NAME OF THE MEDICINAL PRODUCT

Tradename: STELARA™

International Non-Proprietary Name: Ustekinumab

Compound Number: CNTO 1275

QUALITATIVE AND QUANTITATIVE COMPOSITION

Ustekinumab is a fully human IgG1κ monoclonal antibody with an approximate molecular weight of 148,600 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:

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

For excipients, see List of Excipients.

PHARMACEUTICAL FORM
Solution for injection

CLINICAL PARTICULARS
Therapeutic Indications

Plaque Psoriasis:
STELARA is indicated for:
- treatment of psoriasis
- improving quality of life

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

Posology And Method Of Administration
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.

General Consideration for 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.

Comprehensive instructions for the administration of STELARA are given in the "Core Patient Package Insert (CPPI)". Patients should be instructed to inject the full 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.

Contraindications

None

Special Warnings and Special Precautions for Use

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 Undesirable Effects).

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 Undesirable Effects).
- 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.

Hypersensitivity reactions

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

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.

Immunosuppression

The safety and efficacy of STELARA in combination with immunosuppressive agents or phototherapy have not been evaluated. Caution should be exercised when considering concomitant use of immunosuppressive agents and STELARA or when transitioning from other biologic agents used to treat psoriasis.

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.

Special Populations

Pediatric use

Specific studies of STELARA in pediatric patients have not been conducted.

Geriatric use

No major age-related differences in clearance or volume of distribution were observed in clinical studies. No overall differences in efficacy or safety in patients age 65 and older [N=131] who received STELARA were observed compared with younger patients.

Hepatic insufficiency

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

Renal insufficiency

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

Interactions with Other Medicinal Products and Other Forms of Interaction

- 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 Special Warnings and Special Precautions for Use).

Pregnancy and Lactation

Use during 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 psoriasis patients (see Preclinical Safety Data). 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.

Use during lactation

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.

Effects on Ability to Drive and Use Machines
No studies on the effects on the ability to drive and use machines have been performed.

Undesirable Effects
Psoriasis Clinical Studies Experience
The safety data described below reflect exposure to STELARA in 3 adequate and well-controlled studies of 2266 patients, including 1970 exposed for at least 6 months and 1285 exposed for at least 1 year and 373 for at least 18 months.

The following serious adverse reactions were reported:

- Serious infections
- Malignancies

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

Table 1 provides a summary of Adverse Drug Reactions from psoriasis clinical studies. The adverse drug reactions are ranked by frequency, using the following convention:

Very common (≥1/10)
Common (frequent) (≥1/100, <1/10)
Uncommon (infrequent) (≥1/1,000, <1/100)
Rare (≥1/10,000, <1/1,000)

Table 1 SUMMARY OF ADRs IN PSORIASIS CLINICAL STUDIES

Infections and infestations	Very common: Upper respiratory tract infection, nasopharyngitis Common: Viral upper respiratory tract infection, cellulitis Uncommon: Rare
Psychiatric disorders	Very common Common: Depression Uncommon Rare
Nervous system disorders	Very common Common: Dizziness, headache Uncommon: Rare
Respiratory, thoracic and mediastinal disorders	Very common Common: Pharyngolaryngeal pain, nasal congestion Uncommon Rare
Gastrointestinal disorders	Very common Common: Diarrhea Uncommon Rare
Skin and subcutaneous tissue disorders	Very common Common: Pruritus Uncommon Rare
Musculoskeletal and connective tissue disorders	Very common Common: Back pain, myalgia Uncommon Rare
General disorders and administration site conditions	Very common Common: Fatigue, injection site erythema Uncommon: injection site reactions (including pain, swelling, pruritus, induration, hemorrhage, bruising and irritation) Rare

Infections

In controlled studies of psoriasis patients, 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 psoriasis patients, the rate of infection was 1.39 per patient-year of follow-up in STELARA-treated patients, and 1.21 per patient-year of follow-up in placebo-treated patients. Serious infections occurred in 0.01 per patient-year of follow-up in STELARA-treated patients (5 serious infections in 407 patient-years of follow-up) and 0.02 per patient-year of follow-up in placebo-treated patients (3 serious infections in 177 patient-years of follow-up) (see Special Warnings and Special Precautions for Use).

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

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 clinical studies, the incidence of malignancies excluding nonmelanoma skin cancer was 0.25 per 100 patient-years of follow-up for STELARA-treated patients (1 patient in 406 patient-years of follow-up) compared with 0.57 per 100 patient-years of follow-up for placebo-treated patients (1 patient in 177 patient-years of follow-up).

The incidence of nonmelanoma skin cancer was 0.74 per 100 patient-years of follow-up for STELARA-treated patients (3 patients in 406 patient-years of follow-up) compared with 1.13 per 100 patient-years of follow-up for placebo-treated patients (2 patients in 176 patient-years of follow-up).

In the controlled and non-controlled portions of psoriasis clinical studies, the incidence of malignancies excluding nonmelanoma skin cancers was 0.36 per 100 patient-years of follow-up for STELARA-treated patients (8 patients in 2249 patient-years of follow-up) and included breast, colon, head and neck, kidney, prostate, and thyroid cancers. The rate of malignancies reported in STELARA-treated patients was comparable to the rate expected in the general population (standardized incidence ratio = 0.68 [95% confidence interval: 0.29, 1.34]. The incidence of nonmelanoma skin cancer was 0.80 per 100 patient-years of follow-up for STELARA treated patients (18 patients in 2245 patient-years of follow-up).

Hypersensitivity Reactions

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

Immunogenicity

Approximately 5% of patients treated with STELARA developed antibodies to ustekinumab, which were generally low-titer. No apparent correlation of antibody development to injection site reactions was seen. Patients positive for antibodies to STELARA tended to have lower efficacy, however, antibody positivity does not preclude a clinical response.

Post Marketing Experience

The adverse drug reactions in Table 2 are ranked by frequency* using the following convention:

Very common: ≥1/10
Common: ≥1/100 and <1/10
Uncommon: ≥1/1,000 and <1/100
Rare: ≥1/10,000 and <1/1000
Very rare: <1/10,000, including isolated reports

Table 2 Post-Marketing Reports

Immune system disorders	Common: Hypersensitivity reactions (including

	rash, urticaria) Rare: Serious allergic reactions (including angioedema)

*Post-marketing adverse reaction frequency is derived from clinical trials if the adverse reaction was observed during trials, or is estimated to be lower than a certain frequency given the exposure in adequately designed clinical trials where the adverse reaction was not observed.

Overdose

Single doses up to 4.5 mg/kg intravenously have been administered in clinical studies without dose-limiting toxicity. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment be instituted immediately.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

ATC code: L04AC05.

- **Mechanism of action**

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

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

- **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.

  STELARA had no apparent effect on the percentages of circulating immune cell populations including memory and naive T cell subsets or circulating cytokine levels.

  Treatment with 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 posttreatment. 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.

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

response at Week 28 increased with increasing serum ustekinumab trough levels at Week 28.

- **Clinical efficacy**
  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 safety and efficacy of STELARA beyond 3 years have not been established.

  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 (i.e., 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 to52 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 3).

Table 3 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 4). 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 4). 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 4).

Table 4 -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%)

Table 4 -Key psoriasis endpoints– PHOENIX 1 and PHOENIX 2						
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

Table 4 -Key psoriasis endpoints– PHOENIX 1 and PHOENIX 2				
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%)

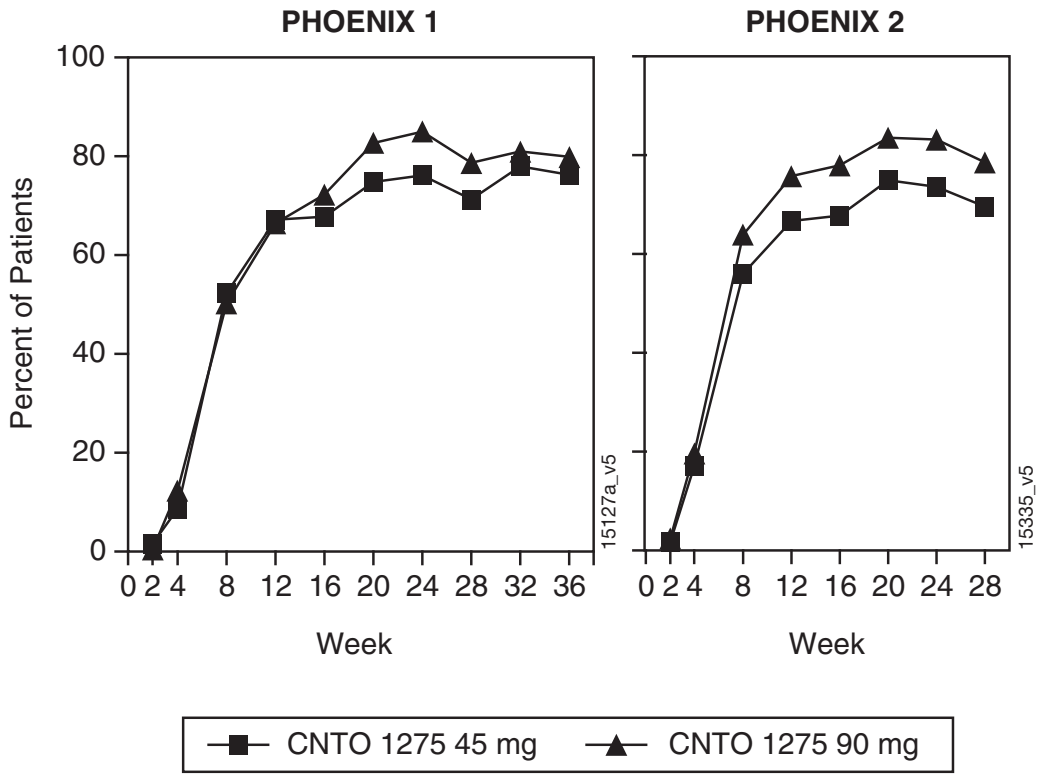
[a] $p < 0.001$ for 45 mg or 90 mg comparison with placebo.
[b] data corrected post EMEA inspection.

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 4).

Figure 1 shows 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 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 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).

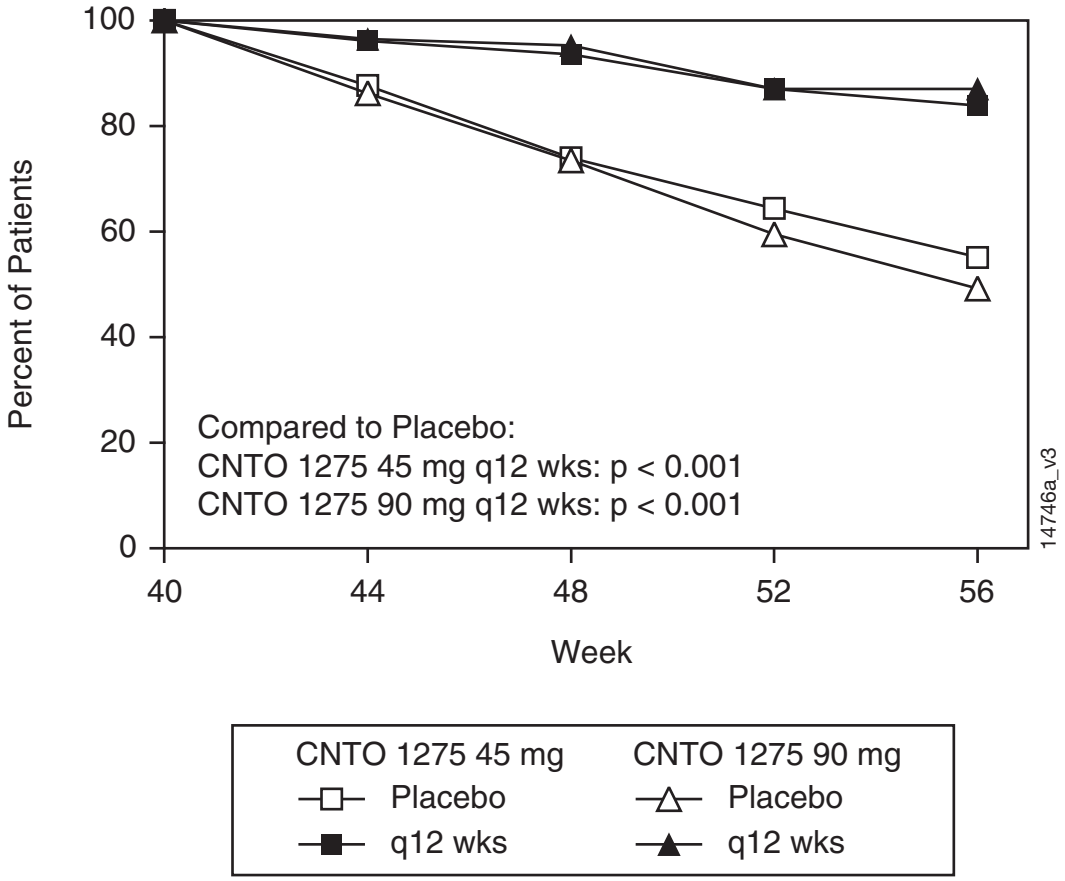


Figure 2 Life-table estimate of percent of patients maintaining PASI 75 response; patients randomized at Week 40 (PHOENIX 1)

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 5 and 6). 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.

Table5	**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

Table5	Quality of Life endpoints through Week 40 – PHOENIX 1		
		STELARA	
	Placebo	45 mg	90 mg
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

Table 6	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

Nail Psoriasis

In PHOENIX 1, the median baseline NAPSI score for nail psoriasis was 4.0 and the median number of fingernails involved with psoriasis was 8.0. Nail psoriasis improved significantly in patients randomized to 45 mg or 90 mg STELARA compared with patients randomized to placebo when measured by the NAPSI score (Tables 7 and 8). Nail psoriasis continued to improve over time through Week 52 in patients treated with STELARA.

Table 7 **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 8 **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 9). HADS improvements were maintained through Week 24 (Table 10).

Table 9 **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.

Table 10 **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

Work Limitations Questionnaire

The Work Limitations Questionnaire obtained at baseline showed impaired work productivity among psoriasis patients evaluated in PHOENIX 2 for the Physical Demands, Time Management, Mental-Interpersonal and Output Demands component scores. Work productivity improved significantly more in patients randomized to STELARA at Week 12 compared with patients randomized to placebo as measured by the four WLQ subscales (Physical Demands, Time Management, Mental-Interpersonal, and Output Demands; Table 11).

Table 11 **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]			

Table 11 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
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 12).

Table 12 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, methotrexate, 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 moderate to severe psoriasis patients. The active-controlled portion of the study was from Week 0 to Week 12, during which patients were randomized to receive etanercept (50mg 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 13). 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 13).

Table 13 Key psoriasis endpoints at Week 12: ACCEPT

	ACCEPT		
	Etanercept (50mg 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, methotrexate, and cyclosporine. Unsuitable conventional systemic agents are defined as those to which patients had had an inadequate response, were intolerant, or had a contraindication.

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 (t1/2) of ustekinumab was approximately 3 weeks in patients with psoriasis, ranging from 15 to 32 days across all psoriasis 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. Steady-state serum concentrations of ustekinumab were achieved by Week 28 after initial subcutaneous doses at Weeks 0 and 4, followed by doses every 12 weeks. The median steady-state trough concentration ranged from 0.21 µg/mL to 0.26 µg/mL (45 mg) and from 0.47 µg/mL to 0.49 µg/mL (90 mg). There was no apparent accumulation in serum ustekinumab concentration over time when given subcutaneously every 12 weeks.

- Impact of Weight on Pharmacokinetics
  Serum ustekinumab concentrations were affected by patient weight. 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, the apparent clearance (CL/F) and apparent volume of distribution (V/F) were 0.465 L/d and 15.7 L, respectively, and the t1/2 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.

    - In the population pharmacokinetic analysis, 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.

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

    - 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 with Other Medicinal Products and Other Forms of Interaction).

- No pharmacokinetic data are available in patients with renal insufficiency.

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

- 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 $\geq$ 65 years.

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

Preclinical Safety Data

In repeated-dose toxicity studies in cynomolgus monkeys, ustekinumab was well-tolerated following IV doses up to 45 mg/kg/week for up to 1 month and following twice-weekly SC doses up to 45 mg/kg for 6 months. There were no ustekinumab -related findings in the immunotoxicity and cardiovascular safety pharmacology evaluations. In histopathology evaluations there were no preneoplastic changes observed.

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

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 PARTICULARS

List of Excipients

Sucrose
L -histidine
L-histidine monohydrochloride monohydrate
Polysorbate 80
Water for injection

Incompatibilities

Not applicable

Shelf Life

Observe expiry date on the outer pack.

Special Precautions for Storage

- 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

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 Special Warnings and Special Precautions for Use). 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

Instructions for Use and Handling <and Disposal>

Following administration of STELARA, the syringe should be disposed of with accepted medical practices for used syringes.

MANUFACTURED BY
See outer carton.

DATE OF REVISION OF THE TEXT
December 2010