

Hepatic impairment

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

Contraindications

Severe hypersensitivity to ustekinumab or to any of the excipients (see *Warnings and Precautions*).

Warnings and Precautions

Infections

STELARA is a selective immunosuppressant 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 in patients receiving STELARA.

STELARA should not be given to patients with a 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, 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. 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 should not be administered until the infection resolves (see *Adverse Reactions*).

Malignancies

STELARA is a selective immunosuppressant. Immunosuppressive agents have the potential to increase the risk of malignancy. Some patients who received STELARA in clinical studies developed cutaneous and noncutaneous malignancies (see *Adverse Reactions*).

STELARA 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.

All patients, in particular those greater than 60 years of age, patients with a medical history of prolonged immunosuppressant therapy or those with a history of PUVA treatment, should be monitored for the appearance of non-melanoma skin cancer (see *Adverse Reactions*).

Hypersensitivity reactions

In post-marketing experience, serious hypersensitivity reactions, including anaphylaxis and angioedema, have been reported. If an anaphylactic or other serious hypersensitivity reaction occurs, institute appropriate therapy and administration of STELARA should be discontinued (see *Adverse Reactions*).

Immunizations

It is recommended that live viral or live bacterial vaccines not be given concurrently with STELARA.

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.

Long term treatment with STELARA does not suppress the humoral immune response to pneumococcal polysaccharide or tetanus vaccines (see *Pharmacodynamic Properties*).

Immunosuppression

In psoriasis studies, the safety and efficacy of STELARA in combination with immunosuppressive agents or phototherapy have not been evaluated. In psoriatic arthritis studies, concomitant MTX use did not appear to influence the safety or efficacy of STELARA. In Crohn's disease studies, concomitant use of immunomodulators (6-mercaptopurine (6-MP), azathioprine (AZA), MTX) or corticosteroids did not appear to influence the safety or efficacy of STELARA. Caution should be exercised when considering concomitant use of immunosuppressive agents and STELARA or when transitioning from other biologic agents.

Immunotherapy

STELARA 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.

General

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.

Interactions

- Drug interaction studies have not been conducted in humans with STELARA (see *Pharmacokinetic Properties*).

- 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). These results do not suggest the need for dose adjustments in patients who are receiving concomitant CYP450 substrates (see *Pharmacokinetic Properties*).

- Live vaccines should not be given concurrently with STELARA (see *Warnings and Precautions*).

Pregnancy, Breast-feeding and Fertility

Pregnancy

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 patients with psoriasis (see *Non-Clinical Information*). However, animal reproductive and developmental studies are not always predictive of human response.

It is not known whether STELARA can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. STELARA should be given to a pregnant woman only if the benefit clearly outweighs the risk.

Breast-feeding

STELARA is excreted in the milk of lactating monkeys administered STELARA. It is not known if STELARA 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 STELARA, a decision should be made whether to discontinue nursing or to discontinue the drug.

Fertility

The effect of STELARA on human fertility has not been evaluated. No adverse effects on female fertility parameters were identified in a female fertility toxicity study conducted in mice (see *Non-Clinical Information*).

Effects on Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed.

Adverse Reactions

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of ustekinumab based on the comprehensive assessment of the available adverse event information. A causal relationship with ustekinumab cannot be reliably established in individual cases. Further, 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 clinical practice.

Clinical Studies Experience in Adult Patients with Psoriasis, Psoriatic Arthritis and Crohn's Disease

The safety data described below reflect exposure to STELARA in 12 Phase 2 and Phase 3 studies in 5884 patients (4135 with psoriasis and/or psoriatic arthritis, and 1749 for Crohn's disease), with duration of exposure to STELARA presented in Table 2.

Table 2: Long term exposure to STELARA in Phase 2 and Phase 3 clinical studies

Exposure	Number of patients
6 months	4105[a]
1 year	2846[a]
≥4 years	1482[b]

≥5 years	838[b]

[a] Total number of patients in the psoriasis, psoriatic arthritis and Crohn's disease studies
[b] Number of patients with psoriasis

The most common adverse reactions (>5%) in controlled periods of the psoriasis, psoriatic arthritis and Crohn's Disease clinical studies with STELARA were nasopharyngitis and headache. Most were considered to be mild and did not necessitate drug discontinuation. The overall safety profile of STELARA was similar for patients with psoriasis, psoriatic arthritis and Crohn's disease.

Table 3 provides a summary of Adverse Reactions from psoriasis, psoriatic arthritis and Crohn's Disease clinical studies. The frequency of these adverse reactions was based on those that occurred during the initial controlled periods of the clinical studies. The adverse reactions are ranked by frequency, using the following convention:

Very common (≥1/10)
Common (frequent) (≥1/100, <1/10)
Uncommon (infrequent) (≥1/1000, <1/100)
Rare (≥1/10000, <1/1000)

Table 3: SUMMARY OF ADVERSE REACTIONS IN CLINICAL STUDIES	
Infections and infestations	Common: Upper respiratory tract infection, nasopharyngitis Uncommon: Cellulitis, dental infections, herpes zoster, viral upper respiratory tract infection, vulvovaginal mycotic infection
Psychiatric disorders	Uncommon: Depression
Nervous system disorders	Common: Dizziness, headache
Respiratory, thoracic and mediastinal disorders	Common: Oropharyngeal pain Uncommon: Nasal congestion
Gastrointestinal disorders	Common: Diarrhea, nausea, vomiting
Skin and subcutaneous tissue disorders	Common: Pruritus Uncommon: Acne
Musculoskeletal and connective tissue disorders	Common: Back pain, myalgia, arthralgia
General disorders and administration site conditions	Common: Fatigue, injection site erythema, injection site pain Uncommon: Injection site reactions (including hemorrhage, hematoma, induration, swelling and pruritus), asthenia

Infections

In the placebo-controlled studies of patients with psoriasis, psoriatic arthritis and Crohn's disease, the rates of infection or serious infection were similar between STELARA-treated patients and those treated with placebo. In the placebo-controlled period of clinical studies of patients with psoriasis, patients with psoriatic arthritis and patients with Crohn's disease, the rate of infection was 1.38 per patient-year of follow-up in STELARA-treated patients, and 1.35 per patient-year of follow-up in placebo-treated patients. Serious infections occurred at a rate of 0.03 per patient-year of follow-up in STELARA-treated patients (27 serious infections in 829 patient-years of follow-up) and 0.03 per patient-year of follow-up in placebo-treated patients (11 serious infections in 385 patient-years of follow-up) (see *Warnings and Precautions*).

In the controlled and non-controlled periods of psoriasis, psoriatic arthritis and Crohn's disease clinical studies representing 10953 patient-years of exposure in 5884 patients, the median follow-up was 0.99 years; 3.2 years for psoriasis studies, 1.0 year for psoriatic arthritis studies and 0.6 year for Crohn's disease studies. The rate of infection was 0.91 per patient-year of follow-up in STELARA-treated patients. The rate of serious infections was 0.02 per patient-year of follow-up in STELARA-treated patients (178 serious infections in 10953 patient-years of follow-up) and included anal abscess, cellulitis, pneumonia, diverticulitis, gastroenteritis and viral infections.

In clinical studies, patients with latent tuberculosis who were concurrently treated with isoniazid did not develop tuberculosis.

Malignancy

In the placebo-controlled period of the psoriasis, psoriatic arthritis and Crohn's disease clinical studies, the incidence of malignancies excluding non-melanoma skin cancer was 0.12 per 100 patient-years of follow-up for STELARA-treated patients (1 patient in 829 patient-years of follow-up) compared with 0.26 per 100 patient-years of follow-up for placebo-treated patients (1 patient in 385 patient-years of follow-up). The incidence of non-melanoma skin cancer was 0.48 per 100 patient-years of follow-up for STELARA-treated patients (4 patients in 829 patient-years of follow-up) compared with 0.52 per 100 patient-years of follow-up for placebo-treated patients (2 patients in 385 patient-years of follow-up).

In the controlled and non-controlled periods of psoriasis, psoriatic arthritis and Crohn's disease clinical studies representing 10935 patient-years of exposure in 5884 patients, the median follow-up was 1.0 years; 3.2 years for psoriasis studies, 1.0 year for psoriatic arthritis studies and 0.6 year for Crohn's disease studies. Malignancies, excluding non-melanoma skin cancers, were reported in 58 patients in 10935 patient-years of follow-up (incidence of 0.53 per 100 patient-years of follow-up for STELARA-treated patients). The incidence of malignancies, reported in STELARA-treated patients was comparable to the incidence expected in the general population (standardized incidence ratio = 0.87 [95% confidence interval: 0.66, 1.14], adjusted for age, gender and race).[1] The most frequently observed malignancies, other than non-melanoma skin cancer, were prostate, melanoma, colorectal and breast. The incidence of non-melanoma skin cancer was 0.49 per 100 patient-years of follow-up for STELARA-treated patients (53 patients in 10919 patient-years of follow-up). The ratio of patients with basal versus squamous cell skin cancers (4:1) is comparable with the ratio expected in the general population (see *Warnings and Precautions*).

[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.

Hypersensitivity and Infusion Reactions

Subcutaneous administration

During the controlled periods of the psoriasis and psoriatic arthritis clinical studies of STELARA, rash and urticaria have each been observed in <1% of patients.

IV administration

In Crohn's disease induction studies, no events of anaphylaxis or other serious infusion reactions were reported. In these studies, 2.4% of 466 placebo treated patients and 2.6% of 470 patients treated with the recommended dose of STELARA reported adverse events occurring during or within an hour of the infusion.

Immunogenicity

In psoriasis and psoriatic arthritis clinical studies, approximately 6-12.4% of patients treated with STELARA developed antibodies to ustekinumab. In Crohn's disease clinical studies, less than 3% of patients treated with STELARA developed antibodies to ustekinumab. No apparent association between the development of antibodies to ustekinumab and the development of injection site reactions was observed. Patients positive for antibodies to ustekinumab tended to have lower efficacy, however, antibody positivity did not preclude a clinical response. The majority of patients who were positive for antibodies to ustekinumab had neutralizing antibodies.

Overdose

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

Post Marketing Experience

The adverse reactions in Table 4 are ranked by frequency* using the following convention:

Very common: ≥1/10
Common: ≥1/100 and <1/10
Uncommon: ≥1/1000 and <1/100
Rare: ≥1/10000 and <1/1000
Very rare: <1/10000, including isolated reports

Table 4: Post-Marketing Reports

Immune system disorders	Uncommon: Hypersensitivity reactions (including rash, urticaria) Rare: Serious hypersensitivity reactions (including anaphylaxis and angioedema)
Infections and infestations	Uncommon: Lower respiratory tract infection
Skin and subcutaneous tissue disorders	Uncommon: Pustular psoriasis Rare: Erythrodermic psoriasis

* Post-marketing adverse reaction frequency is derived from the placebo-controlled portion of the 11 clinical trials if the adverse reaction was observed in those trials. Otherwise, it is estimated to be lower than a certain frequency given the exposure in the 11 clinical trials where the adverse reaction was not observed.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic group: Immunosuppressants, interleukin inhibitors, ATC code: L04AC05.

Mechanism of action

STELARA is a fully human IgG1κ monoclonal antibody that binds with specificity to the shared p40 protein subunit of human cytokines interleukin (IL)-12 and IL-23. STELARA inhibits the bioactivity of human IL-12 and IL-23 by preventing p40 from binding to the IL-12Rβ1 receptor protein expressed on the surface of immune cells. STELARA cannot bind to IL-12 or IL-23 that is already bound to IL-12Rβ1 cell surface receptors. Thus, STELARA is not likely to contribute to complement or antibody mediated cytotoxicity of cells expressing IL-12 and/or IL-23 receptors.

IL-12 and IL-23 are heterodimeric cytokines secreted by activated antigen presenting cells, such as macrophages and dendritic cells. IL-12 stimulates natural killer (NK) cells and drives the differentiation of CD4+ T cells toward the T helper 1 (Th1) phenotype and stimulates interferon gamma (IFNγ) production. IL-23 induces the T helper 17 (Th17) pathway and promotes secretion of IL-17A, IL-21, and IL-22. Levels of IL-12 and IL-23 are elevated in the skin and blood of patients with psoriasis, and serum IL12/23p40 distinguishes patients with psoriatic arthritis from healthy individuals, implicating IL-12 and IL-23 in the pathophysiology of psoriatic inflammatory diseases. Genetic polymorphisms in IL23A, IL23R, and IL-12B genes confer susceptibility to these disorders. Additionally, IL-12 and IL-23 are highly expressed in lesional psoriatic skin, and IL-12-mediated induction of IFNγ correlates with psoriasis disease activity. IL-23 responsive T-cells have been found in the entheses in a mouse model of inflammatory arthritis, where IL-23 drives entheseal inflammation. In addition, there is pre-clinical evidence implicating IL-23 and downstream pathways in bone erosion and destruction through up-regulation of receptor activator of nuclear factor-κB ligand (RANKL), which activates osteoclasts.

In patients with Crohn's disease, IL-12 and IL-23 are elevated in the intestines and lymph nodes. This is accompanied by increases in serum IFNγ and IL-17A levels, suggesting that IL-12 and IL-23 promote Th1 and Th17 activation in Crohn's disease. Both IL-12 and IL-23 can also stimulate TNFα production by T cells, resulting in chronic intestinal inflammation and epithelial cell injury. Significant associations have been found between Crohn's disease and genetic polymorphisms in the IL23R and IL12B genes, suggesting a potential causal role for IL-12/23 signaling in the disease. This is supported by pre-clinical data demonstrating that IL-12/23 signaling is required for intestinal injury in mouse models of inflammatory bowel disease.

By binding the shared p40 subunit of IL-12 and IL-23, STELARA may exert its clinical effects in psoriasis, psoriatic arthritis and Crohn's disease through interruption of the Th1 and Th17 cytokine pathways, which are central to the pathology of these diseases.

Pharmacodynamic effects

Treatment with STELARA resulted in significant improvement in histological measures of psoriasis including epidermal hyperplasia and cell proliferation. These results are consistent with the clinical efficacy observed.

In patients with psoriasis and/or psoriatic arthritis, STELARA had no apparent effect on the percentages of circulating immune cell populations including memory and naive T cell subsets or circulating cytokine levels. Systemic markers of inflammation were measurable in the serum at baseline and 4 markers (MDC, VEGF, MCSF-1 and YKL-40) showed modest differences in concentration post-treatment in STELARA-treated patients as compared to placebo.

Treatment with STELARA 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 2 weeks post-treatment. In addition, STELARA 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 STELARA treatment in psoriasis.

In psoriasis and psoriatic arthritis studies, clinical response (improvement in PASI or ACR measurements, respectively) appeared to be related to serum ustekinumab levels. Patients with psoriasis with higher PASI response had higher median serum concentrations of ustekinumab than those with lower clinical responses. In psoriasis studies, the proportion of patients 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. In psoriatic arthritis studies, patients achieving an ACR 20 response had higher median serum concentrations of ustekinumab than ACR 20 non-responders. The proportion of patients who achieved ACR 20 and ACR 50 response increased with increasing serum levels of ustekinumab.

In patients with Crohn's disease, treatment with STELARA resulted in a significant decrease in inflammatory markers including C-Reactive Protein (CRP) and fecal calprotectin. Reductions in serum IFNγ and IL-17A, which are IL-12 and IL-23 regulated pro-inflammatory cytokines, were achieved and maintained in STELARA treated patients through Week 44 compared to placebo. Expression of genes such as IL-12Rβ1 and IL-23 was reduced in inflamed colon tissue from Crohn's disease patients, responders to STELARA treatment while no significant changes were observed in placebo treated patients at Week 6.

Immunization

During the long term extension of a Phase 3 psoriasis study (PHOENIX 2), patients treated with STELARA for at least 3.5 years mounted similar antibody responses to both pneumococcal polysaccharide and tetanus vaccines as a non-systemically treated psoriasis control group. Similar proportions of patients developed protective levels of anti-pneumococcal and anti-tetanus antibodies and antibody titers were similar among STELARA-treated and control patients.

Clinical studies

Clinical Efficacy-Plaque Psoriasis

The safety and efficacy of STELARA was assessed in 2 Phase 3, multicenter, randomized, double-blind, placebo-controlled studies in patients with moderate to severe plaque psoriasis (PHOENIX 1 and PHOENIX 2). A total of 1996 patients were enrolled in these studies.

The studies enrolled adults (≥ 18 years) with chronic (> 6 months) plaque psoriasis who had a minimum body surface area (BSA) involvement of 10%, and PASI score ≥ 12 and who were candidates for systemic therapy or phototherapy. Patients with guttate, erythrodermic, or pustular psoriasis were excluded from the studies. No concomitant antipsoriatic therapies were allowed during the study with the exception of low-potency topical corticosteroids on the face and groin after week 12.

The PASI is a composite score that assesses the fraction of body surface area involved with psoriasis and the severity of psoriatic changes within the affected regions (plaque thickness/induration, erythema, and scaling). PASI numeric scores range from 0 to 72, with higher scores representing more severe disease.

Patients achieving ≥ 75% improvement in PASI from baseline (PASI 75) were considered PASI 75 responders. Patients originally randomized to STELARA who were PASI 75 responders at both Weeks 28 and 40 were considered long-term PASI 75 responders. Patients achieving ≥ 90% improvement in PASI from baseline (PASI 90) were considered PASI 90 responders and patients with ≥ 50% improvement in PASI from baseline (PASI 50) were considered PASI 50 responders. Patients who achieved ≥ 50% but less than 75% improvement in PASI from baseline were considered partial responders. Patients with < 50% improvement in PASI from baseline were considered nonresponders.

Other key efficacy assessments included:

- The Physician's Global Assessment (PGA), a 6-category scale: 0 =cleared, 1 = minimal, 2 = mild, 3= moderate, 4 = marked and 5 = severe, that indicates the physician's overall assessment of psoriasis focusing on plaque thickness/induration, erythema, and scaling. The PGA was assessed in PHOENIX 1 and 2.
- 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. DLQI scores range from 0 to 30, with a lower score representing a better quality of life. A decrease of 5 in the DLQI score from baseline is considered a clinically meaningful improvement. The DLQI was assessed in PHOENIX 1 and 2.
- The SF-36, a health survey questionnaire consisting of multi-item scales measuring 8 health concepts. The SF-36 yields composite scores that provide a measure of disease impact on physical and mental health status. Higher SF-36 scores indicate a better quality of life. The SF-36 was assessed in PHOENIX 1.
- The Nail Psoriasis Severity Index (NAPSI), a physician-assessed score that measures the severity of nail involvement. The scale consists of 4 components of nail matrix disease and 4 components of nail bed disease with scores from 0 to 8, with a lower scores representing milder disease. The NAPSI was assessed in PHOENIX 1.
- The Hospital Anxiety and Depression Scale (HADS), a self-rating tool developed to evaluate psychological measures in patients with physical

ailments. It consists of 2 subscales, one measuring anxiety (A-scale) and one measuring Depression (D-scale), which are scored separately. Lower HADS scores correspond to lesser psychological impairment. The HADS was assessed in PHOENIX 2.

- 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. The WLQ assesses four aspects of work and productivity: Physical Demands, Time Management, Mental-Interpersonal Demand, and Output Demand. The four subscales range from 0-100 with the lower score indicating fewer work limitations. The WLQ was assessed in PHOENIX 2.
- The Itch Visual Analog Scale, used to assess the severity of itch at the time of the assessment. Itch is assessed using a 10 cm horizontal line, or a Visual Analog Scale (VAS), representing the range of itch severity, from 0 (no itch at all) to 10 (severe itch). The Itch VAS was assessed in PHOENIX 1.

PHOENIX 1

PHOENIX 1 evaluated the safety and efficacy of STELARA versus placebo in 766 patients with plaque psoriasis and the efficacy of every 12 week dosing for patients who were PASI 75 responders.

Patients randomized to STELARA received 45 mg or 90 mg doses at Weeks 0 and 4 followed by the same doses every 12 weeks. Patients randomized to receive placebo at Weeks 0 and 4 crossed over to receive STELARA (either 45 mg or 90 mg) at Weeks 12 and 16 followed by the same dose every 12 weeks.

Maintenance dosing (every 12 weeks)

To evaluate the therapeutic benefit of maintenance dosing with STELARA, patients originally randomized to STELARA who were PASI 75 responders at both Weeks 28 and 40 were re-randomized to either maintenance dosing of STELARA every 12 weeks or to placebo (ie, withdrawal of therapy). Patients who were re-randomized to placebo at Week 40 reinitiated STELARA at their original dosing regimen when they experienced at least a 50% loss of their PASI improvement obtained at Week 40.

Dose Adjustment (every 8 weeks)

At Week 28, patients who were nonresponders discontinued treatment and patients who were partial responders 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.

All patients were followed for up to 76 weeks following first administration of study treatment.

PHOENIX 2

PHOENIX 2 evaluated the safety and efficacy of STELARA versus placebo in 1230 patients with plaque psoriasis. Patients randomized to STELARA received 45 mg or 90 mg doses at

Weeks 0 and 4 followed by an additional dose at Week 16. Patients randomized to receive placebo at Weeks 0 and 4 crossed over to receive STELARA (either 45 mg or 90 mg) at Weeks 12 and 16 followed by the same dose every 12 weeks.

Dose Adjustment (every 8 weeks)

At Week 28, patients who were nonresponders discontinued treatment and patients who were partial responders were re-randomized to continue every-12-week dosing or switch 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.

All patients were followed for up to 52 weeks following first administration of study agent.

Baseline disease characteristics: PHOENIX 1 and 2

Baseline disease characteristics across PHOENIX 1 and 2 were similar (Table 5).

Table 5: Baseline Disease Characteristics

	PHOENIX 1		*PHOENIX 2*	
	Placebo	*STELARA*	*Placebo*	*STELARA*
Patients randomized at Week 0	*N=255*	*N=511*	*N=410*	*N=820*
Median BSA	*22.0*	*21.0*	*20.0*	*21.0*
BSA ≥ 20%	*145 (57%)*	*276 (54%)*	*217 (53%)*	*445 (54%)*
Median PASI	*17.80*	*17.40*	*16.90*	*17.60*
PASI ≥ 20	*91 (36%)*	*169 (33%)*	*133 (32%)*	*300 (37%)*
PGA of marked or severe	*112 (44%)*	*223 (44%)*	*160 (39%)*	*328 (40%)*
History of psoriatic arthritis	*90 (35%)*	*168 (33%)*	*105 (26%)*	*200 (24%)*
Prior phototherapy	*150 (59%)*	*342 (67%)*	*276 (67%)*	*553 (67%)*
Prior conventional systemic therapy excluding biologics	*142 (56%)*	*282 (55%)*	*241 (59%)*	*447 (55%)*
Prior conventional systemic or biologic therapy	*189 (74%)*	*364 (71%)*	*287 (70%)*	*536 (65%)*
Failed to respond to, had contraindication for, or intolerant to ≥ 1 conventional therapy	*139 (55%)*	*270 (53%)*	*254 (62%)*	*490 (60%)*
Failed to respond to, had contraindication for, or intolerant to ≥ 3 conventional therapies	*30 (12%)*	*54 (11%)*	*66 (16%)*	*134 (16%)*

Efficacy at the Primary Endpoint, PHOENIX 1 and 2

In both the PHOENIX 1 and PHOENIX 2 studies, a significantly greater proportion of patients randomized to treatment with STELARA were PASI 75 responders compared with placebo at Week 12 (Table 6). In the PHOENIX 1 study, 67% and 66% of patients receiving STELARA 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 STELARA 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 STELARA 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 modeling

suggested a trend towards higher CL/F in patients with diabetes, a consistent effect on efficacy was not observed.

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 STELARA achieved a cleared or minimal PGA score, and significantly greater proportions of patients randomized to 45 mg or 90 mg STELARA were PASI 90 and PASI 50 responders at Week 12 (Table 6). In the PHOENIX 1 study, 59% and 61% of the patients treated with 45 mg and 90 mg STELARA, 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 STELARA, respectively, had cleared or minimal PGA scores compared with 4% 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 STELARA, respectively, compared with 2% of placebo-treated patients. In PHOENIX 2, the percentage of patients achieving PASI 90 was 42% in the 45 mg STELARA group, 51% in the 90 mg STELARA group and 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 STELARA groups, respectively, compared with 10% in the placebo group. Similarly, 84% of patients treated with 45 mg STELARA, 89% of patients treated with 90 mg STELARA and 10% of patients treated with placebo reached PASI 50 in PHOENIX 2 (Table 6).

Table 6: Key psoriasis endpoints– PHOENIX 1 and PHOENIX 2

Week 12

	PHOENIX 1			PHOENIX 2		
		STELARA			STELARA	
	Placebo	45 mg	90 mg	Placebo	45 mg	90 mg
Patients randomized at Week 0	255	255	256	410	409	411
PASI response						
PASI 50 response[a]	26 (10%)	213 (84%)	220 (86%)	41 (10%)	342 (84%)	367 (89%)
PASI 75 response[a]	8 (3%)	171 (67%)	170 (66%)	15 (4%)	273 (67%)	311 (76%)
PASI 90 response[a]	5 (2%)	106 (42%)	94 (37%)	3 (1%)	173 (42%)	209 (51%)
PGA of Cleared or Minimal[a,b]	10 (4%)	151 (59%)	156 (61%)	18 (4%)	277 (68%)	300 (73%)
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[b]	7 (4%)	108 (64%)	103 (63%)	14(5%)	220 (74%)	216 (75%)
>100 kg						
N	89	87	92	120	112	121
PGA response[b]	3 (3%)	43 (49%)	53 (58%)	4 (3%)	57 (51%)	84 (69%)

Week 28

	PHOENIX 1		PHOENIX 2	
	STELARA		STELARA	
	45 mg	90 mg	45 mg	90 mg
N	250	243	397	400
PASI response				
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%)
PGA of Cleared or Minimal[b]-	146 (58%)	160 (66%)	241 (61%)	279 (70%)
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[b]	106 (65%)	106 (69%)	192 (67%)	207 (74%)
>100 kg				
N	86	90	110	119
PGA response	40 (47%)	54 (60%)	49 (45%)	71 (60%)

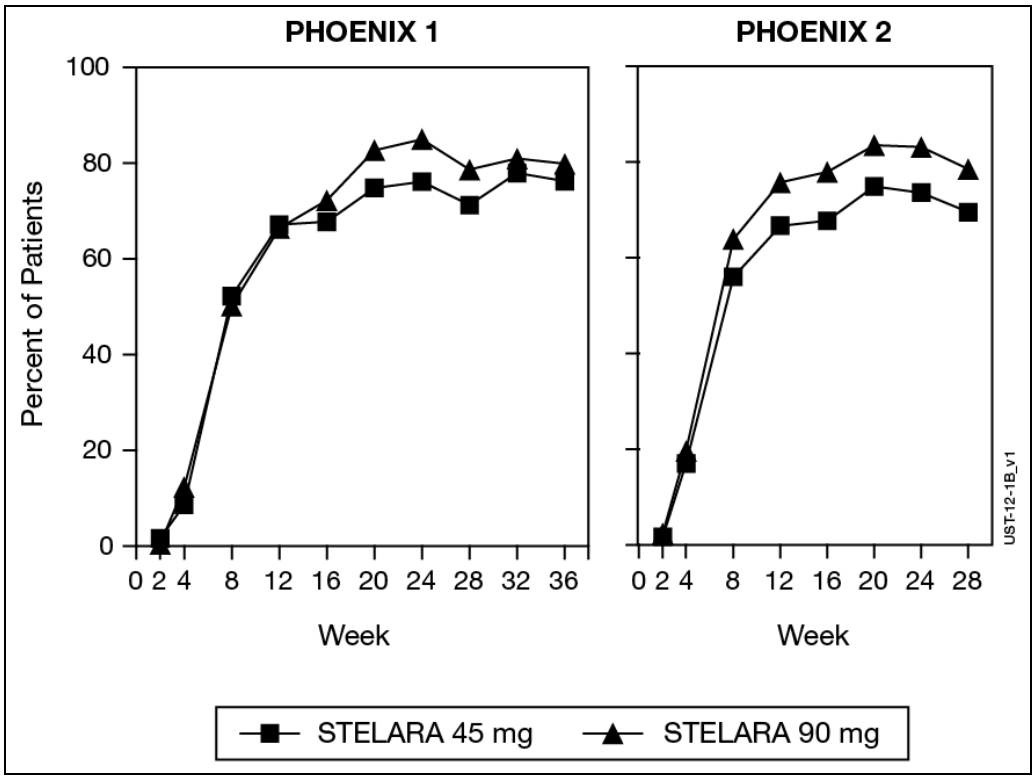
[a] p < 0.001 for 45 mg or 90 mg comparison with placebo.
[b] data corrected post EMEA inspection

Response over time

In PHOENIX 1, significantly greater proportions of STELARA-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 STELARA achieved PASI 75 responses (9% and 12% for the 45 mg and 90 mg STELARA 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–STELARA treatment groups, and response rates were generally sustained through Week 36 (Figure 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 STELARA 90 mg than in those receiving STELARA 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.

In pre-specified analyses of efficacy by body weight in PHOENIX 1 and PHOENIX 2, no consistent pattern of dose response was seen in patients ≤ 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 6).

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



Therapeutic benefit of Long-term continuous use

At Week 40 in PHOENIX 1, 162 patients were randomized to receive STELARA (maintenance) and 160 were randomized to receive placebo (treatment withdrawal). Maintenance of PASI 75 was significantly superior with continuous treatment compared with treatment withdrawal ($p<0.001$). Similar results were seen with each dose of STELARA (Figure 2). At 1 year (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) ($p<0.001$). At 18 months (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). At 3 years (Week 148), 82% of patients re-randomized to maintenance treatment were PASI 75 responders. At 5 years (Week 244), 80% of patients re-randomized to maintenance treatment were PASI 75 responders.

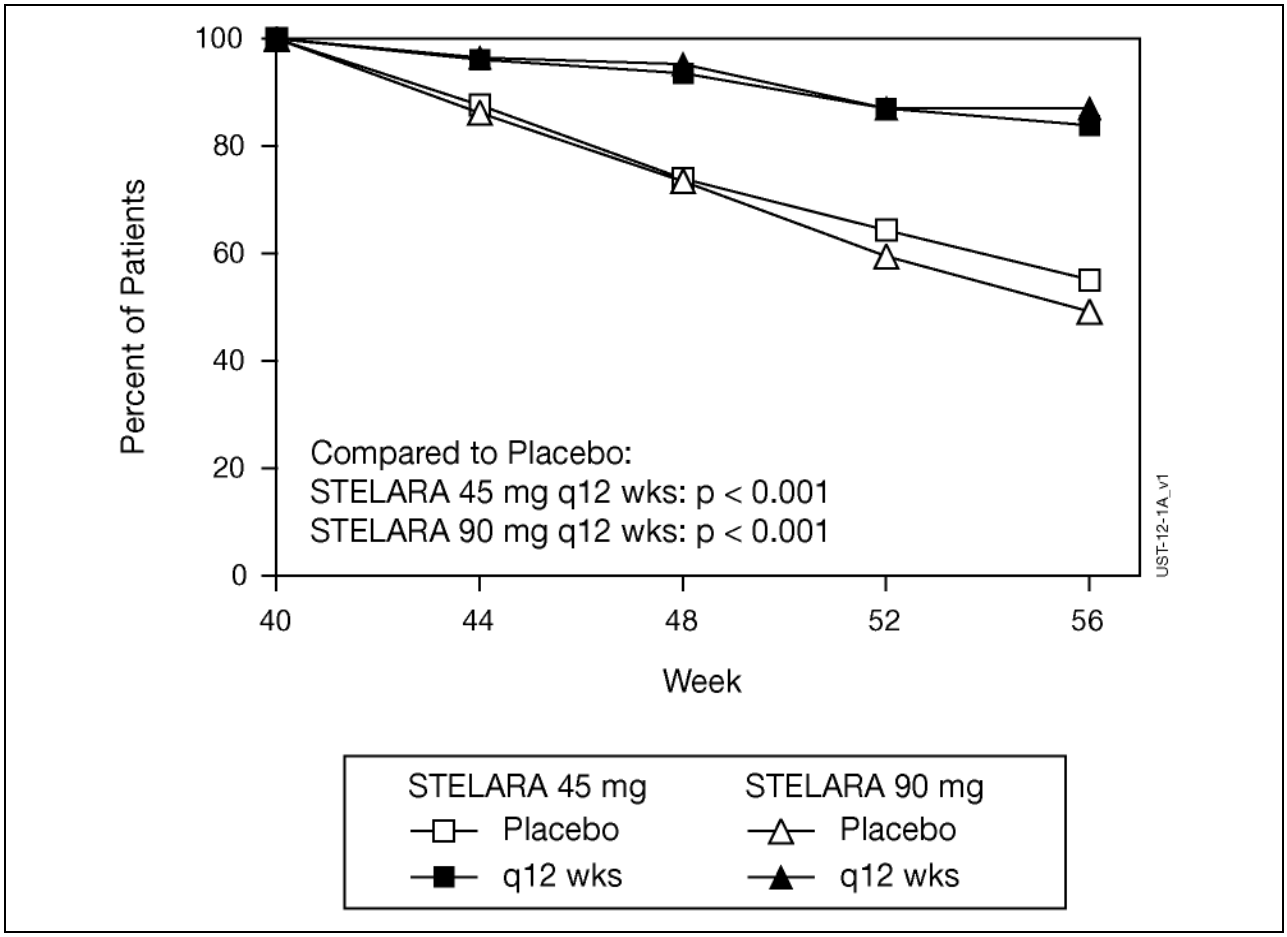


Figure 2: Life-table estimate of percent of patients maintaining PASI 75 response; patients randomized at Week 40 (PHOENIX 1)

Efficacy of retreatment

In PHOENIX 1, after withdrawal from therapy, patients reinitiated their original STELARA treatment regimen after loss of ≥ 50% of PASI improvement. Retreatment with STELARA 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.

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 STELARA compared with patients randomized to placebo as evaluated by DLQI in PHOENIX 1 and 2 and SF-36 in PHOENIX 1 (Tables 7 and 8). Quality of life improvements were significant as early as 2 weeks in patients treated with STELARA and these improvements were maintained over time with continued dosing.

Table 7: Quality of Life endpoints through Week 40 – PHOENIX 1

		STELARA	
	Placebo	45 mg	90 mg
Patients randomized at Week 0	255	255	256
DLQI			
Baseline			
N	254	255	255
Mean ± SD	11.8 ± 7.41	11.1 ± 7.09	11.6 ± 6.92
Median	10.0	10.0	11.0
Change from baseline			
Week 2[a]			
N	253	255	254
Mean ± SD	-0.9 ± 4.88	-3.6 ± 4.51	-4.5 ± 5.31
Median	-1.0	-3.0	-4.0
Week 12[a]			
N	252	254	249
Mean ± SD	-0.6 ± 5.97	-8.0 ± 6.87	-8.7 ± 6.47
Median	0.0	-6.0	-7.0
Week 28			
N	NA	249	241
Mean ± SD	NA	-8.1±7.23	-9.6±7.17
Median	NA	-7.0	-8.0
Week 40			
N	NA	246	236
Mean ± SD	NA	-8.2±7.23	-9.5±6.96
Median	NA	-7.0	-9.0
SF-36			
Physical component summary			
Baseline			
N	254	255	255
Mean ± SD	47.22 ± 10.240	48.90 ± 9.555	47.51 ± 9.224

Median	50.70	51.60	49.60
Change from Baseline			
Week 12[a]			
N	250	255	249
Mean ± SD	-0.53 ± 7.457	1.97 ± 7.422	3.23 ± 7.590
Median	-0.25	1.30	1.50
Week 28			
N	NA	250	239
Mean ± SD	NA	1.86±8.301	3.17±7.855
Median	NA	1.00	1.90
Week 40			
N	NA	246	236
Mean ± SD	NA	1.77±8.402	2.96±8.027
Median	NA	0.80	2.10
Mental component summary			
Baseline			
N	254	255	255
Mean ± SD	49.62 ± 10.582	50.02 ± 10.425	49.86 ± 10.175
Median	53.35	52.90	53.10
Change from Baseline			
Week 12[a]			
N	250	255	249
Mean ± SD	-1.33 ± 7.473	2.12 ± 9.308	2.54 ± 9.506
Median	-0.60	0.80	1.50
Week 28			
N	NA	250	239
Mean ± SD	NA	1.80 ± 9.578	3.47 ± 9.587
Median	NA	0.40	1.50
Week 40			
N	NA	246	236
Mean ± SD	NA	2.17 ± 9.137	2.91 ± 9.418
Median	NA	0.95	1.10

[a] $p < 0.001$ for 45 mg or 90 mg comparison with placebo.

NA = not applicable

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578

579

Table 8: Quality of Life endpoints through Week 24 – PHOENIX 2

		STELARA	
	Placebo	45 mg	90 mg
Patients randomized at Week 0	410	409	411
DLQI			
Baseline			
N	408	406	408
Mean ± SD	12.3 ± 6.86	12.2 ± 7.07	12.6 ± 7.29
Median	11.0	12.0	12.0
Change from baseline			
Week 4[a]			
N	405	404	404
Mean ± SD	-1.4 ± 4.68	-6.9 ± 6.07	-7.0 ± 5.86
Median	-1.0	-6.0	-6.0
Week 12[a]			
N	400	401	402
Mean ± SD	-0.5 ± 5.66	-9.3 ± 7.12	-10.0 ± 6.67
Median	-0.5	-8.0	-9.0
Week 24			
N	NA	394	399
Mean ± SD	NA	-9.5 ± 7.26	-10.3 ± 6.96
Median	NA	-8.0	-9.0

[a] $p < 0.001$ for 45 mg or 90 mg comparison with placebo.
NA=not applicable

580

581 ***Nail Psoriasis***

582 In PHOENIX 1, the median baseline NAPSI score for nail psoriasis was 4.0 and the median
583 number of fingernails involved with psoriasis was 8.0. Nail psoriasis improved significantly in
584 patients randomized to 45 mg or 90 mg STELARA compared with patients randomized to
585 placebo when measured by the NAPSI score (Tables 9 and 10). Nail psoriasis continued to
586 improve over time through Week 52 in patients treated with STELARA.

Table 9: Summary of percent improvement from baseline in NAPSI at Week 12; patients randomized at Week 0 with nail psoriasis present at Week 0 - PHOENIX 1

		STELARA	
	Placebo	45 mg	90 mg
Patients randomized at Week 0 with nail psoriasis present at Week 0	176	182	187
Week 12[a]			
N	174	182	184
Mean ± SD	11.8 ± 51.09	26.7 ± 56.80	24.9 ± 48.90

Median	0.0	25.0	25.0

[a] $p \leq 0.001$ for 45 mg or 90 mg comparison with placebo.

Table 10: Summary of percent improvement from baseline in NAPSI at Week 24; patients randomized at Week 0 with nail psoriasis present at Week 0 - PHOENIX 1

	STELARA			
	Placebo → 45 mg	Placebo → 90 mg	45 mg	90 mg
Patients randomized at Week 0 with nail psoriasis present at Week 0	93	83	182	187
Week 24				
N	89	77	179	181
Mean ± SD	29.1 ± 60.83	40.5 ± 43.37	46.5 ± 47.41	48.7 ± 45.58
Median	33.3	42.9	50.0	50.0

Hospital Anxiety and Depression Scale

At baseline in PHOENIX 2, the mean HADS anxiety and depression scores were 6.9 and 5.1, respectively. Both anxiety and depression scores were reduced significantly in patients randomized to 45 mg or 90 mg STELARA at Week 12 compared with patients randomized to placebo (Table 11). HADS improvements were maintained through Week 24 (Table 12).

Table 11: Summary of change from baseline in Hospital Anxiety and Depression at Week 12; patients randomized at Week 0 - PHOENIX 2

		STELARA	
	Placebo	45 mg	90 mg
Patients randomized at Week 0	410	409	411
Anxiety score[a]			
N	395	399	399
Mean ± SD	-0.11 ± 2.689	-1.59 ± 3.570	-1.60 ± 3.351
Median	0.00	-1.00	-1.00
Depression score[a]			
N	398	399	401
Mean ± SD	0.21 ± 2.757	-1.71 ± 3.124	-2.06 ± 3.420
Median	0.00	-1.00	-1.00

[a] $p < 0.001$ for 45 mg or 90 mg comparison with placebo.

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Table 12: Summary of change from baseline in Hospital Anxiety and Depression at Week 24; patients randomized at Week 0 – PHOENIX 2

	STELARA			
	Placebo → 45 mg	Placebo → 90 mg	45 mg	90 mg
Patients randomized at Week 0	205	205	409	411
Anxiety score				
n	183	191	393	395
Mean ± SD	-1.52 ± 3.148	-1.76 ± 3.245	-1.80 ± 3.725	-1.99 ± 3.463
Median	-1.00	-1.00	-1.00	-1.00
Depression score				
n	184	190	391	398
Mean ± SD	-1.65 ± 3.207	-1.42 ± 3.013	-1.77 ± 3.449	-2.26 ± 3.490
Median	-1.00	-1.00	-1.00	-2.00

598

599 ***Work Limitations Questionnaire***

600 The Work Limitations Questionnaire obtained at baseline showed impaired work productivity
601 among patients with psoriasis evaluated in PHOENIX 2 for the Physical Demands, Time
602 Management, Mental-Interpersonal and Output Demands component scores. Work productivity
603 improved significantly more in patients randomized to STELARA at Week 12 compared with
604 patients randomized to placebo as measured by the four WLQ subscales (Physical Demands,
605 Time Management, Mental-Interpersonal, and Output Demands; Table 13).

Table 13: Summary of change from baseline in Work Limitations Questionnaire at Week 12; patients randomized at Week 0 – PHOENIX 2

		STELARA	
	Placebo	45 mg	90 mg
Patients randomized at Week 0	410	409	411
Physical Demands score[a]			
n	277	277	281
Mean ± SD	-0.20 ± 30.991	-7.61 ± 30.917	-5.05 ± 34.050
Median	0.00	0.00	0.00
Time Management score[b]			
n	259	255	265
Mean ± SD	0.74 ± 18.962	-6.58 ± 21.634	-9.06 ± 24.239
Median	0.00	-5.00	-3.30

Mental - Interpersonal score[b]			
n	272	275	276
Mean ± SD	1.11 ± 18.881	-7.82 ± 22.684	-7.51 ± 19.366
Median	0.00	-2.80	-1.35
Output Demands score[b]			
n	276	274	279
Mean ± SD	1.08 ± 16.062	-6.82 ± 22.367	-6.98 ± 20.866
Median	0.00	0.00	0.00

[a] p = 0.001 and 0.060 for the 45 mg and 90 mg comparisons, respectively, with placebo
[b] p < 0.001 for 45 mg or 90 mg comparison with placebo

Itch VAS

Itch associated with psoriasis improved significantly (p<0.001) at Week 12 in patients randomized to 45 mg or 90 mg STELARA compared with patients randomized to placebo as evaluated by Itch VAS in PHOENIX 1 (Table 14).

Table 14: Summary of change from baseline in itch VAS at Week 12; patients randomized at Week 0 – PHOENIX 1

		STELARA	
	Placebo	45 mg	90 mg
Patients randomized at Week 0	255	255	256
Week 12[a]			
n	252	253	249
Mean ± SD	-0.78 ± 2.538	-4.91 ± 3.142	-5.14 ± 3.020
Median	-0.30	-5.50	-5.50

[a] p < 0.001 for 45 mg or 90 mg comparison with placebo.

ACCEPT

In addition, a multicenter, randomized, single-blind, 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 ≥12, Physician Global Assessment (PGA) score ≥3, who were candidates for phototherapy or systemic therapy, and who had had an inadequate response to, intolerance to, or contraindication to cyclosporine, MTX, or PUVA therapy. A total of 903 patients were enrolled in the study.

The ACCEPT trial compared the efficacy of ustekinumab to etanercept and evaluated the safety of ustekinumab and etanercept in patients with moderate to severe psoriasis. The active-controlled portion of the study was from Week 0 to Week 12, during which patients were randomized to receive etanercept (50 mg twice a week) ustekinumab 45 mg at Weeks 0 and 4, or

ustekinumab 90 mg at Weeks 0 and 4. This trial was powered to test the superiority of each ustekinumab dose to etanercept on the primary endpoint of the proportion of patients who achieved a PASI 75 at week 12.

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 (57%). 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 15). 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).

In pre-specified analyses of efficacy by body weight in ACCEPT, minimal dose response to ustekinumab was evident in patients ≤ 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 15).

Table 15: Key psoriasis endpoints at Week 12: ACCEPT

	ACCEPT		
	Etanercept (50 mg twice a week)	Ustekinumab (week 0 and week 4)	
		45 mg	90 mg
Patients randomized	347	209	347
PASI RESPONSE			
PASI 50 response	286 (82%)	181 (87%)	320 (92%)[a]
PASI 75 response	197 (57%)	141 (67%)[b]	256 (74%)[a]
PASI 90 response	80 (23%)	76 (36%)[a]	155 (45%)[a]
PASI 100 response	22 (6%)	25 (12%)[c]	74 (21%)[a]
PGA of Cleared or Minimal	170 (49%)	136 (65%)[a]	245 (71%)[a]
PASI 75 RESPONSE BY WEIGHT			
≤ 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%)
PGA OF CLEARED OR MINIMAL BY WEIGHT			

≤ 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%)
PASI 75 RESPONSE BY NUMBER OF UNSUITABLE CONVENTIONAL SYSTEMIC AGENTS[g]			
-at least one therapy			
N	347	209	346
PASI 75 Response	197 (57%)	141 (67%)[b]	256 (74%)[a]
-at least two therapies			
N	186	118	185
PASI 75 Response	94 (51%)	79 (67%)[d]	137 (74%)[a]
-at least three therapies			
N	52	31	47
PASI 75 Response	20 (38%)	17 (55%)[e]	34 (72%)[f]

[a] p <0.001 for ustekinumab 45 mg or 90 mg comparison with etanercept.
[b] p =0.012 for ustekinumab 45 mg comparison with etanercept.
[c] p =0.020 for ustekinumab 45 mg comparison with etanercept
[d] p=0.004 for ustekinumab 45 mg comparison with etanercept.
[e] p=0.303 for ustekinumab 45 mg comparison with etanercept.
[f] p=0.001 for ustekinumab 90 mg comparison with etanercept.
[g] Conventional systemic agents include psoralen plus ultraviolet A, MTX, and cyclosporine. Unsuitable conventional systemic agents are defined as those to which patients had had an inadequate response, were intolerant, or had a contraindication.

Clinical Efficacy – Psoriatic arthritis (PsA)

The safety and efficacy of STELARA was assessed in two multicenter, randomized, double-blind, placebo-controlled, Phase 3 studies, PSUMMIT I and PSUMMIT II, in patients with active psoriatic arthritis. Patients were randomized to receive treatment with either STELARA 45 mg, 90 mg, or placebo subcutaneous injections at Weeks 0 and 4 followed by every 12 week (q12w) dosing. The primary endpoint in these studies was the reduction in the signs and symptoms of psoriatic arthritis (PsA) as measured by the percentage of ACR 20 responders at Week 24. Secondary endpoints included change from baseline in Disability Index of the Health Assessment Questionnaire (HAQ-DI), PASI 75, ACR 50, ACR 70 and change from baseline in total radiographic scores of the hands and feet, at Week 24. Efficacy data were collected and analyzed through Week 52 for both studies and through Week 100 for PSUMMIT I. These studies included 927 (PSUMMIT I, n=615; PSUMMIT II, n=312) adult patients (≥18 years) who had active psoriatic arthritis (≥5 swollen joints and ≥5 tender joints, despite disease modifying antirheumatic (DMARD) and/or nonsteroidal anti-inflammatory (NSAID) therapy). Methotrexate use was allowed during the studies but was not mandatory. Approximately 50% of patients continued on stable doses of MTX (≤25 mg/week). In

PSUMMIT I and PSUMMIT II, 80% and 86% of the patients, respectively, had been previously treated with DMARDs.

In PSUMMIT I patients, who had been previously treated with anti-TNFα therapy, prior to the first study dose, were excluded. In PSUMMIT II, the majority of patients (58%, n=180) had been previously treated with one or more anti-TNFα agent(s) for at least 8 weeks (14 weeks with infliximab) or had discontinued anti-TNFα for intolerance at any time. Among the patients who had been previously treated with an anti-TNFα agent, over 70% had discontinued their anti-TNFα treatment for lack of efficacy or intolerance.

Patients with each subtype of psoriatic arthritis were enrolled, including polyarticular arthritis with no evidence of rheumatoid nodules (39%, N=362), spondylitis with peripheral arthritis (28%, N=255), asymmetric peripheral arthritis (21%, N=193), distal interphalangeal (DIP) arthritis (12%, N=112) and arthritis mutilans (0.5%, N=5). Over 70% and 40% of the patients in both studies had enthesitis and dactylitis at baseline, respectively.

In both studies, a significantly greater proportion of patients achieved ACR 20 and ACR 50 responses at Week 24 in the STELARA 45 mg and 90 mg groups compared to placebo (see Table 16). In PSUMMIT I, a significantly greater proportion of patients and in PSUMMIT II a numerically greater proportion of patients (p=NS) achieved ACR 70 responses in the STELARA 45 mg and 90 mg groups compared to placebo (see Table 16).

In both studies, the proportion of patients achieving a modified PsA response criteria (PsARC) or a Disease Activity Index Score 28 using C-reactive protein (DAS28-CRP) response was significantly greater in the STELARA 45 mg and 90 mg groups compared to placebo. In PSUMMIT I the proportion of patients achieving DAS28-CRP remission was significantly greater in the STELARA 45 mg and 90 mg groups compared to placebo. In PSUMMIT II, the proportion of patients who achieved DAS28-CRP remission was significantly greater in the STELARA 90 mg group compared to placebo (see Table 16). DAS28-CRP and PsARC responses were maintained through Week 52 in both studies and through Week 100 in PSUMMIT I.

Table 16: Number of patients who achieved ACR 20, ACR 50, ACR 70, PsARC, DAS28-CRP response and DAS28-CRP remission at Week 24.

	PSUMMIT I			**PSUMMIT II**		
		STELARA			**STELARA**	
	Placebo (N=206)	**45 mg (N=205)**	**90 mg (N=204)**	**Placebo (N=104)**	**45 mg (N=103)**	**90 mg (N=105)**
ACR 20	47 (23%)	87 (42%)[a]	101 (50%)[a]	21 (20%)	45 (44%)[a]	46 (44%)[a]
ACR 50	18 (9%)	51 (25%)[a]	57 (28%)[a]	7 (7%)	18 (17%)[b]	24 (23%)[a]
ACR 70	5 (2%)	25 (12%)[a]	29 (14%)[a]	3 (3%)	7 (7%)[c]	9 (9%)[c]
PsARC	77 (37%)	115 (56%)[a]	132 (65%)[a]	32 (31%)	57 (55%)[a]	54 (51%)[b]
DAS28-CRP[*]	71 (34%)	135 (66%)[a]	138 (68%)[a]	31 (30%)	56 (54%)[a]	56 (53%)[a]
DAS28 Remission[**]	17 (8%)	42 (20%)[a]	40 (20%)[a]	4 (4%)	11 (11%)[c]	16 (15%)[b]

[a] p<0.001

[b] p<0.05

[c] p= NS

[*] Combining tender joints (28 joints), swollen joints (28 joints), CRP, and the Patient Global Assessment of disease activity using CRP.

DAS28 responders include patients with moderate or good response.

** DAS28 remitters include patients with a DAS28 value of < 2.6 at a visit.

An ACR 20 response (Felson et al, 1995) was defined as:

1. ≥ 20% improvement in swollen joint count (66 joints) and tender joint count (68 joints); and
2. ≥ 20% improvement in 3 of the following 5 assessments:
   - Patient's assessment of pain [Visual Analog Scale (VAS)]
   - Patient's global assessment of disease activity (VAS)
   - Physician's global assessment of disease activity (VAS)
   - Patient's assessment of physical function as measured by the HAQ-DI
   - CRP

ACR 50 or ACR 70 are similarly defined.

The time course for ACR 20 response rates during the first 24 weeks in both studies for patients receiving STELARA or placebo are summarized in Figure 3. ACR 20 responses showed improvement at the first assessment (Week 4). ACR 20, 50 and 70 responses continued to improve or were maintained through Week 52 (see Table 17). In PSUMMIT I, ACR responses were maintained through Week 100.

Figure 3: Percent of patients achieving ACR 20 response through Week 24

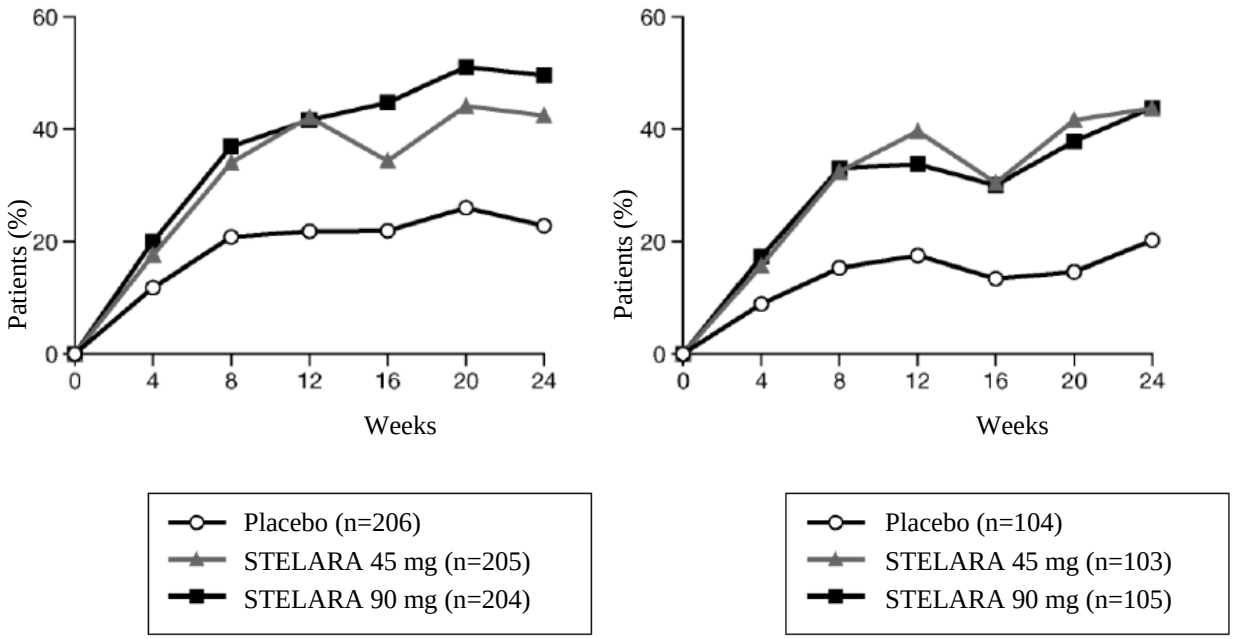


Table 17: Proportion of patients who achieved ACR 20, ACR 50, ACR 70 response at Week 52.

	PSUMMIT I		PSUMMIT II	
	STELARA		STELARA	
	45 mg	90 mg	45 mg	90 mg

N	194	189	94	95
ACR response				
ACR 20	55.7%	60.3%	46.8%	48.4%
ACR 50	31.4%	37.0%	27.7%	26.3%
ACR 70	18.0%	21.2%	12.8%	17.9%

In PSUMMIT I, of 205 subjects randomized to STELARA 45 mg, 153 continued the same dose and were available for evaluation at Week 52. Among those, ACR 20, 50 and 70 responses were achieved by 99 (64.7%), 57 (37.3%) and 34 (22.2%) subjects respectively. Of 204 subjects randomized to STELARA 90 mg, 185 were available for evaluation at Week 52. Among those, ACR 20, 50 and 70 responses were achieved by 120 (64.9%), 74 (40%) and 41 (22.2%) subjects respectively.

In PSUMMIT I, of 205 subjects randomized to STELARA 45 mg, 138 continued the same dose and were available for evaluation at Week 100. Among those, ACR 20, 50 and 70 responses were achieved by 89 (64.5%), 63 (45.7%) and 41 (29.7%) subjects respectively. Of 204 subjects randomized to STELARA 90 mg, 166 were available for evaluation at Week 100. Among those, ACR 20, 50 and 70 responses were achieved by 116 (69.9%), 84 (50.6%) and 41 (24.7%) subjects respectively.

In PSUMMIT II, of 103 subjects randomized to STELARA 45 mg, 68 continued the same dose and were available for evaluation at Week 52. Among those, ACR 20, 50, and 70 responses were achieved by 41 (60.3%), 23 (33.8%) and 11 (16.2%) subjects respectively. Of 105 subjects randomized to STELARA 90 mg, 83 were available for evaluation at Week 52. Among those, ACR 20, 50 and 70 responses were achieved by 49 (59%), 26 (31.3%) and 17 (20.5%) subjects respectively.

Additionally, within each weight group (≤100 kg and >100 kg), ACR 20, ACR 50 and ACR 70 responses were consistently higher in the STELARA 45 and 90 mg groups than in the placebo group (see Table 18).

Table 18: Number of patients who achieved ACR 20, ACR 50 and ACR 70 responses by weight through Week 24

	PSUMMIT I			**PSUMMIT II**		
		STELARA			**STELARA**	
	Placebo (N=206)	**45 mg (N=205)**	**90 mg (N=204)**	**Placebo (N=104)**	**45 mg (N=103)**	**90 mg (N=105)**
Patients randomized with weight ≤100 kg at baseline	154	153	154	74	74	73
ACR 20	39 (25%)	67 (44%)	78 (51%)	17 (23%)	32 (43%)	34 (47%)
ACR 50	14 (9%)	38 (25%)	48 (31%)	6 (8%)	15 (20%)	21 (29%)

ACR 70	5 (3%)	20 (13%)	26 (17%)	3 (4%)	6 (8%)	8 (11%)
Patients randomized with weight >100 kg at baseline	52	52	50	30	29	31
ACR 20	8 (15%)	20 (38%)	23 (46%)	4 (13%)	13 (45%)	12 (39%)
ACR 50	4 (8%)	13 (25%)	9 (18%)	1 (3%)	3 (10%)	3 (10%)
ACR 70	0	5 (10%)	3 (6%)	0	1 (3%)	1 (3%)

STELARA treatment resulted in significantly greater improvement compared with placebo for each ACR component (see Table 19).

Table 19: Summary of percent improvement from baseline in ACR components at Week 24

	PSUMMIT I			**PSUMMIT II**		
		STELARA			**STELARA**	
	Placebo (N=206)	**45 mg (N=205)**	**90 mg (N=204)**	**Placebo (N=104)**	**45 mg (N=103)**	**90 mg (N=105)**
Number of swollen joints[d]						
Median	21.54	58.82[a]	60.00[a]	0.00	52.94[b]	50.00[c]
Number of tender joints[e]						
Median	13.61	45.45[a]	51.51[a]	0.00	33.33[a]	35.00[c]
Patient's assessment of pain[f]						
Median	0.00	31.33[a]	42.58[a]	0.00	24.19[a]	24.29[a]
Patient global assessment[f]						
Median	4.11	32.84[a]	42.44[a]	0.00	21.25[a]	22.54[a]
Physician global assessment[f]						
Median	17.64	48.39[a]	55.91[a]	0.83	36.67[a]	36.11[a]
Disability index (HAQ-DI)[g]						
Median	0.00	22.22[a]	32.46[a]	0.00	12.50[a]	14.29[a]
CRP (mg/dL)[h]						
Median	0.00	38.56[a]	48.30[a]	0.00	25.61[c]	33.69[a]

[a] p<0.001
[b] p<0.05
[c] p<0.01
[d] Number of swollen joints counted (0-66)
[e] Number of tender joints counted (0-68)
[f] Visual analogue scale; 0= best, 10=worst.
[g] 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.
[h] CRP: (Normal Range 0.0-1.0 mg/dL)

Methotrexate Use

The proportion of patients achieving ACR responses were consistently greater in patients treated with STELARA than those treated with placebo regardless of concomitant MTX use (see Table

20). Responses observed in the STELARA groups were similar in patients receiving or not receiving concomitant MTX. ACR responses were maintained through Week 52 in PSUMMIT I and II and through Week 100 in PSUMMIT I.

Table 20: Summary of patients achieving ACR 20, ACR 50 and ACR 70 responses through Week 24 by methotrexate usage

PSUMMIT I						
	Receiving MTX at baseline			*Not receiving MTX at baseline*		
		STELARA			**STELARA**	
	Placebo (N=206)	**45 mg (N=205)**	**90 mg (N=204)**	**Placebo (N=206)**	**45 mg (N=205)**	**90 mg (N=204)**
Patients randomized	96	99	101	110	106	103
ACR 20	25 (26%)	43 (43%)	46 (46%)	22 (20%)	44 (42%)	55 (53%)
ACR 50	8 (8%)	23 (23%)	27 (27%)	10 (9%)	28 (26%)	30 (29%)
ACR 70	2 (2%)	11 (11%)	13 (13%)	3 (3%)	14 (13%)	16 (16%)
PSUMMIT II						
	Receiving MTX at baseline			*Not receiving MTX at baseline*		
		STELARA			**STELARA**	
	Placebo (N=104)	**45 mg (N=103)**	**90 mg (N=105)**	**Placebo (N=104)**	**45 mg (N=103)**	**90 mg (N=105)**
Patients randomized	49	54	52	55	49	53
ACR 20	14 (29%)	27 (50%)	21 (40%)	7 (13%)	18 (37%)	25 (47%)
ACR 50	4 (8%)	10 (19%)	12 (23%)	3 (5%)	8 (16%)	12 (23%)
ACR 70	2 (4%)	4 (7%)	3 (6%)	1 (2%)	3 (6%)	6 (11%)

Prior Anti-TNFα therapy

PSUMMIT II evaluated 180 patients who were previously treated with one or more anti-TNFα agents for at least 8 weeks (14 weeks with infliximab), or had documented intolerance of anti-TNFα therapy at any time in the past.

Among patients previously treated with anti-TNFα agents, a significantly greater proportion of STELARA-treated patients achieved an ACR 20 response at Week 24 compared to placebo (see Table 21). ACR 20, 50 and 70 responses were generally maintained through Week 52.

Table 21: Number of patients previously treated with anti-TNFα agent(s) who achieved ACR 20, ACR 50 and ACR 70 responses through Week 24

PSUMMIT II		**STELARA**	
	Placebo (N=104)	**45 mg (N=103)**	**90 mg (N=105)**
Patients randomized	62	60	58
ACR 20	9 (15%)	22 (37%)[a]	20 (34%)[b]
ACR 50	4 (6%)	9 (15%)[c]	9 (16%)[c]

ACR 70	1 (2%)	3 (5%)[c]	3 (5%)[c]

[a] p<0.01
[b] p<0.05
[c] p=NS

Enthesitis and Dactylitis

For patients with enthesitis and/or dactylitis at baseline, in PSUMMIT I, a significant improvement in enthesitis and dactylitis score was observed in the STELARA 45 mg and 90 mg groups compared to placebo. In PSUMMIT II, a significant improvement in enthesitis score and numerical improvement in dactylitis score were observed in the 90 mg group (p=NS) compared with the placebo group (see Table 22). In both studies, improvement in enthesitis score and dactylitis score were maintained at Week 52. In PSUMMIT I, the improvement in enthesitis score and dactylitis score was maintained through Week 100.

Table 22: Summary of percent change in enthesitis and dactylitis scores at Week 24

	PSUMMIT I			PSUMMIT II		
		STELARA			STELARA	
	Placebo (N=206)	45 mg (N=205)	90 mg (N=204)	Placebo (N=104)	45 mg (N=103)	90 mg (N=105)
Enthesitis score[d]						
Patients randomized with enthesitis at baseline	145	142	154	73	72	76
N	137	140	148	68	70	70
Median	0.00	-42.86[a]	-50.00[b]	0.00	-33.33[c]	-48.33[a]
Dactylitis score[e]						
Patients randomized with dactylitis at baseline	96	101	99	38	48	41
N	92	99	95	33	46	38
Median	0.00	-75.00[b]	-70.83[b]	0.00	0.00[c]	-64.58[c]

[a] p<0.01
[b] p<0.001
[c] p=NS
[d] Enthesitis was assessed based on the Maastricht Ankylosing Spondylitis Enthesis Score (MASES) index modified for PSA (an instrument that counts 15 body sites).
[e] Dactylitis was assessed in both hands and feet using a scoring system from 0 to 60.

A higher proportion of patients treated with STELARA, that have spondylitis with peripheral arthritis as their primary presentation, demonstrated Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) 50 and 70 percent improvement in BASDAI scores at Week 24 compared with placebo (see Table 23).

Table 23: Number of patients who achieved improvement from baseline in BASDAI at Week 24

	PSUMMIT I		PSUMMIT II	
		STELARA		STELARA

	Placebo (N=206)	45 mg (N=205)	90 mg (N=204)	Placebo (N=104)	45 mg (N=103)	90 mg (N=105)
Patients randomized with spondylitis and peripheral joint involvement at baseline	70	52	64	22	26	22
N	61	51	60	18	25	21
BASDAI 20	16 (26%)	25 (49%)[a]	35 (58%)[b]	10 (56%)	15 (60%)[c]	11 (52%)[c]
BASDAI 50	8 (13%)	12 (24%)[c]	19 (32%)[a]	1 (6%)	7 (28%)[c]	8 (38%)[a]
BASDAI 70	0	7 (14%)[d]	9 (15%)[d]	0	3 (12%)*	5 (24%)*

[a] p≤0.05
[b] p<0.001
[c] p=NS
[d] p≤0.01
* p value not calculated

PASI Response

In PSUMMIT I and PSUMMIT II, the proportion of patients with psoriasis involvement of ≥3% BSA at baseline who achieved a ≥75% improvement in the PASI assessment at Week 24 was significantly greater in the STELARA 45 mg and 90 mg groups compared with the placebo group (see Table 24). In both studies the proportion of patients achieving the PASI 75 response was maintained through Week 52 (PSUMMIT I, STELARA 45 mg-70.1% and 90 mg- 68.1%; PSUMMIT II, STELARA 45 mg-56.5% and 90 mg- 64.4%). In PSUMMIT I, the PASI 75 response was maintained through Week 100.

The proportion of patients who achieved both a PASI 75 response and an ACR 20 response was evaluated for those patients with ≥3% BSA psoriasis skin involvement at baseline. A significantly higher proportion of patients achieved the combined response in the STELARA 45 mg and 90 mg groups compared with the placebo group at Week 24 (see Table 24). In both studies the proportion of patients achieving both a PASI 75 response and an ACR20 response was maintained through Week 52 (PSUMMIT I, STELARA 45 mg-44.8% and 90 mg-44.3%; PSUMMIT II, STELARA 45 mg-36.8% and 90 mg- 43.1%). In PSUMMIT I, the proportion of patients achieving the combined PASI 75 and ACR20 response was maintained through Week 100.

Table 24: Number of patients who achieved PASI 75, PASI 90 and PASI 100 responses as well as a combination of skin and joint responses at Week 24

	PSUMMIT I			PSUMMIT II		
		STELARA [a]			STELARA [a]	
	Placebo (N=206)	45 mg (N=205)	90 mg (N=204)	Placebo (N=104)	45 mg (N=103)	90 mg (N=105)
Patients with ≥3% BSA psoriasis skin involvement at baseline	146	145	149	80	80	81
PASI 75	16 (11%)	83 (57%)	93 (62%)	4 (5%)	41 (51%)	45 (56%)
PASI 90	4 (3%)	60 (41%)	65 (44%)	3 (4%)	24 (30%)	36 (44%)
PASI 100	2 (1%)	29 (20%)	41 (28%)	1 (1%)	13 (16%)	17 (21%)
Combination of skin and joint responses						
PASI 75 and ACR 20	8 (5%)	40 (28%)	62 (42%)	2 (3%)	24 (30%)	31 (38%)

[a] p<0.001 for 45 mg or 90 mg comparison with placebo.

Additionally, within each weight group (≤100 kg and >100 kg), PASI 75, 90 and 100 responses were consistently higher in the STELARA 45 and 90 mg groups than in the placebo group (see Table 25).

Table 25: Summary of patients who achieved PASI 75, PASI 90 and PASI 100 responses by weight through Week 24

	PSUMMIT I			PSUMMIT II		
		STELARA			STELARA	
	Placebo (N=206)	45 mg (N=205)	90 mg (N=204)	Placebo (N=104)	45 mg (N=103)	90 mg (N=105)
Patients randomized with weight ≤100 kg at baseline*	105	105	111	54	58	57
PASI 75	14 (13%)	64 (61%)	73 (66%)	4 (7%)	31 (53%)	32 (56%)
PASI 90	4 (4%)	46 (44%)	48 (43%)	3 (6%)	20 (34%)	27 (47%)
PASI 100	2 (2%)	21 (20%)	30 (27%)	1 (2%)	11 (19%)	13 (23%)
Patients randomized with weight >100 kg at baseline*	41	40	38	26	22	24
PASI 75	2 (5%)	19 (48%)	20 (53%)	0	10 (45%)	13 (54%)
PASI 90	0	14 (35%)	17 (45%)	0	4 (18%)	9 (38%)
PASI 100	0	8 (20%)	11 (29%)	0	2 (9%)	4 (17%)

* Patients randomized with ≥ 3% BSA psoriasis skin involvement at baseline

Methotrexate Use

In both studies, the proportion of patients who achieved a PASI 75 response at Week 24 was consistently higher in STELARA 45 mg and 90 mg groups compared with placebo regardless of concomitant MTX use. PASI 75 responses were maintained through Week 52 in both PSUMMIT I and II. In PSUMMIT I, PASI 75 response was maintained at Week 100.

Prior Anti-TNFα Therapy

In PSUMMIT II, the proportion of patients who achieved a PASI 75 response at Week 24 was significantly greater in STELARA 45 mg and 90 mg groups compared with placebo in patients previously treated with an anti-TNFα agent.

Radiographic Response

Structural damage in both hands and feet was assessed by readers unaware of treatment group and order of visits, and expressed as change in total van der Heijde-Sharp score (vdH-S score), modified for PsA by addition of hand distal interphalangeal (DIP) joints, compared to baseline. A pre-specified integrated analysis combining data from 927 subjects in both PSUMMIT I & II was performed. At Week 24, based on this integrated analysis, the STELARA 45 mg or 90 mg treatment significantly inhibited progression of structural damage, when compared to placebo (see Table 26). Beyond Week 24, STELARA treatment continued to inhibit the progression of structural damage through Week 52. The mean change from Week 24 to 52 in total modified vdH-S score (0.18 and 0.26 in the STELARA 45 mg and 90 mg groups respectively) was less than the mean change from Week 0 to 24 (see Table 26). In PSUMMIT I, the effect of STELARA on inhibition of structural damage progression was maintained through Week 100. Among subjects treated with STELARA 45 mg and 90 mg with no radiographic progression from baseline to Week 52 (n=103, and 113, respectively), 81.5% and 88.8% continued to show no radiographic progression at Week 100.

Table 26: Summary of change from baseline in total modified vdH-S score at Week 24 (Integrated analysis of PSUMMIT I and PSUMMIT II)

		STELARA	
	Placebo	45 mg	90 mg
Total Modified vdH-S score at Baseline			
N	306	303	300
Mean ± SD	28.01 ± 55.771	30.40 ± 50.688	27.97 ± 42.137
Change from Baseline			
N	310	308	309
Mean ± SD	0.97 ± 3.852	0.40 ± 2.110[b]	0.39 ± 2.403[a]

[a] p value < 0.001 for the difference between STELARA and Placebo, Week 24 (integrated analysis)
[b] p value < 0.05

At Week 24, patients treated with STELARA demonstrated less progression of structural damage compared to placebo, irrespective of concomitant MTX use.

The effect of STELARA on progression of structural damage in patients with prior anti-TNFα experience has not been established although it has not been adequately studied.

Physical Function and Health-Related Quality of Life

In PSUMMIT I and PSUMMIT II, physical function and health-related quality of life were assessed using the Disability Index of the Health Assessment Questionnaire (HAQ-DI), Dermatology Life Quality Index (DLQI) and the SF-36 health survey.

Patients treated with STELARA showed significant improvement in physical function as assessed by the HAQ-DI at Week 24. The proportion of patients achieving a clinically meaningful ≥0.3 improvement in HAQ-DI score from baseline at Week 24 was also significantly greater in the STELARA groups when compared with placebo (see Table 27). Improvement was observed at the first assessment (Week 4), reached maximum at Week 12 and was maintained through Week 24. Improvement in HAQ-DI score from baseline was maintained in both studies at Week 52 and through Week 100 in PSUMMIT I.

In both studies, the improvement in HAQ-DI at Week 24 was consistently greater in the STELARA 45 mg and 90 mg groups compared with placebo regardless of concomitant MTX use.

In PSUMMIT II, the improvement in HAQ-DI at Week 24 was significantly greater in the STELARA 45 mg and 90 mg groups compared with placebo in patients previously treated with anti-TNFα agents.

Table 27: Improvement in physical function as measured by HAQ-DI at Week 24

	PSUMMIT I			PSUMMIT II		
		STELARA			STELARA	
	Placebo (N=206)	**45 mg (N=205)**	**90 mg (N=204)**	**Placebo (N=104)**	**45 mg (N=103)**	**90 mg (N=105)**
HAQ-DI Baseline Score						
N	204	205	204	104	103	104
Mean (SD)	1.24 (0.647)	1.22 (0.610)	1.22 (0.634)	1.25 (0.723)	1.34 (0.704)	1.29 (0.666)
Median	1.25	1.25	1.25	1.25	1.38	1.25
Improvement in HAQ-DI						
N	206	205	204	104	103	105
Mean (SD)	0.10 (0.390)	0.31 (0.521)	0.40 (0.514)	0.03 (0.380)	0.21 (0.461)	0.22 (0.436)
Median	0.00	0.25[a]	0.25[a]	0.00	0.13[b]	0.25[a]
HAQ-DI Responders*	58 (28%)	98 (48%)[a]	97 (48%)[a]	17 (16%)	35 (34%)[b]	40 (38%)[a]

[a] $p<0.001$

[b] p<0.01
* achieving a ≥0.3 improvement from baseline

In PSUMMIT I, of 205 subjects randomized to STELARA 45 mg, 153 continued the same dose and were available for evaluation at Week 52. Among those, the HAQ-DI response was achieved by 83 (54.2%) subjects. Of 204 subjects randomized to STELARA 90 mg, 185 were available for evaluation at Week 52. Among those, HAQ-DI response was achieved by 102 (55.1%) subjects.

In PSUMMIT II, of 103 subjects randomized to STELARA 45 mg, 68 continued the same dose and were available for evaluation at Week 52. Among those, the HAQ-DI response was achieved by 29 (42.6%) subjects. Of 105 subjects randomized to STELARA 90 mg, 83 were available for evaluation at Week 52. Among those, HAQ-DI response was achieved by 44 (53%) subjects.

The DLQI was assessed by comparing the change in DLQI scores from baseline for those patients with ≥3% BSA at baseline. In both studies at Week 24, there was a significant improvement from baseline in DLQI scores in both the STELARA 45 mg and 90 mg groups as compared with placebo (see Table 28) and the improvement was maintained at Week 52. In PSUMMIT I, the improvement from baseline in DLQI scores was maintained through Week 100.

In both PSUMMIT I and PSUMMIT II, at Week 24, the change from baseline in the SF-36 physical component summary (PCS) scores was significantly greater in the STELARA 45 mg and 90 mg groups compared with the placebo group. In both studies, the change from baseline in the SF-36 mental component summary (MCS) scores at Week 24 was greater in both STELARA groups compared with the placebo group (p<0.001 for PSUMMIT I - 90 mg group, p=NS for other groups) (see Table 28). The change from baseline in the SF-36 PCS and MCS scores was maintained at Week 52 in both studies, and at Week 100 in PSUMMIT I.

In PSUMMIT II, a significant change from baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scores was observed at Week 24 in the STELARA 45 mg and 90 mg groups compared with the placebo group (median improvement, all 3.0 vs 0.0; p<0.007). Similarly, the percentage of patients with clinically significant improvement in fatigue from baseline (4 points in FACIT-F) was significantly greater in the STELARA 45 mg (49% [p<0.001]) and 90 mg groups (49% [p<0.001]) compared with the placebo group (25.8%). The change from baseline in the FACIT-F scores was maintained at Week 52.

Table 28: Summary of change from baseline in DLQI and SF-36 and scores at Week 24

	PSUMMIT I			**PSUMMIT II**		
		STELARA			**STELARA**	
	Placebo (N=206)	**45 mg (N=205)**	**90 mg (N=204)**	**Placebo (N=104)**	**45 mg (N=103)**	**90 mg (N=105)**
DLQI						
Patients randomized with ≥ 3% BSA psoriasis skin involvement at baseline	146	145	149	80	80	81

Baseline						
N	145	145	149	80	80	81
Mean (SD)	11.68 (7.705)	11.02 (7.308)	10.54 (7.179)	11.93 (7.622)	12.09 (7.667)	11.98 (7.754)
Median	11.00	10.00	9.00	11.00	11.00	10.00
Change from baseline						
N	140	142	146	73	77	75
Mean (SD)	-1.40 (6.177)	-6.63 (6.776)	-7.54 (6.524)	-0.75 (5.666)	-6.95 (7.719)	-7.16 (6.748)
Median	-1.00	-6.00[a]	-6.00[a]	0.00	-6.00[a]	-6.00[a]
SF-36						
Physical component summary						
Baseline						
N	203	203	204	104	102	104
Mean (SD)	31.39 (8.785)	31.16 (8.511)	31.45 (8.152)	30.28 (9.361)	28.69 (8.501)	28.93 (8.480)
Median	30.40	29.80	29.70	29.35	27.95	28.15
Change from baseline						
N	196	200	197	97	99	97
Mean (SD)	1.4 (7.094)	4.89 (9.333)	6.22 (8.747)	1.09 (5.892)	4.29 (8.594)	4.67 (8.758)
Median	1.15	3.90[a]	5.80[a]	0.00	2.70[c]	3.50[a]
Mental component summary						
Baseline						
N	203	203	204	104	102	104
Mean (SD)	43.51 (10.848)	42.77 (10.908)	43.48 (11.608)	42.11 (12.507)	43.27 (12.911)	42.81 (11.953)
Median	43.90	42.00	41.65	41.80	43.70	41.40
Change from baseline						
N	196	200	197	97	99	97
Mean (SD)	1.53 (9.582)	3.35 (10.016)	4.79 (10.054)	0.63 (8.238)	3.01 (11.144)	3.52 (11.274)
Median	0.25	2.65[b]	4.40[a]	0.00	0.70[b]	2.20[b]

[a] $p \leq 0.001$
[b] p=NS
[c] $p < 0.05$

Health Economics

Health economics data on time lost from work, employability, and daily productivity at work, school, or home were collected through questionnaires at baseline and Week 24. To assess productivity, patients were asked to indicate how much their disease affected their productivity at work, school or at home in the past 4 weeks, using a 10 cm Visual Analogue Scale (VAS) (not at all affected [0] to affected very much [10]).

The improvement in self-reported productivity was significantly greater in the STELARA 45 mg and 90 mg groups compared to placebo at Week 24. The improvement in self-reported productivity was maintained in both studies at Week 52 and through Week 100 in PSUMMIT I.

Clinical Efficacy – Crohn's Disease

The safety and efficacy of STELARA were evaluated in three randomized, double-blind, placebo-controlled clinical trials in adult patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] score of 220 to 450). The clinical development program consisted of two 8-week IV induction studies (UNITI-1 and UNITI-2) followed by a 44-week subcutaneous randomized withdrawal maintenance study (IM-UNITI) representing 52 weeks of therapy.

Induction of Clinical Response and Remission

UNITI-1 and UNITI-2 studies included 1409 (UNITI-1, n=769; UNITI-2 n=640) patients. In both studies, patients were permitted to concomitantly receive oral 5-ASA compounds, immunomodulators, corticosteroids, and/or antibiotics. Patients were randomized to receive a single IV administration of either 130 mg STELARA, or approximately 6 mg/kg STELARA designed as a tiered dose based on patient body weight (Table 1) or placebo at Week 0. The primary endpoint was clinical response (defined as a reduction in CDAI score of ≥100 points or CDAI score <150) at Week 6. Secondary endpoints included clinical remission at Week 8, clinical response at Week 8, 70-point response at Week 3, and 70-point response at Week 6. Efficacy data were collected and analyzed through Week 8 for both studies.

In UNITI-1, patients had failed or were intolerant to prior anti-TNFα therapy. At baseline, approximately 46% (n=340) patients were receiving corticosteroids (including budesonide) and 31.4% of patients were receiving immunomodulators. Approximately 48% had failed 1 prior anti-TNFα therapy and 52% had failed 2 or 3 prior anti-TNFα therapies (40.8% and 10.4%, respectively). In this study, 29.1% patients had an inadequate initial response (primary non-responders), 69.4% responded but subsequently lost response (secondary non-responders), and 36.4% were intolerant to anti-TNFα therapies.

Patients in UNITI-2 had failed at least one conventional therapy (corticosteroids or immunomodulators) and were either anti-TNFα naïve (68.6%) or had previously received but not failed anti-TNFα therapy (31.4%). At baseline, approximately 40% patients were receiving corticosteroids (including budesonide) and 35% patients were receiving immunomodulators.

In these induction studies, efficacy was higher and better sustained in the tiered dose group compared to the 130 mg dose group, and tiered dosing is therefore the recommended IV

induction dose. In both UNITI-1 and UNITI-2, a significantly greater proportion of patients were in clinical response and remission in the group treated with STELARA, compared to placebo (Table 29, Figure 4). Clinical response and remission were significant as early as Week 3 in STELARA treated patients and continued to improve through Week 8 (Figure 4).

Table 29: Induction of Clinical Response and Remission in UNITI-1* and UNITI 2**

	UNITI-1		UNITI-2	
	Placebo N=247	**STELARA N=249**	**Placebo N=209**	**STELARA N=209**
Clinical Remission, Week 8	18 (7.3%)	52 (20.9%)[a]	41 (19.6%)	84 (40.2%)[a]
Clinical Response (100 point), Week 6	53 (21.5%)	84 (33.7%)[b]	60 (28.7%)	116 (55.5%)[a]
Clinical Response (100 point), Week 8	50 (20.2%)	94 (37.8%)[a]	67 (32.1%)	121 (57.9%)[a]
70 Point Response, Week 3	67 (27.1%)	101 (40.6%)[b]	66 (31.6%)	106 (50.7%)[a]
70 Point Response, Week 6	75 (30.4%)	109 (43.8%)[b]	81 (38.8%)	135 (64.6%)[a]

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

* Anti-TNFα failures

** Conventional therapy failures

[a] $p < 0.001$

[b] $p < 0.01$

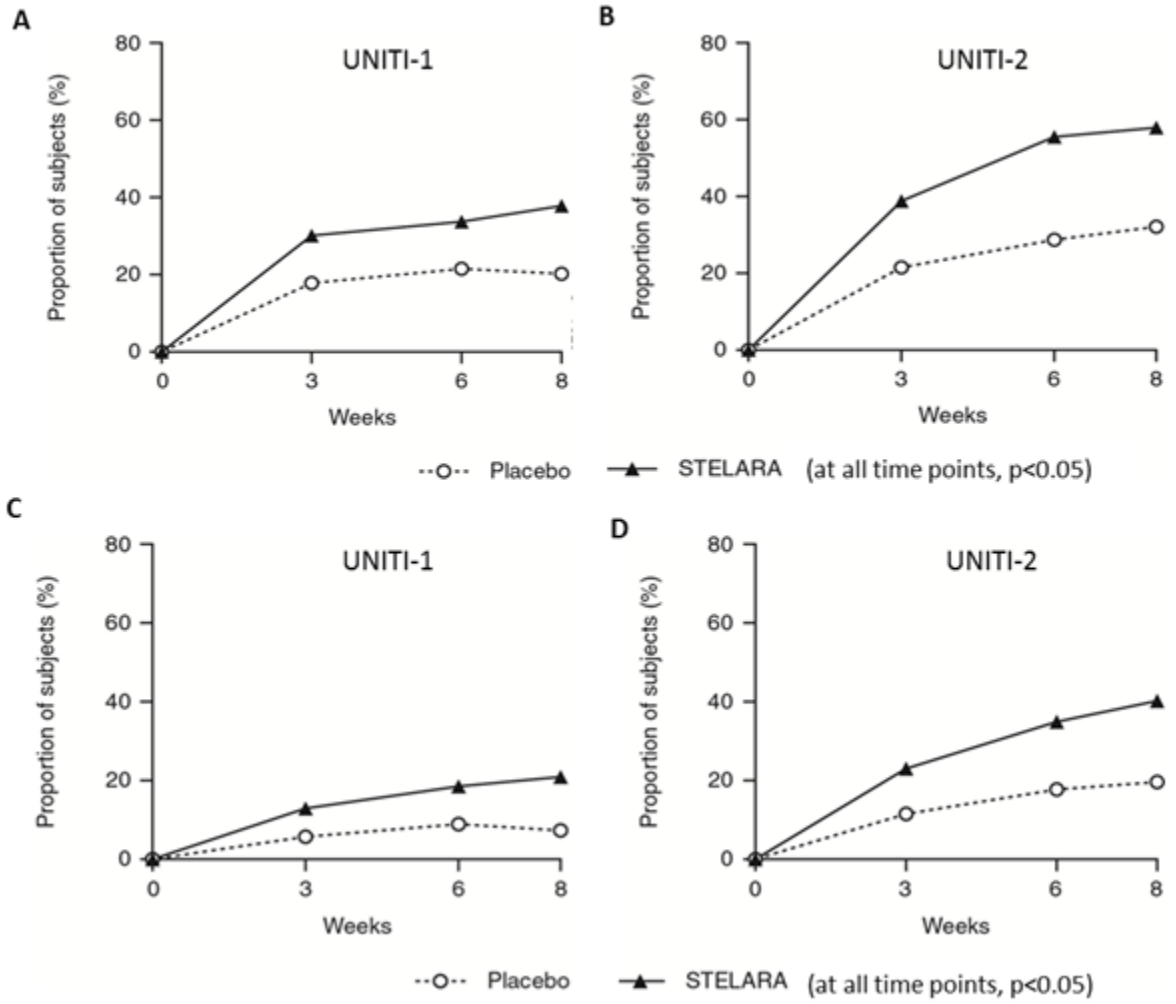


Figure 4: Proportion of STELARA treated patients in clinical response (A, B) and remission (C, D) through Week 8 in UNITI-1 and UNITI-2 studies

Maintenance of Response and Remission

The maintenance study (IM-UNITI) evaluated 388 patients who achieved clinical response (≥100 point reduction in CDAI score) at Week 8 of induction with STELARA in UNITI-1 or UNITI-2. Of those, approximately 60% of the patients entered the maintenance study in remission. Patients were randomized to receive a subcutaneous maintenance regimen of either 90 mg STELARA every 8 weeks, 90 mg STELARA every 12 weeks or placebo for 44 weeks.

Concomitant doses of oral 5-ASA compounds, immunomodulators corticosteroids and antibiotics were permitted. Corticosteroids were tapered at the start of the maintenance trial. The primary endpoint was clinical remission (CDAI < 150) at Week 44. Secondary endpoints assessed at Week 44 included clinical response, clinical remission among STELARA treated patients in clinical remission after induction, corticosteroid-free remission, and clinical remission in the subset of patients who were refractory or intolerant to anti-TNFα treatment.

Significantly higher proportions of patients maintained clinical remission and response in the STELARA treated groups as compared to placebo at Week 44 (Table 30, Figure 5). A higher proportion of STELARA treated patients compared to placebo achieved sustained clinical remission (clinical remission at Week 36, 40 and 44).

Table 30: Maintenance of Clinical Response and Remission in IM-UNITI (Week 44; 52 weeks from initiation of the induction dose)

	Placebo* **N=131†**	**90 mg STELARA every 8 weeks** **N=128†**	**90 mg STELARA every 12 weeks** **N=129†**
Clinical Remission	36%	53%[a]	49%[b]
Clinical Response	44%	59%[b]	58%[b]
Corticosteroid-Free Clinical Remission	30%	47%[a]	43%[c]
Sustained Clinical Remission‡	26%	46%[c]	40%[c]
Clinical Remission in patients:			
in remission at the start of maintenance therapy	46% (36/79)	67% (52/78)[a]	56% (44/78)
who are Anti-TNFα refractory/intolerant	26% (16/61)	41% (23/56)	39% (22/57)
who failed conventional therapy but not anti-TNFα therapy	44% (31/70)	63% (45/72)[c]	57% (41/72)
who are Anti-TNFα naïve	49% (25/51)	65% (34/52)[c]	57% (30/53)

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

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

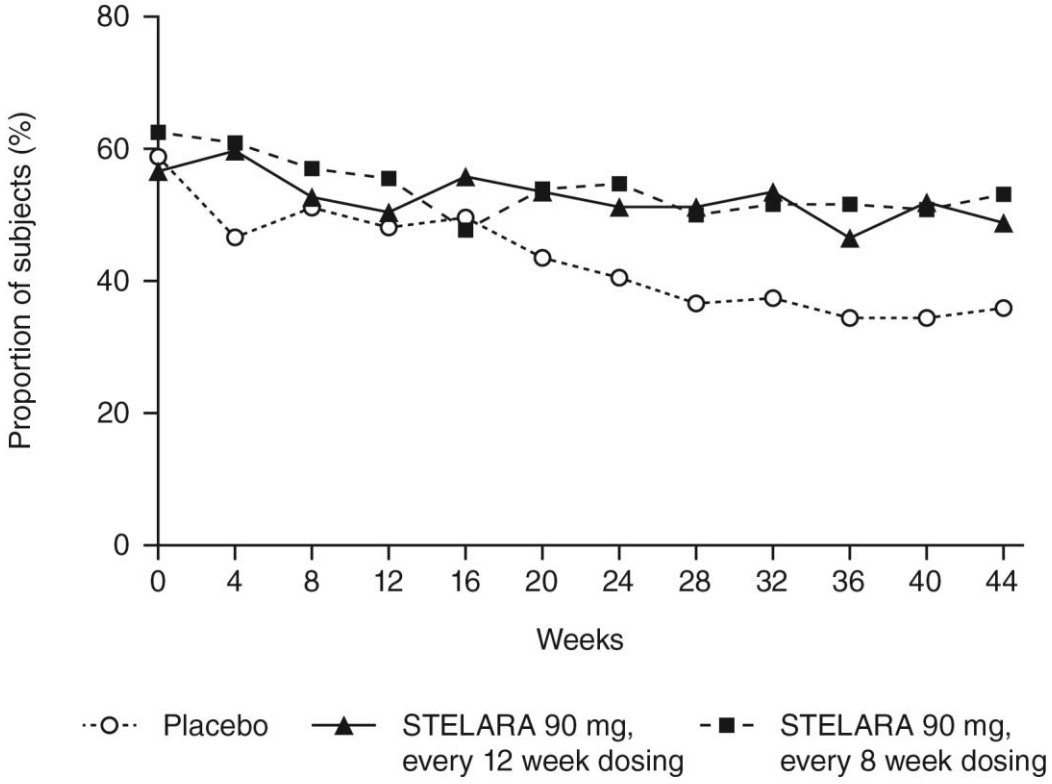
† Patients who achieved a clinical response to STELARA at start of maintenance therapy

‡ Defined as clinical remission at Week 36, 40 and 44.

[a] $p < 0.01$

[b] $p < 0.05$

[c] nominally significant ($p<0.05$)



981

982 **Figure 5:** Proportion of patients in clinical remission at each visit through Week 44.
983
984 *Delayed response*
985 Patients who were not in clinical response to STELARA induction received a 90 mg
986 subcutaneous injection of STELARA upon entry into the maintenance study. Eight weeks later,
987 50.5% of the patients achieved clinical response and continued to receive maintenance dosing
988 every 8 weeks; among these patients with continued maintenance dosing, a majority achieved
989 levels of response (68.1%) and remission (50.2%) similar to the patients who initially responded
990 to STELARA induction.

991 *Dosing in patients with a lower inflammatory burden*
992 In patients with a lower inflammatory burden as reflected by CRP $\leq$ 10 mg/L at initiation of
993 induction or initiation of maintenance therapy, the efficacy of the every 12 week dosing regimen
994 was similar to that of the every 8 week dosing regimen.

995 *Dosing frequency adjustment*
996 In IM-UNITI, patients who did not maintain response to STELARA when treated every 12
997 weeks were allowed to increase the frequency of dosing and receive STELARA every 8 weeks.
998 In these patients, clinical remission was achieved in 41.4% of patients 16 weeks after dosing
999 frequency adjustment.

1000 *Resumption of treatment*
1001 Patients that responded to STELARA induction and who were randomized to the placebo group
1002 at the start of the maintenance study received 90 mg STELARA subcutaneously every 8 weeks at

time of loss of response. Of these patients, 70.6% achieved clinical response and 39.2% achieved clinical remission 16 weeks after receiving the first subcutaneous dose of STELARA.

Corticosteroid Use in maintenance

In patients that were in clinical response to STELARA induction therapy, a greater proportion of patients in the STELARA treated group were in remission and corticosteroid-free compared to the placebo group after 44 weeks of maintenance treatment (Table 30). In addition, a higher proportion of patients were in clinical response and not receiving corticosteroids in the STELARA treated group compared to placebo.

Endoscopic Healing of the Mucosa

Endoscopic healing of the mucosa was evaluated in 252 patients with baseline endoscopic disease activity in a substudy. At Week 8, after a single IV induction dose, reduction in mucosal inflammation, as measured by the Simplified Endoscopic Activity Score for Crohn's Disease (SES-CD), was greater in patients treated with STELARA (n=83) compared with patients treated with placebo (n=97) (-3.0 vs -0.7, p=0.009). Similar reductions in histologic inflammation were also observed.

Reduction in endoscopic and histologic inflammation was observed in patients treated with STELARA in maintenance. However, due to the small number of patients, the efficacy of STELARA in the maintenance of endoscopic healing could not be definitively established.

Fistula Response

In patients with draining fistulas at baseline (8.8%), a numerically greater proportion of STELARA treated patients achieved a fistula response (defined as $\geq$ 50% reduction from baseline of the induction study in the number of draining fistulas) compared with placebo over 44 weeks (p=NS). The proportion of patients in fistula response at Week 44 was 45.5% (5/11) for placebo group, 71.4% (5/7) for STELARA 90 mg every 12 week dosing group, and 87.5% (7/8) for STELARA 90 mg every 8 week dosing group.

Health-Related Quality of Life Measures

Improvement in general and disease specific health-related quality of life was assessed using the SF-36 and Inflammatory Bowel Disease Questionnaire (IBDQ) respectively.

SF-36

A higher proportion of patients treated with STELARA showed clinically meaningful improvements in SF-36 Physical Component Summary (PCS) and Mental Component Summary (MCS) scores, and these improvements were significantly greater at week 8 compared with the placebo group in UNITI-1 (MCS) and UNITI-2 (PCS, MCS and all subscores). These improvements in the PCS and MCS scores were maintained in STELARA treated patients in the IM-UNITI maintenance study through Week 44.

IBDQ

At Week 8 in UNITI-1 and UNITI-2, significant improvement from baseline in the inflammatory bowel disease questionnaire (IBDQ) total score and all subscales, was observed in the patients

treated with STELARA compared to placebo. In both studies, a higher proportion of patients with clinically meaningful improvement in IBDQ total scores were observed in patients treated with STELARA compared to placebo. These improvements in the IBDQ total scores were maintained in STELARA treated patients in the IM-UNITI maintenance study through Week 44.

Pharmacokinetic Properties

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. 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 of ustekinumab following a single subcutaneous administration was estimated to be 57.2% in patients with psoriasis.

Distribution

Median volume of distribution during the terminal phase (Vz) following a single intravenous administration to patients with psoriasis ranged from 57 to 83 mL/kg.

Metabolism

The exact metabolic pathway for ustekinumab is unknown.

Elimination

Median systemic clearance (CL) following a single intravenous administration to patients with psoriasis ranged from 1.99 to 2.34 mL/day/kg.

Median half-life ($t_{1/2}$) of ustekinumab was approximately 3 weeks in patients with Crohn's disease, psoriasis and/or psoriatic arthritis, ranging from 15 to 32 days across all psoriasis and psoriatic arthritis studies.

Dose Linearity

The systemic exposure of ustekinumab (C_{max} and AUC) increased in an approximately dose-proportional manner after a single intravenous administration at doses ranging from 0.09 mg/kg to 4.5 mg/kg or 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. In patients with psoriasis, 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 mcg/mL to 0.26 mcg/mL (45 mg) and from 0.47 mcg/mL to 0.49 mcg/mL

(90 mg). There was no apparent accumulation in serum ustekinumab concentration over time when given subcutaneously every 12 weeks.

In patients with Crohn's disease, following the recommended IV induction dose, median peak serum ustekinumab concentration was 126.1 mcg/mL. Starting at Week 8, subcutaneous maintenance dosing of 90 mg ustekinumab was administered every 8 or 12 weeks. Steady state ustekinumab concentration was achieved by the start of the second maintenance dose. Median steady-state trough concentrations ranged from 1.97 mcg/mL to 2.24 mcg/mL and from 0.61 mcg/mL to 0.76 mcg/mL for 90 mg ustekinumab every 8 weeks or every 12 weeks respectively. The steady-state trough ustekinumab levels resulting from 90 mg ustekinumab every 8 weeks were associated with higher clinical remission rates as compared to the steady-state trough levels following 90 mg every 12 weeks.

Impact of Weight on Pharmacokinetics

Serum ustekinumab concentrations were affected by weight in patients with psoriasis and/or psoriatic arthritis. Within each dose (45 mg or 90 mg), patients of higher weight (> 100 kg) had lower median serum ustekinumab concentrations compared with those in patients of lower weight (≤ 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 (≤ 100 kg) in the 45 mg group.

Population Pharmacokinetic Analysis

In a population pharmacokinetic analysis using data from patients with psoriasis, the apparent clearance (CL/F) and apparent volume of distribution (V/F) were 0.465 L/d and 15.7 L, respectively, and the $t_{1/2}$ was approximately 3 weeks in patients with psoriasis. The CL/F of ustekinumab was not impacted by sex, age, or race. The CL/F was impacted by body weight, with a trend toward higher CL/F in patients with higher body weight. The median CL/F in patients with weight > 100 kg was approximately 55% higher compared with patients with weight ≤ 100 kg. The median V/F in patients with weight > 100 kg was approximately 37% higher as compared with patients with weight ≤ 100 kg. Similar results were obtained from a confirmatory population pharmacokinetic analysis using data from patients with psoriatic arthritis.

In the population pharmacokinetic analysis using data from patients with psoriasis, the effect of comorbidities (past and current history of diabetes, hypertension, and hyperlipidemia) on pharmacokinetics of ustekinumab was evaluated. The pharmacokinetics of ustekinumab were impacted by the comorbidity of diabetes, with a trend towards higher CL/F in patients with diabetes. The mean CL/F in patients with diabetes was approximately 29% higher compared with patients without diabetes.

Population pharmacokinetic analysis showed that there was a trend towards a higher clearance of ustekinumab in patients with positive immune response.

No specific drug-drug interaction studies have been conducted in healthy subjects or patients with psoriasis, psoriatic arthritis or Crohn's disease.

In the population pharmacokinetic analyses, 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 MTX, cyclosporine, or other biological therapeutics for the treatment of psoriasis. The pharmacokinetics of ustekinumab was not impacted by concomitant use of MTX, NSAIDs, oral corticosteroids, 6-MP, AZA or prior exposure to anti-TNFα agents in patients with psoriatic arthritis or Crohn's disease.

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 (see *Interactions*).

Special populations

Elderly (65 years of age and older)

No specific studies have been conducted in elderly patients. The population pharmacokinetic analysis indicated there were no apparent changes in CL/F and V/F estimates in patients ≥ 65 years.

Renal impairment

No pharmacokinetic data are available in patients with renal insufficiency.

Hepatic impairment

No pharmacokinetic data are available in patients with impaired hepatic function.

Other populations

The pharmacokinetics of ustekinumab were generally comparable between Asian and non-Asian patients with psoriasis or Crohn's disease.

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

NON-CLINICAL INFORMATION

In repeated-dose toxicity studies in juvenile 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.

Dose levels in animal studies were up to approximately 45-fold higher than the highest equivalent dose intended to be administered to patients with psoriasis and resulted in peak serum concentrations in monkeys that were more than 100-fold higher than observed in humans.

Carcinogenicity and Mutagenicity

Carcinogenicity studies were not performed with ustekinumab due to the lack of appropriate models for an antibody with no cross-reactivity to rodent IL-12/23 p40.

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 behavior, 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.

PHARMACEUTICAL INFORMATION

List of Excipients

45 mg or 90 mg Pre-filled syringe/vial

L-histidine

L-histidine monohydrochloride monohydrate

Polysorbate 80

Sucrose

Water for injection

130 mg vial

EDTA disodium salt dihydrate

L-histidine

L-histidine hydrochloride monohydrate

L-methionine

Polysorbate 80

Sucrose

Water for injection

Incompatibilities

Not applicable.

Shelf Life

Observe expiry date after the word "Exp." on the outer pack.

Storage Conditions

- Store in a refrigerator
  - 2ºC to 8ºC
  - 36ºF - 46ºF
- Store in original carton until time of use
- Protect from light
- Do not freeze
- Do not shake
- Keep out of reach of children.

Nature and Contents of Container

For subcutaneous injection

STELARA is supplied as a sterile solution in a single-use (Type 1) glass vial. The vial is stoppered with a coated stopper.

STELARA is also 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*). The syringe is fitted with a passive safety guard.

The solution is clear to slightly opalescent, colorless to light yellow with a pH of approximately 6.0. Each mL of STELARA contains 90 mg of ustekinumab, 1.0 mg L histidine and L histidine hydrochloride, 76 mg sucrose, 0.04 mg polysorbate 80, and Water for Injection, USP. STELARA does not contain preservatives.

There are two strengths of STELARA available: 45 mg of ustekinumab in 0.5 mL, or 90 mg of ustekinumab in 1.0 mL.

STELARA is available in the following packaging presentations:

- 1 single use vial
- 1 single-use pre-filled syringe

For intravenous infusion only

STELARA 130 mg vial is supplied as a sterile solution in a single-use (Type 1) glass vial. The vial is stoppered with a coated stopper.

The solution is clear, colorless to light yellow with a pH of approximately 6.0. Each mL of STELARA contains 5.0 mg of ustekinumab, 0.8 mg L-histidine, 1.1 mg L-histidine hydrochloride monohydrate, 85 mg sucrose, 0.40 mg polysorbate 80, 0.40 mg L-methionine, and 0.02 mg EDTA disodium salt dihydrate. STELARA does not contain preservatives. STELARA is available for intravenous infusion in one strength, 130 mg in 26 mL, and packaged as 1 single use vial.

Instructions for Use, Handling and Disposal

Following administration of STELARA, discard any unused portion. The syringe should be disposed of with accepted medical practices for used syringes. The syringe, needle and vial must never be re-used.

Instructions for dilution of STELARA 130 mg for IV infusion (Crohn's disease)

STELARA 130 mg solution must be diluted and prepared for IV infusion by a healthcare professional using aseptic technique.

1. Calculate the dose and the number of STELARA vials needed based on patient's body weight (see Table 1). Each 26 mL vial of STELARA contains 130 mg of ustekinumab.
2. Withdraw and then discard a volume of the 0.9% w/v sodium chloride solution from the 250 mL infusion bag equal to the volume of STELARA to be added. (discard 26 mL sodium chloride for each vial of STELARA needed, for 2 vials-discard 52 mL, for 3 vials- discard 78 mL, for 4 vials- discard 104 mL).
3. Withdraw 26 mL of STELARA from each vial needed and add it to the 250 mL infusion bag. The final volume in the infusion bag should be 250 mL. Gently mix.
4. Visually inspect the diluted solution before administration. Do not use if visibly opaque particles, discoloration or foreign particles are observed.
5. Administer the diluted solution over a period of at least one hour. Once diluted, the infusion solution may be stored for up to four hours prior to infusion.
6. Use only an infusion set with an in-line, sterile, non-pyrogenic, low protein-binding filter (pore size 0.2 micrometer).

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

8. Each vial is for single use only and any unused medicinal product should be disposed of in accordance with local requirements.

Storage

If necessary, the diluted infusion solution may be stored for up to four hours at room temperature. Do not freeze. Discard any unused portion of the infusion solution.

[See Core Patient Package Insert for comprehensive instructions for the use, handling, and disposal.]

Manufactured by

Cilag AG, Schaffhausen, Swiss Confederation

Product Name	Marketing Authorization Numbers	Date of Authorization
STELARA	1C 17/57 (NB)	24 June 2014
STELARA 130 MG	1C 15029/61 (NBC)	9 May 2018

Date of Revision of The Text

4 August 2017

Imported by

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