AUSTRALIAN PRODUCT INFORMATION
UTEKNIX
(ustekinumab)
solution for subcutaneous injection

1 NAME OF THE MEDICINE

Ustekinumab

UTEKNIX is a biosimilar medicine to Stelara (ustekinumab). The evidence for comparability supports the use of UTEKNIX for the listed indication(s).

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

UTEKNIX 45 mg solution for injection in pre-filled syringe

Each pre-filled syringe contains 45 mg ustekinumab in 0.5 mL.

UTEKNIX 90 mg solution for injection in pre-filled syringe

Each pre-filled syringe contains 90 mg ustekinumab in 1 mL.

For the full list of excipients, see section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Solution for subcutaneous injection.

The solution is clear, colourless to slightly yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Plaque psoriasis

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

Psoriatic arthritis (PsA)

UTEKNIX, alone or in combination with methotrexate, is indicated for the treatment of signs and symptoms of active psoriatic arthritis in adult patients (18 years and older) where response to previous non-biological DMARD therapy has been inadequate.

UTEKNIX has not been approved for use in children or adolescents under the age of 18 years.

UTEKNIX has not been approved for use in patients with Crohn’s disease or ulcerative colitis.

4.2 Dose and method of administration

Dosing

Plaque psoriasis

Adults

For the treatment of plaque psoriasis, UTEKNIX is administered by subcutaneous injection. The recommended dose of UTEKNIX is 45 mg administered at Weeks 0 and 4, then every 12 weeks thereafter. Alternatively, 90 mg administered over Weeks 0 and 4, then every 12 weeks thereafter may be used in patients with a body weight greater than 100 kg.

Dose adjustment

For patients who inadequately respond to dosing every 12 weeks, consideration may be given to treating as often as every 8 weeks. Treatment should be discontinued in patients who have shown no response after 28 weeks of treatment.

Re-treatment

After interruption of therapy, re-treatment with a dosing regimen of Weeks 0 and 4, then every 12 weeks thereafter has been shown to be safe and effective.

Psoriatic arthritis

For the treatment of psoriatic arthritis, UTEKNIX is administered by subcutaneous injection. The recommended dose of UTEKNIX is 45 mg administered at Weeks 0 and 4, then every 12 weeks thereafter. Some patients with a body weight greater than 100 kg received a 90 mg dose in clinical trials and observed a clinical benefit.

Treatment should be discontinued in patients who have shown no response after 28 weeks of treatment.

Use in patients with hepatic or renal impairment

UTEKNIX has not been studied in these patient populations. No dose recommendations can be made (see section 5.2 Pharmacokinetic properties – Population pharmacokinetic analysis).

Administration

UTEKNIX 45 mg and 90 mg pre-filled syringes are for subcutaneous injection only. Do not inject into areas where the skin is tender, bruised, red, hard, thick, scaly or affected by psoriasis.

Each pre-filled syringe is for single use only and any unused medicinal product should be disposed of in accordance with local requirements.

UTEKNIX is intended for use under the guidance and supervision of a health care professional. Patients or their caregivers may inject UTEKNIX 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 subcutaneous administration of UTEKNIX are given in the Consumer Medicine Information for pre-filled syringe. Patients should be instructed to inject the full amount of UTEKNIX subcutaneously according to the directions provided in the Consumer Medicine Information.

The solution should be visually inspected for particulate matter or discolouration prior to subcutaneous administration. The solution is clear and colourless to slightly yellow and practically free from visible particles. The medicinal product should not be used if the solution is frozen, discoloured or cloudy, or has large particles. Any unused medicinal product remaining in the syringe should not be used. Any

unused medicinal product or waste material should be disposed of in accordance with local requirements.

Each pre-filled syringe is for single dose only. Patients may encounter resistance while injecting. It is important to instruct patients to inject the full amount to receive either 45 mg or 90 mg of UTEKNIX.

4.3 Contraindications

Severe hypersensitivity to ustekinumab or to any of the excipients (see section 4.4 Special warnings and precautions for use).

UTEKNIX should not be given to patients with a clinically important, active infection.

4.4 Special warnings and precautions for use

Serious infections

Ustekinumab 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 ustekinumab. Caution should be exercised when considering the use of ustekinumab in patients with a chronic infection or a history of recurrent infection.

Prior to initiating treatment with ustekinumab, patients should be evaluated for tuberculosis infection. Ustekinumab should not be given to patients with active tuberculosis. Treatment of latent tuberculosis infection should be initiated prior to administering ustekinumab. Anti-tuberculosis therapy should also be considered prior to initiation of ustekinumab in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. Patients receiving ustekinumab 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 ustekinumab should not be administered until the infection resolves (see section 4.8 Adverse effects (Undesirable effects)).

Non-infectious pneumonia

Cases of interstitial pneumonia, eosinophilic pneumonia and cryptogenic organizing pneumonia have been reported during post-approval use of ustekinumab. Clinical presentations included cough, dyspnoea, and interstitial infiltrates following one to three doses. Serious outcomes have included respiratory failure and prolonged hospitalization. Patients improved with discontinuation of therapy and in certain cases administration of corticosteroids. If diagnosis is confirmed, discontinue ustekinumab and institute appropriate treatment.

Malignancies

Ustekinumab is a selective immunosuppressant. Immunosuppressive agents have the potential to increase the risk of malignancy. Some patients who received ustekinumab in clinical studies developed cutaneous and non-cutaneous malignancies (see section 4.8 Adverse effects (Undesirable effects)).

Ustekinumab has not been studied in patients with a history of malignancy. Caution should be exercised when considering the use of ustekinumab 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 section 4.8 Adverse effects (Undesirable effects)).

Hypersensitivity

In post-marketing experience, serious hypersensitivity reactions, including anaphylaxis and angioedema, have been reported.

If an anaphylactic or other serious hypersensitivity occurs, appropriate therapy should be instituted and administration of ustekinumab should be discontinued immediately (see section 4.8 Adverse effects (Undesirable effects)).

Immunisations

It is recommended that live viral or live bacterial vaccines (such as Bacillus of Calmette and Guérin [BCG]) not be given concurrently with ustekinumab.

Before live viral or live bacterial vaccination, treatment with ustekinumab should be withheld for at least 15 weeks after the last dose and can be resumed at least 2 weeks after vaccination. Prescribers should consult the Product Information for the specific vaccine for additional information and guidance on concomitant use of immunosuppressive agents post vaccination and considering the benefit risk of ustekinumab treatment in the patient.

No data are available on the secondary transmission of infection by live vaccines in patients receiving ustekinumab. Caution is advised when administering some live vaccines to household contacts of patients receiving ustekinumab because of the potential risk for shedding from the household contact and transmission to the patient.

Patients receiving ustekinumab may receive concurrent inactivated or non-live vaccinations.

Long term treatment with ustekinumab does not suppress the humoral immune response to pneumococcal polysaccharide or tetanus vaccines (see section 5.1 Pharmacodynamic properties).

Infant exposure in utero

For infants exposed *in utero* to ustekinumab, a six month waiting period following birth is recommended before the administration of live vaccines. Administration of a live vaccine prior to 6 months of age may be considered if ustekinumab serum levels are undetectable in the infant and the benefit of the vaccination clearly outweighs the theoretical risk of administration of live vaccines to the infant (see section 4.6 Fertility, pregnancy and lactation).

Immunosuppression

In psoriasis studies, the safety and efficacy of ustekinumab in combination with immunosuppressive agents or phototherapy have not been evaluated. In psoriatic arthritis studies, concomitant methotrexate (MTX) use did not appear to influence the safety or efficacy of ustekinumab. Caution should be exercised when considering concomitant use of immunosuppressive agents and ustekinumab or when transitioning from other biologic agents.

Immunotherapy

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

Posterior reversible encephalopathy syndrome (PRES)

Posterior reversible encephalopathy syndrome (PRES), also known as Reversible Posterior Leukoencephalopathy Syndrome (RPLS) is a neurological disorder, which is not caused by

demyelination or a known infectious agent. Conditions with which it has been associated include preeclampsia, eclampsia, acute hypertension, cytotoxic agents and immunosuppressive therapy. Fatal outcomes have been reported in this condition.

Two cases of PRES were reported in clinical trials. Cases have also been reported in postmarketing experience in patients with psoriasis and psoriatic arthritis. Clinical presentation included headaches, seizures, confusion, visual disturbances, and imaging changes consistent with PRES a few days to several months after ustekinumab initiation. A few cases reported latency of a year or longer. Patients recovered with supportive care following withdrawal of ustekinumab. Monitor all patients treated with UTEKNIX for signs and symptoms of PRES.

If PRES is suspected, promptly administer appropriate treatment and discontinue UTEKNIX.

Serious skin conditions

In patients with psoriasis, exfoliative dermatitis has been reported following ustekinumab treatment. Patients with plaque psoriasis may develop erythrodermic psoriasis, with symptoms that may be clinically indistinguishable from exfoliative dermatitis, as part of the natural course of their disease. As part of the monitoring of the patient's psoriasis, physicians should be alert for symptoms of erythrodermic psoriasis or exfoliative dermatitis. If these symptoms occur, appropriate therapy should be instituted. UTEKNIX should be discontinued if a drug reaction is suspected.

General

The primary packaging is not made with dry natural rubber latex.

Use in the elderly

Of the 6709 patients exposed to ustekinumab, a total of 252 were 65 years or older (183 patients with psoriasis and 69 patients with psoriatic arthritis). No major age-related differences in clearance or volume of distribution were observed in clinical studies. Although no overall differences in efficacy or safety were observed between older and younger patients in clinical studies in approved indications, the number of patients aged 65 and over is not sufficient to determine whether they respond differently from younger patients.

Paediatric use

UTEKNIX has not been approved for use in children or adolescents. Use in patients below the age of 18 years is not recommended.

Effects on laboratory tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

Specific drug interaction studies have not been conducted with ustekinumab (see section 5.2 Pharmacokinetic properties).

Live vaccines should not be given concurrently with ustekinumab. Recommendations for infants exposed to ustekinumab *in utero* are provided (see section 4.4 Special warnings and precautions for use – Immunisations).

CYP450 substrates

The formation of CYP450 enzymes can be altered by increased levels of certain cytokines (e.g. IL-1, IL-6, IL-10, TNFα, IFN) during chronic inflammation. Thus, ustekinumab, an antagonist of IL-12 and IL-23, could normalize the formation of CYP450 enzymes. Upon initiation of ustekinumab in patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index,

monitoring for therapeutic effect (e.g. for warfarin) or drug concentration (e.g. for ciclosporin) should be considered and the individual dose of the drug adjusted as needed.

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

4.6 Fertility, pregnancy and lactation

Effects on fertility

In a male fertility study in cynomolgus monkeys, no ustekinumab-related effects on mating behaviour, sperm parameters, or serum concentrations of male hormones were observed following twice weekly subcutaneous administration of ustekinumab at doses up to 45 mg/kg.

The effect of ustekinumab on female fertility has not been evaluated. 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.

It is not known whether ustekinumab can affect reproductive potential.

Use in pregnancy

Category B1

The available clinical experience with use of ustekinumab is limited. Data from prospectively collected pregnancies following exposure to ustekinumab resulting in live birth with known outcomes, including more than 450 pregnancies exposed during the first trimester, do not indicate an increased risk of malformations in the newborn. However, the risk of harm to a fetus from ustekinumab use in pregnancy cannot be completely excluded.

Developmental toxicity studies of ustekinumab were conducted in cynomolgus monkeys. No evidence of maternal toxicity, embryotoxicity or teratogenicity was observed at doses up to 45 mg/kg following weekly or twice weekly administration via the intravenous or subcutaneous routes, respectively, during the period of organogenesis. However, animal reproductive and developmental studies are not always predictive of human response.

Ustekinumab may be given to a pregnant woman if the benefit clearly outweighs the risk.

Use in lactation

Limited data from published literature suggests that ustekinumab is excreted in human breast milk in very small amounts. While systemic exposure to a breastfed infant is expected to be low because ustekinumab is a large molecule and is likely degraded in the gastrointestinal tract, it is not known if ustekinumab is absorbed systemically after ingestion. Because of the potential for adverse reactions in nursing infants from ustekinumab, a decision on whether to discontinue breast-feeding during treatment and up to 15 weeks after treatment or to discontinue therapy with ustekinumab must be made, taking into account the benefit of breast-feeding to the child and the benefit of ustekinumab therapy to the woman.

Maternal treatment of monkeys with ustekinumab at doses up to 45 mg/kg twice weekly subcutaneous from gestation Day 20 to post-partum Day 33 had no adverse effects on offspring development. However, animal reproductive and developmental studies are not always predictive of

human response.

4.7 Effects on ability to drive and use machines

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

4.8 Adverse effects (undesirable effects)

Clinical Studies Experience in Adult Patients with Psoriasis and Psoriatic Arthritis

The safety data described below in Table 1 reflect exposure to ustekinumab in 14 Phase 2 and Phase 3 studies in 6709 patients, with duration of exposure to ustekinumab presented in Table 1.

Table 1 Long term exposure to ustekinumab in Phase 2 and Phase 3 clinical studies

Exposure	Number of patients
6 months	4577 [a]
1 year	3253 [a]
≥4 years	1482 [b]
≥5 years	838 [b]

a. Total number of patients in the psoriasis, psoriatic arthritis and other indications
b. Number of patients with psoriasis

The most common adverse reactions (>5%) in controlled periods of the clinical studies with ustekinumab among all indications were nasopharyngitis and headache. Most were considered to be mild and did not necessitate drug discontinuation. The overall safety profile of ustekinumab was similar for patients among all indications.

Table 2 provides a summary of Adverse Drug Reactions from the 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 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 2 Summary of ADRs in Clinical Studies

System Organ Class	Frequency: Adverse reaction
Infections and infestations	Common: Upper respiratory tract infection, nasopharyngitis, sinusitis Uncommon: Herpes zoster, cellulitis, dental infections, 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: Diarrhoea, 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 haemorrhage, haematoma, induration, swelling and pruritus), asthenia

Infections

In the placebo-controlled studies of patients with psoriasis and psoriatic arthritis, the rates of infection or serious infection were similar between ustekinumab-treated patients and those treated with placebo. In the placebo-controlled period of the clinical studies of patients with psoriasis and patients with psoriatic arthritis, the rate of infection was 1.36 per patient-year of follow-up in ustekinumab-treated patients, and 1.34 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 ustekinumab-treated patients (30 serious infections in 930 patient-years of follow-up) and 0.03 per patient-year of follow-up in placebo-treated patients (15 serious infections in 434 patient-years of follow-up) (see section 4.4 Special warnings and precautions for use).

In the controlled and non-controlled portions of psoriasis and psoriatic arthritis clinical studies representing 11581 patient-years of exposure in 6709 patients, the median follow-up was 1.0 years; 1.1 years for psoriatic disease studies. The rate of infection was 0.91 per patient-year of follow-up in ustekinumab-treated patients. The incidence of serious infections was 0.02 per patient-year of follow-up in ustekinumab-treated patients (199 serious infections in 11581 patient-years of follow-up) and included pneumonia, anal abscess, cellulitis, diverticulitis, osteomyelitis, viral infections, gastroenteritis, and urinary tract infections.

In clinical studies, patients with latent tuberculosis who were concurrently treated with isoniazid did not develop tuberculosis. One case of tuberculosis reactivation occurred in a subject with abnormal baseline chest X-Ray and without treatment for latent TB while on ustekinumab therapy. The subject fully recovered with appropriate treatment.

Malignancy

In the placebo-controlled period of the psoriasis and psoriatic arthritis clinical studies, the incidence of malignancies excluding non-melanoma skin cancer was 0.11 per 100 patient-years of follow-up for ustekinumab-treated patients (1 patient in 929 patient-years of follow-up) compared with 0.23 per 100 patient-years of follow-up for placebo-treated patients (1 patient in 434 patient-years of follow-up).

The incidence of non-melanoma skin cancer was 0.43 per 100 patient-years of follow-up for ustekinumab-treated patients (4 patients in 929 patient-years of follow-up) compared with 0.46 per 100 patient-years of follow-up for placebo-treated patients (2 patients in 433 patient-years of follow-up).

In the controlled and non-controlled periods of the psoriasis and psoriatic arthritis clinical studies representing 11561 patient-years of exposure in 6709 patients, the median follow-up was 1.0 years; 1.1 years for psoriatic disease studies. Malignancies excluding non-melanoma skin cancers were reported in 62 patients in 11561 patient-years of follow-up (incidence of 0.54 per 100 patient-years of follow-up for ustekinumab-treated patients). The rate of malignancies reported in ustekinumab-treated patients was comparable to the rate expected in the general population (standardized incidence ratio = 0.93 [95% confidence interval:0.71,1.20]). The most frequently observed malignancies, other than non-melanoma skin cancer, were prostate, colorectal, melanoma *in situ* and breast. The incidence of non-melanoma skin cancer was 0.49 per 100 patient-years of follow-up for ustekinumab-treated patients (56 patients in 11545 patient-years of follow-up). The ratio of patients with basal versus squamous cell skin cancers (3:1) is comparable with the ratio expected in the general population (see section 4.4 Special warnings and precautions for use).

Hypersensitivity

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

Immunogenicity

Stelara

In psoriasis and psoriatic arthritis clinical studies, up to 12.4% of patients treated with ustekinumab developed antibodies to ustekinumab. Patients positive for antibodies to ustekinumab tended to have lower efficacy, however, antibody positivity did not preclude a clinical response. In psoriasis studies, the majority of patients who were positive for antibodies to ustekinumab had neutralising antibodies.

UTEKNIX

Immunogenicity of UTEKNIX and Stelara® was evaluated both in Study AVT04-GL-101 as well as the Study AVT04-GL-301 for antidrug antibodies-(ADAs) and neutralizing antibodies.

Patients in the Study AVT04-GL-301 were tested at multiple time points for antibodies to Stelara® and UTEKNIX during the 52-week study period. Up to Week 16, the percentage of patients with binding anti-drug antibodies (ADAs) was lower in the UTEKNIX group compared with the EU-Stelara group (49 patients [25.4%] and 184 patients [48.2%]), respectively.

Of these, 13 patients (26.5%) in the UTEKNIX group and 57 patients (31.0%) in the EU-Stelara group had neutralising antibodies (Nabs). Up to end of the study (Week 52), 39 patients (21.2%) in the UTEKNIX/UTEKNIX group, 56 patients (31.5%) in the Stelara®/UTEKNIX group, and 48 patients (26.7%) in the Stelara®/Stelara® group had binding ADAs. Of these, 13 patients (33.3%) in the UTEKNIX/UTEKNIX group, 10 patients (17.9%) in the Stelara®/UTEKNIX group, and 11 patients (22.9%) in the Stelara®/Stelara® group had NAbs. The Stelara®/ UTEKNIX group reflects data for subjects exposed to both Stelara® and UTEKNIX before and after the transition. The safety and immunogenicity profiles of patients who transitioned from Stelara® to UTEKNIX were comparable to those who continued on Stelara® until the end of the study (week 52).

In the Study AVT04-GL-101, a total of 278 healthy subjects were evaluated for the presence of ADAs and Nabs of UTEKNIX and Stelara® following a single subcutaneous injection of either UTEKNIX, EU-Stelara® or US-Stelara® (45 mg/0.5 mL). Across all treatment groups, the overall incidence of ADAs increased over the duration of the study, with the highest positivity rates seen at Day 92: 27.6% in the UTEKNIX group, 48.5% in the EU-approved Stelara® group, and 45.4% in the US-licensed Stelara® group. The frequency of subjects with at least 1 positive ADA result was 36.7% in the UTEKNIX group, 59.6% in EU-approved Stelara® and 53.6% in US-licensed Stelara® groups. The frequency of ADA-positive subjects with at least 1 positive NAb result was 33.3% in the UTEKNIX group, 42.4% in EU-approved Stelara® and 53.8% in US-licensed Stelara® groups. The safety and immunogenicity profile of UTEKNIX was generally similar to that of EU-approved Stelara® and US-licensed Stelara®.

Safety and efficacy data for UTEKNIX across the clinical development program show no evidence that observed differences in immunogenicity between UTEKNIX and Stelara are clinically impactful.

Adverse events

The following adverse events have been reported in patients treated with ustekinumab. A causal relationship to ustekinumab is uncertain.

In psoriasis clinical trials of ustekinumab, serious cardiovascular events, including cardiovascular death, myocardial infarction, and stroke, were reported in 0.3% of patients who received

ustekinumab compared with 0% of patients treated with placebo, during the placebo-controlled period. Individuals with chronic inflammatory diseases, such as psoriasis, have higher rates of cardiovascular risk factors and cardiovascular events. Rates of myocardial infarction and stroke reported in ustekinumab-treated patients were comparable to rates expected in the general population.

Adverse events of depression were reported in some patients who received ustekinumab in psoriasis clinical trials, including rare events of suicidality. Individuals with psoriasis have higher rates of depression, and it is not known if ustekinumab may have contributed to these events since ustekinumab also resulted in improvements of the Hospital Anxiety and Depression Scale (see section 5.1 Pharmacodynamic properties – Clinical trials).

Post-marketing data

The adverse drug reactions in Table 3 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 < 1/1,000
Very rare < 1/10,000, including isolated reports

Table 3 Post-Marketing Reports

System Organ Class	Frequency: Adverse reaction
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
Respiratory, thoracic and mediastinal disorders	Rare: Allergic alveolitis Unknown: Interstitial pneumonia, eosinophilic pneumonia, cryptogenic organizing pneumonia
Skin and subcutaneous tissue disorders	Uncommon: Pustular psoriasis, exfoliative dermatitis Rare: Erythrodermic psoriasis; hypersensitivity vasculitis Very rare: Bullous pemphigoid

* 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.

There have been reports of rapidly growing and/or multiple squamous cell carcinomas of the skin in patients receiving ustekinumab who had multiple pre-existing risk factors for developing non-melanoma skin cancer. A causal relationship of these adverse events to ustekinumab is uncertain.

Comparability of UTEKNIX with Stelara®

UTEKNIX Study AVT04-GL-301 showed clinical equivalence between UTEKNIX and Stelara® (see section 5.1 Pharmacodynamic properties, Clinical trials).

Table 4 includes adverse events on exposure upto Week 16 to UTEKNIX in 194 subjects and Stelara® in 387 subjects treated at the recommended dose.

Table 4 Adverse events reported in at least 1% of patients treated with UTEKNIX and Stelara® up to Week 16 (All Patients)

Adverse events (preferred term)	UTEKNIX n =194 (%)	Stelara® n = 387 (%)
Infections and infestations	33 (17.0)	56 (14.5)
Nasopharyngitis	8 (4.1)	17 (4.4)
Upper respiratory tract infection	9 (4.6)	14 (3.6)
COVID-19	7 (3.6)	9 (2.3)
Pharyngitis	2 (1.0)	4 (1.0)
Sinusitis	1 (0.5)	4 (1.0)
Bronchitis	3 (1.5)	1 (0.3)
Influenza	3 (1.5)	0
Investigations	16 (8.2)	33 (8.5)
Alanine aminotransferase increased	5 (2.6)	8 (2.1)
Blood creatine phosphokinase increased	3 (1.5)	8 (2.1)
Gamma-glutamyltransferase increased	3 (1.5)	6 (1.6)
Hepatic enzyme increased	1 (0.5)	7 (1.8)
Blood triglycerides increased	0	4 (1.0)
Liver function test increased	2 (1.0)	0
General disorders and administration site conditions	4 (2.1)	13 (3.4)
Injection site reaction	2 (1.0)	9 (2.3)
Metabolism and nutrition disorders	7 (3.6)	8 (2.1)
Hyperglycaemia	3 (1.5)	3 (0.8)
Hypertriglyceridaemia	3 (1.5)	3 (0.8)
Nervous system disorders	4 (2.1)	8 (2.1)
Headache	3 (1.5)	5 (1.3)
Vascular disorders	2 (1.0)	10 (2.6)
Hypertension	1 (0.5)	6 (1.6)
Skin and subcutaneous tissue disorders	0	11 (2.8)
Pruritus	0	4 (1.0)
Respiratory, thoracic and mediastinal disorders	2 (1.0)	5 (1.3)
Oropharyngeal pain	2 (1.0)	0

The data in Table 5 reflects exposure from Week 16 to Week 28 to UTEKNIX/ UTEKNIX in 193 subjects, Stelara®/ Stelara® in 192 subjects, and Stelara®/ UTEKNIX in 189 subjects treated at the recommended dose (see section 5.1 Clinical trials).

The overall safety profiles of the UTEKNIX/ UTEKNIX, Stelara®/ Stelara® and Stelara®/ UTEKNIX groups were similar.

Table 5 Adverse events reported in at least 1 % of patients treated with UTEKNIX, Stelara® or Stelara® switched to UTEKNIX in psoriasis study (All patients)

Adverse events (preferred term)	UTEKNIX/ UTEKNIX n =193 (%)	Stelara®/ UTEKNIX n =192 (%)	Stelara®/ Stelara® n = 189 (%)
Infections and infestations	8 (4.1)	15 (7.8)	17 (9.0)
COVID-19	2 (1.0)	7 (3.6)	10 (5.3)
Nasopharyngitis	3 (1.6)	3 (1.6)	4 (2.1)
Upper respiratory tract infection	0	3 (1.6)	0
Tuberculosis	0	0	2 (1.1)
Investigations	4 (2.1)	8 (4.2)	6 (3.2)
Mycobacterium tuberculosis complex test positive	1 (0.5)	1 (0.5)	2 (1.1)
Alanine aminotransferase increased	1 (0.5)	0	2 (1.1)
General disorders and administration site conditions	1 (0.5)	2 (1.0)	4 (2.1)

Vaccination site pain	0	0	2 (1.1)
Metabolism and nutrition disorders	3 (1.6)	2 (1.0)	0
Hypertriglyceridaemia	3 (1.6)	0	0
Nervous system disorders	5 (2.6)	0	0
Sciatica	4 (2.1)	0	0
Vascular disorders	0	2 (1.0)	3 (1.6)
Hypertension	0	1 (0.5)	2 (1.1)
Musculoskeletal and connective tissue disorders	3 (1.6)	1 (0.5)	0
Pain in extremity	2 (1.0)	0	0

n = number of patients treated in the relevant Safety Analysis Set and was used as the denominator for percentage calculations. n (%) represents number and % of patients with events starting on or after the Week 16 dose but before the Week 28 dose.
COVID-19 = coronavirus disease 2019.

Table 6 reflects exposure from Week 28 to End of study (Week 52) to UTEKNIX/ UTEKNIX in 191 subjects, Stelara®/ Stelara® in 184 subjects, and Stelara®/ UTEKNIX in 184 subjects.

The overall safety profiles of the UTEKNIX/ UTEKNIX, Stelara®/ Stelara® and Stelara®/ UTEKNIX groups were similar.

Table 6 Adverse events reported in at least 1 % of patients treated with UTEKNIX, Stelara® or Stelara® switched to UTEKNIX in psoriasis study (All patients)

Adverse events (preferred term)	**UTEKNIX/ UTEKNIX n =191 (%)**	**Stelara®/ UTEKNIX n =184 (%)**	**Stelara®/ Stelara® n = 184 (%)**
Investigations	9 (4.7)	22 (12.0)	20 (10.9)
Blood creatine phosphokinase increased	2 (1.0)	5 (2.7)	4 (2.2)
Gamma-glutamyltransferase increased	3 (1.6)	2 (1.1)	5 (2.7)
Blood triglycerides increased	2 (1.0)	3 (1.6)	3 (1.6)
Alanine aminotransferase increased	1 (0.5)	3 (1.6)	3 (1.6)
Mycobacterium tuberculosis complex test positive	1 (0.5)	2 (1.1)	3 (1.6)
Hepatic enzyme increased	1 (0.5)	2 (1.1)	2 (1.1)
Aspartate aminotransferase increased	1 (0.5)	2 (1.1)	1 (0.5)
Transaminases increased	0	2 (1.1)	0
Infections and infestations	10 (5.2)	10 (5.4)	11 (6.0)
Nasopharyngitis	4 (2.1)	2 (1.1)	3 (1.6)
COVID-19	4 (2.1)	3 (1.6)	0
Upper respiratory tract infection	1 (0.5)	1 (0.5)	5 (2.7)
Metabolism and nutrition disorders	6 (3.1)	5 (2.7)	3 (1.6)
Hypertriglyceridaemia	0	1 (0.5)	3 (1.6)
Hypercholesterolaemia	2 (1.0)	0	0
Hyperglycaemia	0	2 (1.1)	0
Gastrointestinal disorders	1 (0.5)	5 (2.7)	0
Diarrhoea	0	3 (1.6)	0
General disorders and administration site conditions	0	3 (1.6)	2 (1.1)
Injection site reaction	0	1 (0.5)	2 (1.1)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 Overdose

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

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Ustekinumab is a human IgG1kappa monoclonal antibody that specifically binds to the shared p40 protein subunit of the human cytokines interleukin (IL)-12 and IL-23. Ustekinumab inhibits the bioactivity of human IL-12 and IL-23 by preventing p40 from binding to the IL-12Rbeta1 receptor protein expressed on the surface of immune cells. Ustekinumab cannot bind to IL-12 or IL-23 that is already bound to IL-12Rbeta1 cell surface receptors. Thus, Ustekinumab is not expected to contribute to complement- or antibody-mediated cytotoxicity of cells with 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. 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 enthuses 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.

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

Pharmacodynamics

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

In patients with psoriasis and/or psoriatic arthritis, ustekinumab 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 ustekinumab-treated patients as compared to placebo.

In psoriasis and psoriatic arthritis studies, clinical response (improvement in Psoriasis Area and Severity Index [PASI] or ACR measurements, respectively) appeared to be related to serum ustekinumab levels. Patients with psoriasis with PASI response had higher median serum concentrations of ustekinumab than those with lower clinical responses. In psoriasis studies, 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. 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.

Immunisation

During the long-term extension of a Phase 3 psoriasis study (PHOENIX 2), patients treated with ustekinumab 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 titres were similar among ustekinumab-treated and control patients.

Clinical trials

Plaque psoriasis (Adults)

The safety and efficacy of STELARA was assessed in 2 Phase 3 studies (A Phase 3 multicentre, randomised, double-blind, placebo-controlled trial evaluating the efficacy and safety of CNTO 1275 in the treatment of subjects with moderate to severe plaque-type psoriasis followed by long-term extension [PHOENIX] 1 and PHOENIX 2). A total of 1996 patients were enrolled in these studies.

The safety and efficacy of ustekinumab have not been established beyond 4 years.

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 anti-psoriatic therapies were allowed during the study with the exception of low-potency topical corticosteroids on the face and groin after week 12.

The Psoriasis Area and Severity Index (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 randomised 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 non-responders.

Other key efficacy assessments included:

- The Physician's Global Assessment (PGA), a 6-category scale focusing on plaque thickness/induration, erythema, and scaling.
- The Dermatology Life Quality Index (DLQI), a dermatology-specific quality of life instrument, with a lower score indicating an improved quality of life.
- The SF-36, a health survey questionnaire consisting of multi-item scales measuring 8 health

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concepts (PHOENIX 1 only).

- The Nail Psoriasis Severity Index (NAPSI), a physician-assessed score that measures the severity of nail involvement (PHOENIX 1 only).
- The Hospital Anxiety and Depression Scale (HADS), a self-rating tool developed to evaluate psychological measures in patients with physical ailments (PHOENIX 2 only).
- The Work Limitations Questionnaire (WLQ), a 25-item, self-administered questionnaire that was used to measure the impact of chronic health conditions on job performance and work productivity among employed populations (PHOENIX 2 only).
- The Itch Visual Analogue Scale, (Itch VAS) used to assess the severity of itch at the time of the assessment (PHOENIX 1 only).

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 randomised to STELARA received 45 mg or 90 mg doses at Weeks 0 and 4 followed by the same doses every 12 weeks. Patients randomised 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 randomised to STELARA who were PASI 75 responders at both Weeks 28 and 40 were re-randomised to either maintenance dosing of STELARA every 12 weeks or to placebo (i.e., withdrawal of therapy). Patients who were re-randomised 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 non-responders 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 non-responders at Week 40 were adjusted to every-8-week dosing. All patients were followed for at least 52 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 randomised to STELARA received 45 mg or 90 mg doses at Weeks 0 and 4 followed by an additional dose at Week 16. Patients randomised to receive placebo at Weeks 0 and 4 crossed over to receive STELARA (either 45 mg or 90 mg) at Weeks 12 and 16. Patients were followed for 28 weeks.

Baseline disease characteristics: PHOENIX 1 and 2

Baseline disease characteristics across PHOENIX 1 and 2 were similar (Table 7).

Table 7 Baseline Disease Characteristics

PHOENIX 1			PHOENIX 2	
	Placebo	STELARA	Placebo	STELARA
Patients randomised at Week 0	N = 255	N = 511	N = 410	N = 820
Median BSA	22.0	21.0	20.0	21.0
Patients with 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 randomised to treatment with STELARA were PASI 75 responders compared with placebo at Week 12 (Table 8). 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 modelling suggested a trend towards higher apparent clearance (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 randomised to 45 mg or 90 mg STELARA achieved a cleared or minimal PGA score, and significantly greater proportions of patients randomised to 45 mg or 90 mg STELARA were PASI 90 and PASI 50 responders at Week 12 (Table 8). In the PHOENIX 1 study, 60% and 62% 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 5% of the placebo patients. In PHOENIX 1, PASI 90 was achieved by 42% and 37% of the patients treated with 45 mg and 90 mg 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 8).

Table 8 Key psoriasis endpoints – PHOENIX 1 and PHOENIX 2

Response		**PHOENIX 1**					**PHOENIX 2**			
		STELARA					STELARA			
	Placebo	45 mg		90 mg		Placebo	45 mg		90 mg	
	n=255	n=255	n=250	n=256	n=243	n=410	n=409	n=397	n=411	n=400
	Week 12	Week 12	Week 28	Week 12	Week 28	Week 12	Week 12	Week 28	Week 12	Week 28
PASI response										
PASI 50 (%)	26 (10)	213 (84)[a]	228 (91)[b]	220 (86)[a]	234 (96)[b]	41 (10)	342 (84)[a]	369 (93)[b]	367 (89)[a]	380 (95)[b]
PASI 75 (%)	8 (3)	171 (67)[a]	178 (71)[b]	170 (66)[a]	191 (79)[b]	15 (4)	273 (67)[a]	276 (70)[b]	311 (76)[a]	314 (79)[b]
PASI 90 (%)	5 (2)	106 (42)[a]	123 (49)[b]	94 (37)[a]	135 (56)[b]	3 (1)	173 (42)[a]	178 (45)[b]	209 (51)[a]	217 (54)[b]
PGA Cleared or Minimal [a]	10 (4)	151 (59)[a]	146 (58)[b]	156 (61)[a]	160 (66)[b]	18 (4)	277 (68)[a]	241 (61)[b]	300 (73)[a]	279 (70)[b]
PASI 75 response by weight ≤ 100 kg										
n	166	168	164	164	153	290	297	287	289	280
PASI 75 (%) > 100 kg	6 (4)	124 (74)	130 (79)	107 (65)	124 (81)	12 (4)	218 (73)	217 (76)	225 (78)	226 (81)
n	89	87	86	92	90	120	112	110	121	119
PASI 75 (%)	2 (2)	47 (54)	48 (56)	63 (68)	67 (74)	3 (3)	55 (49)	59 (54)	86 (71)	88 (74)
PGA Cleared or Minimal by weight ≤ 100 kg										
n	166	168	164	164	153	290	297	287	289	280
PGA response (%) > 100 kg	7 (4)	108 (64)	106 (65)	103 (63)	106 (70)	14 (5)	220 (74)	192 (67)	216 (74)	207 (74)
n	89	87	86	92	90	120	112	110	121	119
PGA response (%)	3 (3)	44 (51)	40 (47)	54 (59)	54 (60)	4 (3)	59 (53)	49 (45)	85 (70)	71 (60)

a. $p < 0.001$ for 45 mg or 90 mg comparison with placebo at Week 12.

b. No statistical comparisons to placebo were made at Week 28 because the original placebo group began receiving STELARA at Week 12.

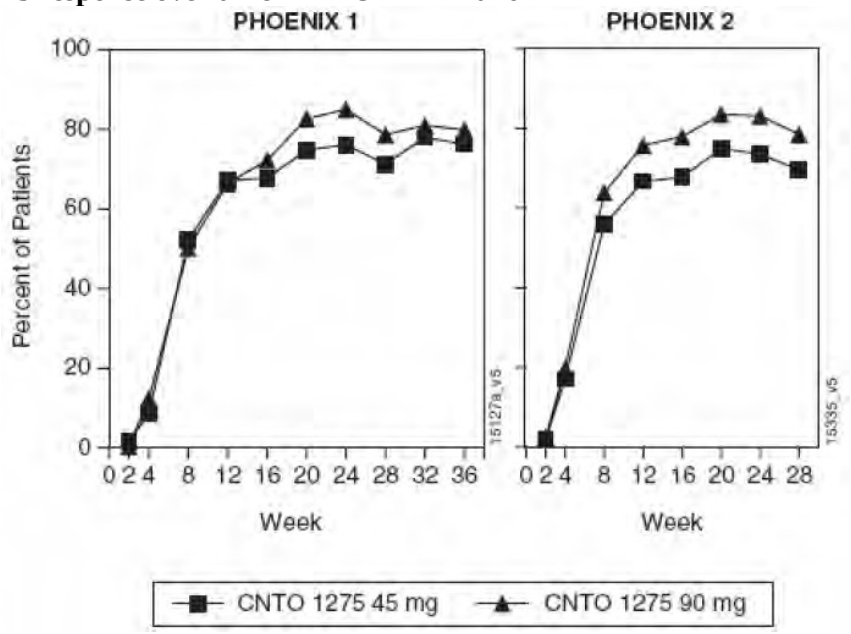
Response over time

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 8). Figure 1 shows PASI 75 response over time in PHOENIX 1 and 2.

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 randomised to receive STELARA (maintenance) and 160 were randomised 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. At Week 52, 89% of patients re-randomised to maintenance treatment were PASI 75 responders compared with 63% of patients re-randomised to placebo (treatment withdrawal) ($p<0.001$).

Efficacy of retreatment

In PHOENIX 1, after withdrawal from therapy, patients re-initiated their original STELARA treatment regimen after loss of ≥ 50% of PASI improvement. Retreatment with STELARA resulted in 76% of evaluated patients regaining PASI 75 response within 8 weeks after reinitiating therapy.

Dosing interval adjustment

In PHOENIX 1, Week 28 and Week 40 partial responders and Week 40 non-responders 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 non-responders 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 randomised to 45 mg or 90 mg ustekinumab compared with patients randomised to placebo as evaluated by DLQI in

PHOENIX 1 and 2 and SF-36 in PHOENIX 1. Quality of life improvements were significant as early as 2 weeks in patients treated with ustekinumab (p<0.001) and these improvements were maintained over time with continued dosing.

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

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

A multicentre, randomised, 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 ciclosporin, 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 randomised 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 (56.8%). PASI 90 response was observed in 36% and 45 % of patients in the ustekinumab 45 mg and 90 mg groups, respectively, compared with 23% of patients receiving etanercept (p<0.001 for each comparison versus etanercept). PASI 100 response was observed in 12% and 21% of patients in the ustekinumab 45 mg and 90 mg groups, respectively, compared to 6% of patients receiving etanercept. 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 9).

Table 9 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 randomised	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 [a]	170 (49%)	136 (65%) [a]	245 (71%) [a]
PASI 75 RESPONSE BY WEIGHT			
≤ 100 kg			
N	251	151	244
PASI 75 response	154 (61.4%)	109 (72.2%)	189 (77.5%)
>100 kg			
N	96	58	103
PASI 75 response	43 (44.8%)	32 (55.2%)	67 (65.0%)
PGA of Cleared or Minimal by weight			
≤ 100 kg			
N	251	151	244
PGA response	131 (52.2%)	110 (72.8%)	185 (75.8%)
>100 kg			
N	96	58	103
PGA response	39 (40.6%)	26 (44.8%)	60 (58.3%)
PASI 75 RESPONSE BY NUMBER OF UNSUITABLE CONVENTIONAL SYSTEMIC AGENTS [g]			
-at least one therapy			
N	347	209	346
PASI 75 Response	197 (56.8%)	141 (67.5%) [b]	256 (74.0%) [a]
-at least two therapies			
N	186	118	185
PASI 75 Response	94 (50.5%)	79 (66.9%) [d]	137 (74.1%) [a]
-at least three therapies			
N	52	31	47
PASI 75 Response	20 (38.5%)	17 (54.8%) [e]	34 (72.3%) [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 ciclosporin. Unsuitable conventional systemic agents are defined as those to which patients had had an inadequate response, were intolerant, or had a contraindication.

Comparability of UTEKNIX with Stelara® - Clinical Trials

The efficacy and safety of UTEKNIX were compared to Stelara® in a randomised active-control, double-blind parallel group, multicentre, clinical Phase III study in 581 patients 18 to 75 years of age with moderate to severe chronic plaque psoriasis (Study AVT04-GL-301-PsO) who were candidates for systemic therapy. Patients had stable moderate to severe chronic plaque psoriasis (PsO) for at least 6

months involving a body surface area (BSA) ≥ 10%, Psoriasis Area and Severity Index (PASI) of ≥ 12, and static Physician's Global Assessment (sPGA) of ≥ 3 at study entry. After randomisation at 1:2 (UTEKNIX:Stelara®) ratio, the patients received UTEKNIX or Stelara® at two initial doses of 45 mg (body weight ≤ 100 kg) or 90 mg (body weight > 100 kg) administered subcutaneous on week 1 and 4, followed by 45 mg or 90 mg subcutaneous once every 12 weeks starting 4 weeks after the initial doses at Weeks 16, 28 and 40. At Week 16, while the patients randomised to UTEKNIX group continued to receive the UTEKNIX until Week 40, the patients randomised to Stelara® group were re-randomised 1:1 to receive UTEKNIX and Stelara® through Week 40.

The primary efficacy endpoint, "*Percent improvement in PASI from Baseline to Week 12*", was measured and compared with ustekinumab (see Table 10). Results at week 52 is presented in Table 11.

Table 10 Efficacy results at week 12 in psoriasis study: UTEKNIX vs Stelara®

	All Patients		Patients with Body Weight ≤100 kg	
	UTEKNIX n = 194	Stelara® n = 383	UTEKNIX n = 164	Stelara® n = 324
PASI % Improvement from baseline (SE*)	87.3 (1.73)	86.8 (1.49)	86.9 (1.91)	86.8 (1.64)

* Standard error

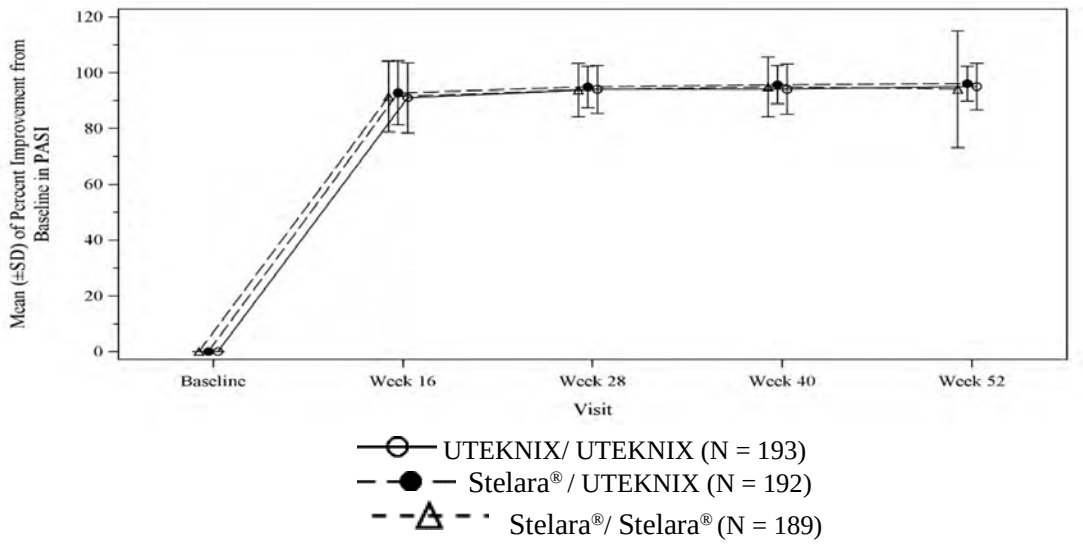
Table 11 Efficacy results at week 52 in psoriasis study

	All Patients			Patients with Body Weight ≤100 kg		
	UTEKNIX/ UTEKNIX n = 191	Stelara®/ UTEKNIX n = 184	Stelara® / Stelara® n = 184	UTEKNIX n = 164	Stelara®/ UTEKNIX n = 156	Stelara® n = 155
PASI % Improvement from baseline (SE*)	93.5 (1.355)	94.6 (1.365)	92.5 (1.383)	92.9 (1.562)	94.2 (1.560)	91.6 (1.587)

At week 12, the PASI percent improvement [LS mean±SE] from baseline was 87.3±1.73% in the UTEKNIX group and 86.8±1.49% in the Stelara® group. The least-squares (LS) mean difference (SE) of PASI percent improvement from baseline to week 12 between UTEKNIX and Stelara® was 0.4 (1.56) with the 2-sided 95% CI of [–2.63, 3.50] and a 90% CI of [-2.14, 3.01]. The results were similar in patients with body weight ≤100 kg (0.1 (-3.25, 3.43)). The 95% and the 90% CIs were within the predefined equivalence margins of ±15% and the ±10% respectively, thus demonstrating clinical equivalence of UTEKNIX with Stelara®.

The mean PASI percent improvement from baseline over the duration of the study is shown in Figure 2.

Figure 2 Mean PASI percent improvement from baseline over the duration of PsO study for UTEKNIX and Stelara®



The comparability of UTEKNIX and STELARA in paediatric patients with moderate to severe chronic plaque psoriasis or adult patients with psoriatic arthritis, Crohn's disease and ulcerative colitis has not been studied in clinical trials.

Psoriatic Arthritis (PsA)

The safety and efficacy of STELARA was assessed in two multicentre, randomised, double-blind, placebo-controlled, phase 3 studies PSUMMIT I and PSUMMIT II, in patients with active psoriatic arthritis. Patients were randomised 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 in baseline in total radiographic scores of the hands and feet, at Week 24. Efficacy data were collected and analysed through Week 52.

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 rheumatic nodules (39%, n=362), spondylitis with peripheral arthritis (28%, n=255), asymmetrical 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 12).

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 12).

In both studies, the proportion of patients achieving a modified PsA response criteria (PsARC) or a Disease Activity 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 12). DAS28-CRP and PsARC responses were maintained through Week 52.

Table 12 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 summarised 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 13).

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

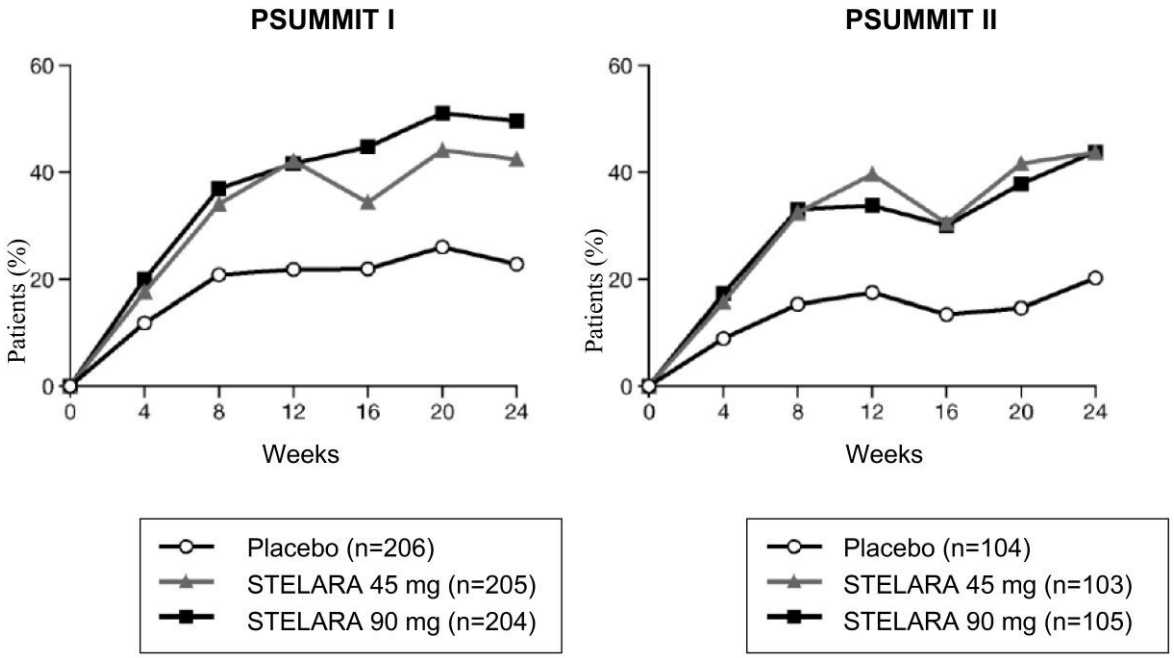


Table 13 Proportion of patients who achieved ACR 20, ACR 50, ACR 70 response at Week 52

	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 randomised 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 randomised 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 II, of 103 subjects randomised 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 randomised 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 mg and 90 mg groups than in the placebo group (see Table 14).

Table 14 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 randomised 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 randomised 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 15).

Table 15 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 16). Responses observed in the STELARA groups were similar in patients receiving or not receiving concomitant MTX. ACR responses were maintained through Week 52.

Table 16 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 randomised	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 randomised	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 17). ACR 20, 50 and 70 responses were generally maintained through Week 52.

Table 17 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 randomised	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 18). In both studies, improvement in enthesitis score and dactylitis score were maintained at Week 52.

Table 18 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 randomised 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 randomised 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.

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 19). In both studies the proportion of patients achieving the PASI 75 response was maintained through Week 52 (PSUMMIT I, STELARA 45mg-70.1% and 90mg- 68.1%; PSUMMIT II, STELARA 45mg-56.5% and 90mg- 64.4%).

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 19). 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 45mg-44.8% and 90mg-44.3%; PSUMMIT II, STELARA 45mg-36.8% and 90mg- 43.1%).

Table 19 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 20).

Table 20 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 randomised 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 randomised 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 randomised 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.

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 21). 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 45mg and 90 mg groups respectively) was less than the mean change from Week 0 to 24 (see Table 21).

Table 21 Summary of change from baseline in total modified vdH-S score at Week 24 (Integrated analysis of PSUMMIT I and PSUMMIT II)

		STELARA	
	Placebo	45mg	90mg
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.

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 22). 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 at Week 52.

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.

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 22 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]

* achieving a ≥ 0.3 improvement from baseline

a. p<0.001

b. p<0.01

In PSUMMIT I, of 205 subjects randomised 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 randomised 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 randomised 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 randomised 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 23) and the improvement was maintained at Week 52.

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 - 90mg group, p=NS for other groups) (see Table 23). In both studies, the change from baseline in the SF-36 PCS and MCS scores was maintained at Week 52.

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 23 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 randomised 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	2.70c	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	0.70b	2.20[b]

a. p≤0.001
b. p=NS
c. p<0.05

5.2 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.

Excretion

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 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 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 microgram/mL to 0.26 microgram/mL (45 mg dose) and from 0.47 microgram/mL to 0.49 microgram/mL (90 mg dose).

Impact of weight on pharmacokinetics

Serum ustekinumab concentrations were affected by weight in patients with psoriasis and/or psoriatic arthritis. Within each dose (45 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, 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. 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 hyperlipidaemia) 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.

No specific drug-drug interaction studies have been conducted in healthy subjects or patients with psoriasis or psoriatic arthritis.

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, ciclosporin, or other biological therapeutics for the treatment of psoriasis. The pharmacokinetics of ustekinumab was not impacted by concomitant use of NSAIDs or prior exposure to anti-TNFα agents in patients with psoriatic arthritis; or by the use of MTX, oral corticosteroids, 6-MP, AZA in patients with psoriatic arthritis.

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 > 65 years. The pharmacokinetics of ustekinumab were not impacted by the use of tobacco or alcohol.

Comparability of UTEKNIX with Stelara® - Pharmacokinetic Properties

The pharmacokinetic (PK) profiles of UTEKNIX and Stelara® were comparable in a randomised, double-blind, three-arm, parallel group clinical Phase I study in 278 healthy subjects following a single subcutaneous injection of either UTEKNIX, EU Stelara® or US Stelara® (45 mg/0.5 mL) (Study AVT04-GL-101). The PK parameters, AUC_{0-t}, AUC_{0-inf} and C_{max}, were compared between UTEKNIX and Stelara®. The summary of the pharmacokinetic profiles of UTEKNIX and Stelara® in healthy volunteers are listed in Table 24.

Table 24 Statistical Comparison of PK Parameters (UTEKNIX vs. EU Stelara® or US Stelara®) (Study AVT04-GL-101)

Parameter (unit)	Combined GeoLSM Ratio (90% CI) *		
	UTEKNIX, /EU-Stelara®	UTEKNIX, /US-Stelara®	US- Stelara® /EU- Stelara®
C_{max} (ng/mL)	109.5 (101.7 – 117.8)	98.4 (91.4 – 106.0)	111.2 (103.3 – 119.8)
AUC_{0-t} (ng·h/mL)	114.7 (106.5 – 123.6)	102.6 (95.2 – 110.6)	111.8 (103.8 – 120.5)
AUC_{0-inf} (ng·h/mL)	116.9 (108.1 – 126.4)	103.8 (95.9 – 112.3)	112.6 (104.1 – 121.8)

AUC_{0-t}: area under the concentration-time curve from time zero to the last quantifiable concentration;
AUC_{0-inf}: area under the concentration-time curve from time zero to infinity;
CI: confidence interval;
C_{max}: maximum serum concentration;
GeoLSM: geometric least square mean.

The mean actual protein content of the dose administered was slightly higher than the nominal 45 mg dose in the UTEKNIX and US-licensed Stelara groups and lower in the EU-approved Stelara group, resulting in a dosing bias of 104.3% and 104.5% in the UTEKNIX and US-licensed Stelara groups and 97.9% in the EU-approved Stelara group. The protein content for EU-approved Stelara was found to deviate from the nominal and expected value (90 mg/mL). Following protein content normalization, the exposure PK parameters for ustekinumab were similar across the 3 treatment groups. When the analysis of covariance (ANCOVA) model was adjusted for protein content in a sensitivity analysis, the PK similarity criteria were met for C_{max}, AUC_{0-inf}, and AUC_{0-t} for all pairwise comparisons.

5.3 Preclinical safety data

Genotoxicity

Ustekinumab has not been evaluated for genotoxic potential.

Carcinogenicity

Ustekinumab has not been evaluated for carcinogenic potential, due to the lack of appropriate models for an antibody with no cross-reactivity to rodent IL-12/23 p40. Ustekinumab is a selective immunosuppressant agent. Immunosuppressive agents have the potential to increase the risk of malignancy (see section 4.4 Special warnings and precautions for use – Malignancies).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each mL of UTEKNIX solution for injection for subcutaneous administration contains:

Ustekinumab 90 mg
Histidine 0.243 mg
Histidine hydrochloride monohydrate 1.013 mg
Sucrose 76 mg
Polysorbate 80 0.04 mg
Water for injections qs

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store at 2°C to 8°C. Refrigerate. Do not freeze.

UTEKNIX pre-filled syringes- Room temperature storage

If needed, UTEKNIX pre-filled syringes may be stored at room temperature up to a maximum of 30°C for a single period of up to 30 days in the original carton protected from light. Record the date when the pre-filled syringe is first removed from the refrigerator on the carton in the space provided. The new expiry date must not exceed the original expiry date printed on the carton. Once the pre-filled syringe has been stored at room temperature, it should not be returned to the refrigerator. Discard the pre-filled syringe if not used within 30 days at room temperature storage.

6.5 Nature and contents of container

UTEKNIX 45 mg solution for injection in pre-filled syringe

0.5 mL solution for injection in a pre-filled type I glass 1 mL syringe with a fixed 29-gauge, extended finger flanges and passive safety needle device, and a plunger stopper (bromobutyl rubber), latex-free plunger stopper and rigid needle shield (RNS).

UTEKNIX 90 mg solution for injection in pre-filled syringe

1 mL solution for injection in a pre-filled syringe type I glass 1 mL syringe with a fixed 29-gauge needle, extended finger flanges and passive needle, safety device and a plunger stopper (bromobutyl rubber), latex-free plunger stopper and rigid needle shield (RNS).

UTEKNIX is available in a pack of 1 pre-filled syringe.

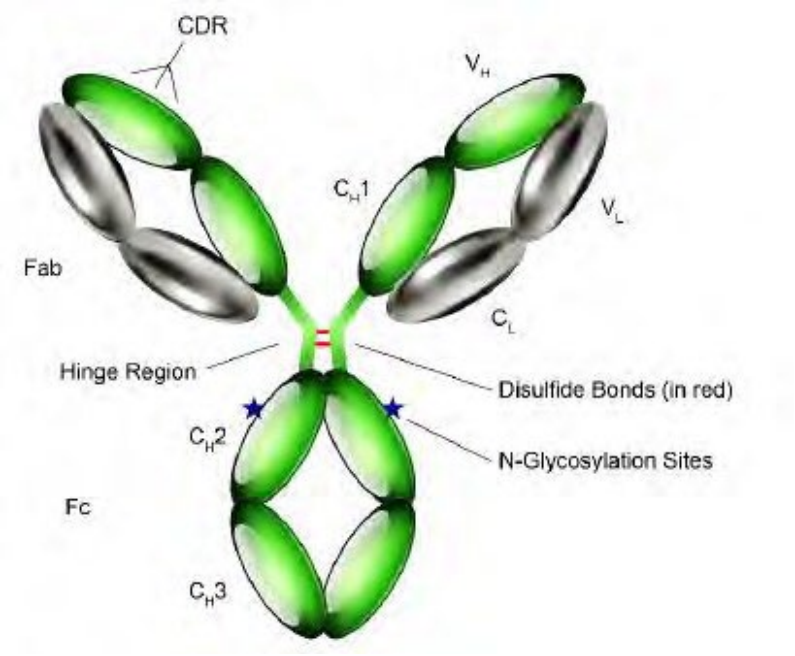
6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 Physicochemical properties

Chemical structure

Figure 4 General structure of ustekinumab



Molecular formula

The molecular formula, based on the amino acid sequence is $C_{2207}H_{3418}N_{582}O_{671}S_{17}$ and $C_{1034}H_{1600}N_{274}O_{337}S_6$ for the heavy and light chain, respectively. The combined molecular formula for the unglycosylated heterodimer connected by 16 disulfide bonds is $C_{6482}H_{10004}N_{1712}O_{2016}S_{46}$.

CAS number: 815610-63-0

UTEKNIX (ustekinumab) is a human IgG1kappa monoclonal antibody with an approximate molecular weight of 148 – 150 kilodaltons. 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.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription Only Medicine

8 SPONSOR

Cipla Australia Pty Ltd
Level 1 / 132-136 Albert Road,
South Melbourne Vic 3205.
drugsafety@cipla.com
Phone: 1800-569-074

9 DATE OF FIRST APPROVAL

[To be completed when the medicine is included in the ARTG]

10 DATE OF REVISION

[Item to be completed at the time of approval]

Summary table of changes

Section changed	Summary of new information
NA	NA

NA = Not applicable.