NAME OF THE MEDICINAL PRODUCT

Steqeyma® 45 mg/0.5 mL solution for injection

Steqeyma® is a biosimilar medicinal product of Stelara.

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 45 mg ustekinumab in 0.5 mL.

Ustekinumab is a fully human IgG1κ monoclonal antibody to interleukin (IL)-12/23 produced in a Chinese Hamster Ovary (CHO) cell line using recombinant DNA technology.

PHARMACEUTICAL FORM

Solution for injection.
The solution is clear to slightly opalescent, colourless to pale yellow.

CLINICAL PARTICULARS

Therapeutic Indications

Plaque Psoriasis
(via subcutaneous administration only)
Steqeyma is indicated for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate (MTX) or PUVA (psoralen and ultraviolet A) (see *Pharmacodynamic Properties*).

Pediatric Plaque Psoriasis
(via subcutaneous administration only with single-use vial)
Steqeyma is indicated for the treatment of moderate to severe plaque psoriasis in children and adolescent patients from the age of 6 years and older, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies (see *Pharmacodynamic Properties*).

Psoriatic Arthritis (PsA)
(via subcutaneous administration only)
Steqeyma alone or in combination with MTX, is indicated for the treatment of active psoriatic arthritis in adult patients when the response to previous non-biological disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate (see *Pharmacodynamic Properties*).

Crohn's Disease
(via intravenous administration for induction dosing, and via subcutaneous administration for maintenance dosing)
Steqeyma is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist or have medical contraindications to such therapies (see *Pharmacodynamic Properties*).

Ulcerative Colitis
(via intravenous administration for induction dosing, and via subcutaneous administration for maintenance dosing)

Steqeyma is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic or have medical contraindications to such therapies (see *Pharmacodynamic Properties*).

Posology and Method of Administration
Steqeyma solution for subcutaneous injection (vial) is intended for use under the guidance and supervision of a physicians experienced in the diagnosis and treatment of conditions for which Steqeyma is indicated.

Posology
Plaque Psoriasis
The recommended posology of Steqeyma is an initial dose of 45 mg administered subcutaneously, followed by a 45 mg dose 4 weeks later, and then every 12 weeks thereafter.

Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment.

Patients with body weight > 100 kg

For patients with a body weight > 100 kg the initial dose is 90 mg administered subcutaneously, followed by a 90 mg dose 4 weeks later, and then every 12 weeks thereafter. In these patients, 45 mg was also shown to be efficacious. However, 90 mg resulted in greater efficacy.

Pediatric population, 6 years and older
For the treatment of plaque psoriasis, Steqeyma should be administered by subcutaneous injection. The recommended dose of Steqeyma based on body weight is shown below (Table 1). Steqeyma should be administered at Weeks 0 and 4, then every 12 weeks thereafter.

Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment.

Table 1: Recommended dose of Steqeyma for pediatric psoriasis

Weight	Recommended Dose	Dosage Form
< 60 kg	0.75 mg/kg*	vial
≥ 60 to ≤ 100 kg	45 mg	(1) 45 mg vial
> 100 kg	90 mg	(2) 45 mg vials

* To calculate the volume of injection (mL) for patients < 60 kg, use the following formula: *body weight* (kg) × *0.0083* (mL/kg). The calculated volume should be rounded to the nearest 0.01 mL and administered using a 1 mL graduated syringe. A 45 mg vial is available for pediatric patients who need to receive less than the full 45 mg dose.

Table 1b: Injection volumes of Steqeyma for pediatric psoriasis patients < 60 kg

Body weight at time of dosing (kg)	Dose (mg)	Volume of injection (mL) from Steqeyma single use vial of 45 mg / 0.5 mL
15	11.3	0.12
16	12.0	0.13
17	12.8	0.14
18	13.5	0.15
19	14.3	0.16
20	15.0	0.17
21	15.8	0.17
22	16.5	0.18
23	17.3	0.19

24	18.0	0.20
25	18.8	0.21
26	19.5	0.22
27	20.3	0.22
28	21.0	0.23
29	21.8	0.24
30	22.5	0.25
31	23.3	0.26
32	24.0	0.27
33	24.8	0.27
34	25.5	0.28
35	26.3	0.29
36	27.0	0.30
37	27.8	0.31
38	28.5	0.32
39	29.3	0.32
40	30.0	0.33
41	30.8	0.34
42	31.5	0.35
43	32.3	0.36
44	33.0	0.37
45	33.8	0.37
46	34.5	0.38
47	35.3	0.39
48	36.0	0.40
49	36.8	0.41
50	37.5	0.42
51	38.3	0.42
52	39.0	0.43
53	39.8	0.44
54	40.5	0.45
55	41.3	0.46
56	42.0	0.46
57	42.8	0.47
58	43.5	0.48
59	44.3	0.49

Psoriatic Arthritis (PsA)
The recommended posology of Steqeyma is an initial dose of 45 mg administered subcutaneously, followed by a 45 mg dose 4 weeks later, and then every 12 weeks thereafter. Alternatively, 90 mg may be used in patients with a body weight > 100 kg.

Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment.

Crohn's Disease and Ulcerative Colitis
Subcutaneous Maintenance Dosing

The first subcutaneous administration of 90 mg Steqeyma should take place at week 8 after the intravenous dose. After this, dosing every 12 weeks is recommended.

Patients who have not shown adequate response at 8 weeks after the first subcutaneous dose, may receive a second subcutaneous dose at this time (see *Pharmacodynamic Properties*).

Patients who lose response on dosing every 12 weeks may benefit from an increase in dosing frequency to every 8 weeks (see *Pharmacodynamic Properties*).

Patients may subsequently be dosed every 8 weeks or every 12 weeks according to clinical judgment (see *Pharmacodynamic Properties*).

Consideration should be given to discontinuing treatment in patients who show no evidence of therapeutic benefit by week 16 or 16 weeks after switching to the 8-weekly dose.

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

If therapy in Crohn's disease or Ulcerative Colitis is interrupted, resumption of treatment with subcutaneous dosing every 8 weeks is safe and effective.

Elderly (≥ 65 years)
No dose adjustment is needed for elderly patients.

Renal and Hepatic Impairment
Steqeyma has not been studied in these patient populations. No dose recommendations can be made.

Paediatric Population
Studies of Steqeyma in pediatric patients below 6 years of age have not been conducted. No studies have been conducted in pediatric patients with Crohn's disease or ulcerative colitis.

Method of administration
Solution for Injection for Subcutaneous Administration (Vial)
Steqeyma 45 mg vials are for subcutaneous injection only. If possible, areas of the skin that show psoriasis should be avoided as injection sites.

After proper training in subcutaneous injection technique, patients or their caregivers may inject Steqeyma if a physician determines that it is appropriate. However, the physician should ensure appropriate follow-up of patients. Patients or their caregivers should be instructed to inject the prescribed amount of Steqeyma according to the directions provided in the package leaflet. Comprehensive instructions for administration are given in the package leaflet.

For further instructions on preparation and special precautions for handling, see *Special Precautions for Disposal and Other Handling*.

Contraindications
Hypersensitivity to active substance or to any of the excipients (see *Warnings and Precautions*).
Clinically important, active infection (e.g. active tuberculosis; see *Warnings and Precautions*).

Warnings and Precautions
Traceability
In order to improve the traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded.

Infections
Ustekinumab may have the potential to increase the risk of infections and reactivate latent infections. In clinical studies and a post-marketing observational study in patients with psoriasis, serious bacterial, fungal, and viral infections have been observed in patients receiving ustekinumab (see section *Adverse Reactions*).

Opportunistic infections including reactivation of tuberculosis, other opportunistic bacterial infections (including atypical mycobacterial infection, listeria meningitis, pneumonia legionella, and nocardiosis), opportunistic fungal infections, opportunistic viral infections (including encephalitis caused by herpes simplex 2), and parasitic infections (including ocular toxoplasmosis) have been reported in patients treated with ustekinumab.

Caution should be exercised when considering the use of ustekinumab in patients with a chronic infection or a history of recurrent infection (see section *Contraindications*).

Prior to initiating treatment with ustekinumab, patients should be evaluated for tuberculosis infection. ustekinumab must not be given to patients with active tuberculosis (see section *Contraindications*). 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 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, the patient should be closely monitored and ustekinumab should not be administered until the infection resolves.

Malignancies
Immunosuppressants like ustekinumab have the potential to increase the risk of malignancy. Some patients who received ustekinumab in clinical studies and in a post-marketing observational study in patients with psoriasis developed cutaneous and non-cutaneous malignancies (see section *Adverse Reactions*). The risk of malignancy may be higher in psoriasis patients who have been treated with other biologics during the course of their disease.

No studies have been conducted that include patients with a history of malignancy or that continue treatment in patients who develop malignancy while receiving ustekinumab. Thus, caution should be exercised when considering the use of ustekinumab in these patients.

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 skin cancer (see section *Adverse Reactions*).

Systemic and respiratory hypersensitivity reactions
Systemic
Serious hypersensitivity reactions have been reported in the postmarketing setting, in some cases several days after treatment. Anaphylaxis and angioedema have occurred. If an anaphylactic or other serious hypersensitivity reaction occurs, appropriate therapy should be instituted and administration of ustekinumab should be discontinued (see section *Adverse Reactions*).

Respiratory
Cases of allergic alveolitis, eosinophilic pneumonia, and non-infectious organising 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 hospitalisation. Improvement has been reported after discontinuation of ustekinumab and also, in some cases, administration of corticosteroids. If infection has been excluded and diagnosis is confirmed, discontinue ustekinumab and institute appropriate treatment (see section *Adverse Reactions*).

Cardiovascular events
Cardiovascular events including myocardial infarction and cerebrovascular accident have been observed in patients with psoriasis exposed to ustekinumab in a post-marketing observational study. Risk factors for cardiovascular disease should be regularly assessed during treatment with ustekinumab.

Vaccinations
It is recommended that live viral or live bacterial vaccines (such as Bacillus of Calmette and Guérin (BCG)) should not be given concurrently with ustekinumab. Specific studies have not been conducted in patients who had recently received live viral or live bacterial vaccines. No data are available on the secondary transmission of infection by live vaccines in patients receiving 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 Summary of Product Characteristics for the specific vaccine for additional information and guidance on concomitant use of immunosuppressive agents post-vaccination.

Administration of live vaccines (such as the BCG vaccine) to infants exposed in utero to ustekinumab is not recommended for twelve months following birth or until ustekinumab infant serum levels are undetectable (see sections *Interactions and Pregnancy, Breast-feeding and Fertility*). If there is a clear clinical benefit for the individual infant, administration of a live vaccine might be considered at an earlier timepoint, if infant ustekinumab serum levels are undetectable.

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 *Pharmacodynamic Properties*).

Concomitant immunosuppressive therapy
In psoriasis studies, the safety and efficacy of ustekinumab in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated. In psoriatic arthritis studies, concomitant MTX use did not appear to influence the safety or efficacy of ustekinumab. In Crohn's disease and ulcerative colitis studies, concomitant use of immunosuppressants or corticosteroids did not appear to influence the safety or efficacy of ustekinumab. Caution should be exercised when considering concomitant use of other immunosuppressants and ustekinumab or when transitioning from other immunosuppressive biologics (see section *Interactions*).

Immunotherapy
Ustekinumab has not been evaluated in patients who have undergone allergy immunotherapy. It is not known whether ustekinumab may affect allergy immunotherapy.

Serious skin conditions
In patients with psoriasis, exfoliative dermatitis has been reported following ustekinumab treatment (see *Adverse Reactions*). 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. Ustekinumab should be discontinued if a drug reaction is suspected.

Lupus-related conditions
Cases of lupus-related conditions have been reported in patients treated with ustekinumab, including cutaneous lupus erythematosus and lupus-like syndrome. If lesions occur, especially in sun exposed areas of the skin or if accompanied by arthralgia, the patient should seek medical attention promptly. If the diagnosis of a lupus-related condition is confirmed, ustekinumab should be discontinued and appropriate treatment initiated.

Special populations

Elderly (≥ 65 years)
No overall differences in efficacy or safety in patients age 65 and older who received ustekinumab were observed compared to younger patients in clinical studies in approved indications, however the number of patients aged 65 and older is not sufficient to determine whether they respond differently from younger patients. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly.

Polysorbate 80
Single-use Vial
Steqeyma contains 0.04 mg (90 mg/1.0mL) or 0.02 mg (45 mg/0.5 mL) of polysorbate 80 (E433) in each dosage unit which is equivalent to 0.04 mg/mL. Polysorbates may cause allergic reactions.

Interactions
Live vaccines should not be given concurrently with ustekinumab.

Administration of live vaccines (such as the BCG vaccine) to infants exposed in utero to ustekinumab is not recommended for twelve months following birth or until ustekinumab infant serum levels are undetectable (see sections *Warnings and Precautions and Pregnancy, Breast-feeding and Fertility*). If there is a clear clinical benefit for the individual infant, administration of a live vaccine might be considered at an earlier timepoint, if infant ustekinumab serum levels are undetectable.

In the population pharmacokinetic analyses of the phase 3 studies, the effect of the most frequently used concomitant medicinal products in patients with psoriasis (including paracetamol, ibuprofen, acetylsalicylic acid, metformin, atorvastatin, levothyroxine) on pharmacokinetics of ustekinumab was explored. There were no indications of an interaction with these concomitantly administered medicinal products. The basis for this analysis was that at least 100 patients (> 5% of the studied population) were treated concomitantly with these medicinal products for at least 90% of the study period. The pharmacokinetics of ustekinumab was not impacted by concomitant use of MTX, NSAIDs, 6-mercaptopurine, azathioprine and oral corticosteroids in patients with psoriatic arthritis, Crohn's disease or ulcerative colitis, or prior exposure to anti-TNFα agents, in patients with psoriatic arthritis or Crohn's disease or by prior exposure to biologics (i.e. anti-TNFα agents and/or vedolizumab) in patients with ulcerative colitis.

The results of an in vitro study and a phase 1 study in subjects with active Crohn's disease do not suggest the need for dose adjustments in patients who are receiving concomitant CYP450 substrates (see section *Pharmacokinetic Properties*).

In psoriasis studies, the safety and efficacy of ustekinumab in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated. In psoriatic arthritis studies, concomitant MTX use did not appear to influence the safety or efficacy of ustekinumab. In Crohn's disease and ulcerative colitis studies, concomitant use of immunosuppressants or corticosteroids did not appear to influence the safety or efficacy of ustekinumab (see section *Warnings and Precautions*).

Pregnancy, Breast-feeding and Fertility

Women of childbearing potential

Women of childbearing potential should use effective methods of contraception during treatment and for at least 15 weeks after treatment.

Pregnancy

Data from a moderate number of prospectively collected pregnancies following exposure to ustekinumab with known outcomes, including more than 450 pregnancies exposed during the first trimester, do not indicate an increased risk of major congenital malformations in the newborn.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development (see section *Non Clinical Information*).

However, the available clinical experience is limited. As a precautionary measure, it is preferable to avoid the use of ustekinumab in pregnancy.

Ustekinumab crosses the placenta and has been detected in the serum of infants born to female patients treated with ustekinumab during pregnancy. The clinical impact of this is unknown, however, the risk of infection in infants exposed in utero to ustekinumab may be increased after birth.

Administration of live vaccines (such as the BCG vaccine) to infants exposed in utero to ustekinumab is not recommended for twelve months following birth or until ustekinumab infant serum levels are undetectable (see sections Warnings and Precautions and Interactions). If there is a clear clinical benefit for the individual infant, administration of a live vaccine might be considered at an earlier timepoint, if infant ustekinumab serum levels are undetectable.

Breast-feeding

Limited data from published literature suggests that ustekinumab is excreted in human breast milk in very small amounts. 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.

Fertility

The effect of ustekinumab on human fertility has not been evaluated (see section *Non Clinical Information*).

Effects on Ability to Drive and Use Machines

Ustekinumab has no or negligible influence on the ability to drive and use machines.

Adverse Reactions

Summary of the safety profile

The most common adverse reactions (> 5%) in controlled periods of the adult psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies with ustekinumab were nasopharyngitis and headache. Most were considered to be mild and did not necessitate discontinuation of study treatment. The most serious adverse reaction that has been reported for ustekinumab is serious hypersensitivity reactions including anaphylaxis (see section *Warnings and Precautions*). The overall safety profile was similar for patients with psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis.

Tabulated list of adverse reactions

The safety data described below reflect exposure in adults to ustekinumab in 14 phase 2 and phase 3 studies in 6,710 patients (4,135 with psoriasis and/or psoriatic arthritis, 1,749 with Crohn's disease and 826 patients with ulcerative colitis). This includes exposure to ustekinumab in the controlled and non-controlled periods of the clinical studies in patients with psoriasis, psoriatic arthritis, Crohn's disease or ulcerative colitis for at least 6 months (4,577 patients) or at least 1 year (3,648 patients). 2,194 patients with psoriasis, Crohn's disease or

ulcerative colitis were exposed for at least 4 years while 1,148 patients with psoriasis or Crohn's disease were exposed for at least 5 years.

Table 2 provides a list of adverse reactions from adult psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies as well as adverse reactions reported from post-marketing experience. The adverse reactions are classified by System Organ Class and frequency, using the following convention: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to < 1/100), Rare (≥ 1/10,000 to < 1/1,000), Very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2 List of adverse reactions

System Organ Class	**Frequency: Adverse reaction**
Infections and infestations	Common: Upper respiratory tract infection, nasopharyngitis, sinusitis Uncommon: Cellulitis, dental infections, herpes zoster, lower respiratory tract infection, viral upper respiratory tract infection, vulvovaginal mycotic infection
Immune system disorders	Uncommon: Hypersensitivity reactions (including rash, urticaria) Rare: Serious hypersensitivity reactions (including anaphylaxis, angioedema)
Psychiatric disorders	Uncommon: Depression
Nervous system disorders	Common: Dizziness, headache Uncommon: Facial palsy
Respiratory, thoracic and mediastinal disorders	Common: Oropharyngeal pain Uncommon: Nasal congestion Rare: Allergic alveolitis, eosinophilic pneumonia Very rare: Organising pneumonia*
Gastrointestinal disorders	Common: Diarrhoea, nausea, vomiting
Skin and subcutaneous tissue disorders	Common: Pruritus Uncommon: Pustular psoriasis, skin exfoliation, acne Rare: Exfoliative dermatitis, hypersensitivity vasculitis Very rare: Bullous pemphigoid, cutaneous lupus erythematosus
Musculoskeletal and connective tissue disorders	Common: Back pain, myalgia, arthralgia Very rare: Lupus-like syndrome
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

* See section Warnings and Precautions, Systemic and respiratory hypersensitivity reactions.

Description of selected adverse reactions

Infections

In the placebo-controlled studies of patients with psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis, the rates of infection or serious infection were similar between ustekinumab-treated patients and those treated with placebo. In the placebo-controlled period of these clinical studies, the rate of infection was 1.36 per patient-year of follow-up in ustekinumab-treated patients, and 1.34 in placebo-treated patients. Serious infections occurred at the 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 in placebo-treated patients (15 serious infections in 434 patient-years of follow-up) (see section *Warnings and Precautions*).

In the controlled and non-controlled periods of psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies, representing 15,227 patient-years of ustekinumab exposure in 6,710 patients, the median follow-up was 1.2 years; 1.7 years for psoriatic disease studies, 0.6 year for Crohn's disease studies, and 2.3 years for ulcerative colitis studies. The rate of infection was 0.85 per patient-year of follow-up in ustekinumab-treated patients, and the rate of serious infections was 0.02 per patient-year of follow-up in ustekinumab-treated patients (289 serious infections in 15,227 patient-years of follow-up) and serious infections reported included pneumonia, anal abscess, cellulitis, diverticulitis, gastroenteritis and viral infections.

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

Malignancies

In the placebo-controlled period of the psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis 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 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 to 0.46 for placebo-treated patients (2 patients in 433 patient-years of follow-up).

In the controlled and non-controlled periods of psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies, representing 15,205 patient-years of exposure in 6,710 patients, the median follow-up was 1.2 years; 1.7 years for psoriatic disease studies, 0.6 year for Crohn's disease studies and 2.3 years for ulcerative colitis studies. Malignancies excluding non-melanoma skin cancers were reported in 76 patients in 15,205 patient-years of follow-up (incidence of 0.50 per 100 patient-years of follow-up for ustekinumab-treated patients). The incidence of malignancies reported in ustekinumab-treated patients was comparable to the incidence expected in the general population (standardised incidence ratio = 0.94 [95% confidence interval: 0.73, 1.18], adjusted for age, gender and race). The most frequently observed malignancies, other than non-melanoma skin cancer, were prostate, melanoma, colorectal, and breast cancers. The incidence of non-melanoma skin cancer was 0.46 per 100 patient-years of follow-up for ustekinumab-treated patients (69 patients in 15,165 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 *Warnings and Precautions*).

Hypersensitivity and infusion reactions

In Crohn's disease and ulcerative colitis intravenous induction studies, no events of anaphylaxis or other serious infusion reactions were reported following the single intravenous dose. In these studies, 2.2% of 785 placebo-treated patients and 1.9% of 790 patients treated with the recommended dose of ustekinumab reported adverse events occurring during or within an hour of the infusion. Serious infusion-related reactions including anaphylactic reactions to the infusion have been reported in the post-marketing setting (see section *Warnings and Precautions*).

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 (see section Warnings and Precautions).

Paediatric population

Paediatric patients 6 years and older with plaque psoriasis

The safety of ustekinumab has been studied in two phase 3 studies of paediatric patients with moderate to severe plaque psoriasis. The first study was in 110 patients from 12 to 17 years of age treated for up to 60 weeks and the second study was in 44 patients from 6 to 11 years of age treated for up to 56 weeks. In general, the adverse

events reported in these two studies with safety data up to 1 year were similar to those seen in previous studies in adults with plaque psoriasis.

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

PHARMACOLOGICAL PROPERTIES

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

Mechanism of action
Ustekinumab is a fully human IgG1κ monoclonal antibody that binds with specificity to the shared p40 protein subunit of human cytokines interleukin (IL)-12 and IL-23. Ustekinumab inhibits the bioactivity of human IL-12 and IL-23 by preventing p40 from binding to the IL-12Rβ1 receptor protein expressed on the surface of immune cells. Ustekinumab cannot bind to IL-12 or IL-23 that is already bound to IL-12Rβ1 cell surface receptors. Thus, ustekinumab is not likely to contribute to complement or antibody mediated cytotoxicity of cells expressing IL-12 and/or IL-23 receptors. IL-12 and IL-23 are heterodimeric cytokines secreted by activated antigen presenting cells, such as macrophages and dendritic cells, and both cytokines participate in immune functions; IL-12 stimulates natural killer (NK) cells and drives the differentiation of CD4+ T cells toward the T helper 1 (Th1) phenotype, IL-23 induces the T helper 17 (Th17) pathway. However, abnormal regulation of IL 12 and IL 23 has been associated with immune mediated diseases, such as psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis.

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

In patients with Crohn's disease, treatment with ustekinumab resulted in a decrease in inflammatory markers including C-Reactive Protein (CRP) and fecal calprotectinduring the induction phase, which were then maintained throughout the maintenance phase. CRP was assessed during the study extension and the reductions observed during maintenance were generally sustained through week 252.

In patients with ulcerative colitis, treatment with ustekinumab resulted in a decrease in inflammatory markers including CRP and fecal calprotectin during the induction phase, which were maintained throughout the maintenance phase and study extension through week 200.

Immunisation
During the long-term extension of Psoriasis Study 2 (PHOENIX 2), adult 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 titers were similar among ustekinumab-treated and control patients.

Clinical Studies
Information below refers to reference biologic drug, Stelara

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

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

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

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

Other key efficacy assessments included:

- The Physician's Global Assessment (PGA), a 6-category scale: 0 = cleared, 1 = minimal, 2 = mild, 3= moderate, 4 = marked and 5 = severe, that indicates the physician's overall assessment of psoriasis focusing on plaque thickness/induration, erythema, and scaling. The PGA was assessed in PHOENIX 1 and 2.
- The Dermatology Life Quality Index (DLQI), a dermatology-specific quality of life instrument designed to assess the impact of the disease on a patient's quality of life. DLQI scores range from 0 to 30, with a lower score representing a better quality of life. A decrease of 5 in the DLQI score from baseline is considered a clinically meaningful improvement. The DLQI was assessed in PHOENIX 1 and 2.
- The SF-36, a health survey questionnaire consisting of multi-item scales measuring 8 health concepts. The SF-36 yields composite scores that provide a measure of disease impact on physical and mental health status. Higher SF-36 scores indicate a better quality of life. The SF-36 was assessed in PHOENIX 1.
- The Nail Psoriasis Severity Index (NAPSI), a physician-assessed score that measures the severity of nail involvement. The scale consists of 4 components of nail matrix disease and 4 components of nail bed disease with scores from 0 to 8, with a lower scores representing milder disease. The NAPSI was assessed in PHOENIX 1.
- The Hospital Anxiety and Depression Scale (HADS), a self-rating tool developed to evaluate psychological measures in patients with physical ailments. It consists of 2 subscales, one measuring anxiety (A-scale) and one measuring Depression (D-scale), which are scored separately. Lower HADS scores correspond to lesser psychological impairment. The HADS was assessed in PHOENIX 2.
- The Work Limitations Questionnaire (WLQ), a 25-item, self-administered questionnaire that was used to measure the impact of chronic health conditions on job performance and work productivity among employed populations. The WLQ assesses four aspects of work and productivity: Physical Demands, Time Management, Mental-Interpersonal Demand, and Output Demand. The four subscales range from 0-100 with the lower score indicating fewer work limitations. The WLQ was assessed in PHOENIX 2.
- The Itch Visual Analog Scale, used to assess the severity of itch at the time of the assessment. Itch is assessed using a 10 cm horizontal line, or a Visual Analog Scale (VAS), representing the range of itch severity, from 0 (no itch at all) to 10 (severe itch). The Itch VAS was assessed in PHOENIX 1.

PHOENIX 1

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

Patients randomized to ustekinumab received 45 mg or 90 mg doses at Weeks 0 and 4 followed by the same doses every 12 weeks. Patients randomized to receive placebo at Weeks 0 and 4 crossed over to receive ustekinumab (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 ustekinumab, patients originally randomized to ustekinumab who were PASI 75 responders at both Weeks 28 and 40 were re-randomized to either maintenance dosing of ustekinumab every 12 weeks or to placebo (i.e., withdrawal of therapy). Patients who were re-randomized to placebo at Week 40 reinitiated Ustekinumab at their original dosing regimen when they experienced at least a 50% loss of their PASI improvement obtained at Week 40.

Dose Adjustment (every 8 weeks)
At Week 28, patients who were nonresponders discontinued treatment and patients who were partial responders were adjusted to every-8-week dosing.

PASI 75 responders at week 28 who became partial responders or nonresponders at Week 40 were adjusted to every-8-week dosing.

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

PHOENIX 2
PHOENIX 2 evaluated the safety and efficacy of ustekinumab versus placebo in 1230 patients with plaque psoriasis. Patients randomized to ustekinumab received 45 mg or 90 mg doses at Weeks 0 and 4 followed by an additional dose at Week 16. Patients randomized to receive placebo at Weeks 0 and 4 crossed over to receive ustekinumab (either 45 mg or 90 mg) at Weeks 12 and 16 followed by the same dose every 12 weeks.

Dose Adjustment (every 8 weeks)
At Week 28, patients who were nonresponders discontinued treatment and patients who were partial responders were re-randomized to continue every-12-week dosing or switch to every-8-week dosing.

PASI 75 responders at week 28 who became partial responders or nonresponders at Week 40 were adjusted to every-8-week dosing.

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

Baseline Disease Characteristics: PHOENIX 1 and 2
Baseline disease characteristics across PHOENIX 1 and 2 were similar (Table 3).

Table 3: Baseline Disease Characteristics

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

Failed to respond to, had contraindication for, or intolerant to ≥ 3 conventional therapies	30 (12%)	54 (11%)	66 (16%)	134 (16%)

Efficacy at the Primary Endpoint, PHOENIX 1 and 2

In both the PHOENIX 1 and PHOENIX 2 studies, a significantly greater proportion of patients randomized to treatment with ustekinumab were PASI 75 responders compared with placebo at Week 12 (Table 4). In the PHOENIX 1 study, 67% and 66% of patients receiving ustekinumab 45 mg and 90 mg, respectively, achieved a PASI 75 response at Week 12 compared with 3% of patients receiving placebo. In the PHOENIX 2 study, 67% and 76% of patients receiving ustekinumab 45 mg and 90 mg respectively achieved a PASI 75 response at Week 12 compared with 4% of patients receiving placebo.

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

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

Other Efficacy Measures at Week 12

In both PHOENIX 1 and PHOENIX 2, compared with placebo, significantly greater proportions of patients randomized to 45 mg or 90 mg ustekinumab achieved a cleared or minimal PGA score, and significantly greater proportions of patients randomized to 45 mg or 90 mg ustekinumab were PASI 90 and PASI 50 responders at Week 12 (Table 4). In the PHOENIX 1 study, 59% and 61% of the patients treated with 45 mg and 90 mg ustekinumab, respectively, achieved PGA scores of cleared or minimal compared with 4% of placebo-treated patients. In PHOENIX 2, 68% and 73 % of patients receiving 45 mg or 90 mg ustekinumab, respectively, had cleared or minimal PGA scores compared with 4% of the placebo patients. In PHOENIX 1, PASI 90 was achieved by 42% and 37% of the patients treated with 45 mg and 90 mg ustekinumab, respectively, compared with 2% of placebo-treated patients. In PHOENIX 2, the percentage of patients achieving PASI 90 was 42% in the 45 mg ustekinumab group, 51% in the 90 mg ustekinumab 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 ustekinumab groups, respectively, compared with 10% in the placebo group. Similarly, 84% of patients treated with 45 mg ustekinumab, 89% of patients treated with 90 mg ustekinumab and 10% of patients treated with placebo reached PASI 50 in PHOENIX 2 (Table 4).

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

Week 12						
	PHOENIX 1			PHOENIX 2		
		Ustekinumab			Ustekinumab	
	Placebo	45 mg	90 mg	Placebo	45 mg	90 mg
Patients randomized at Week 0	255	255	256	410	409	411
PASI response						
PASI 50 response[a]	26 (10%)	213 (84%)	220 (86%)	41 (10%)	342 (84%)	367 (89%)
PASI 75 response[a]	8 (3%)	171 (67%)	170 (66%)	15 (4%)	273 (67%)	311 (76%)
PASI 90 response[a]	5 (2%)	106 (42%)	94 (37%)	3 (1%)	173 (42%)	209 (51%)
PGA of Cleared or Minimal [a,b]	10 (4%)	151 (59%)	156 (61%)	18 (4%)	277 (68%)	300 (73%)
PASI 75 response by weight						

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

Week 28				
	PHOENIX 1		PHOENIX 2	
	Ustekinumab		Ustekinumab	
	45 mg	90 mg	45 mg	90 mg
N	250	243	397	400
PASI response				
PASI 50 response	228 (91%)	234 (96%)	369 (93%)	380 (95%)
PASI 75 response	178 (71%)	191 (79%)	276 (70%)	314 (79%)
PASI 90 response	123 (49%)	135 (56%)	178 (45%)	217 (54%)
PGA of Cleared or Minimalb-	146 (58%)	160 (66%)	241 (61%)	279 (70%)
PASI 75 response by weight				
≤ 100 kg				
N	164	153	287	280
PASI 75 response	130 (79%)	124 (81%)	217 (76%)	226 (81%)
>100 kg				
N	86	90	110	119
PASI 75 response	48 (56%)	67 (74%)	59 (54%)	88 (74%)
PGA of Cleared or Minimal by weight				
≤ 100 kg				
N	164	153	287	280
PGA response[b]	106 (65%)	106 (69%)	192(67%)	207 (74%)
>100 kg				
N	86	90	110	119
PGA response	40 (47%)	54 (60%)	49 (45%)	71 (60%)

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

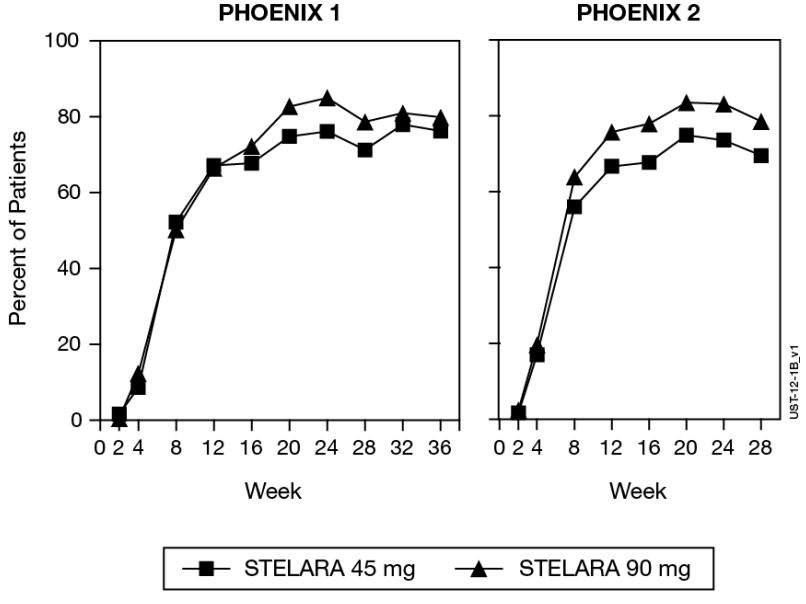
Response Over Time

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

receiving ustekinumab 90 mg than in those receiving ustekinumab 45 mg by Week 16 and these higher response rates were sustained through Week 36 (Figure 1). Similar results were observed in the PHOENIX 2 study through Week 28.

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 5).

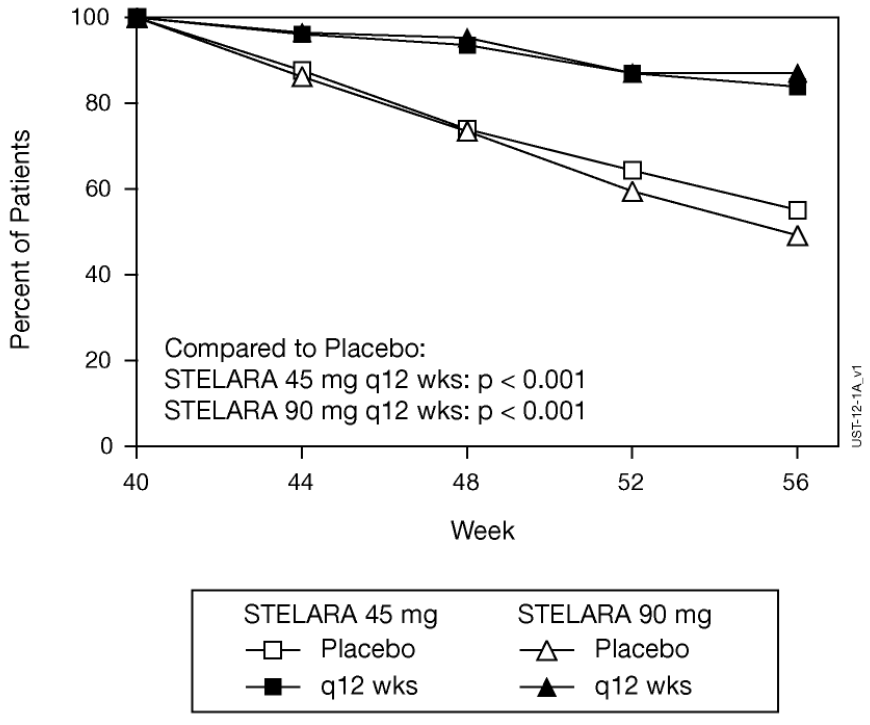
Figure 1: PASI 75 response over time in PHOENIX 1 and 2



Therapeutic Benefit of Long-term Continuous Use

At Week 40 in PHOENIX 1, 162 patients were randomized to receive ustekinumab (maintenance) and 160 were randomized to receive placebo (treatment withdrawal). Maintenance of PASI 75 was significantly superior with continuous treatment compared with treatment withdrawal ($p<0.001$). Similar results were seen with each dose of ustekinumab (Figure 2). At 1 year (Week 52), 89% of patients re-randomized to maintenance treatment were PASI 75 responders compared with 63% of patients re-randomized to placebo (treatment withdrawal) ($p<0.001$). At 18 months (Week 76), 84% of patients re-randomized to maintenance treatment were PASI 75 responders compared with 19% of patients re-randomized to placebo (treatment withdrawal). At 3 years (Week 148), 82% of patients re-randomized to maintenance treatment were PASI 75 responders. At 5 years (Week 244), 80% of patients re-randomized to maintenance treatment were PASI 75 responders.

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



Efficacy of Retreatment

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

Dosing Interval Adjustment

In PHOENIX 1, Week 28 and Week 40 Partial Responders and Week 40 Nonresponders were adjusted from every 12 week to every 8 week dosing. Approximately 40%-50% of Week 28 Partial Responders to every 12 week dosing achieved PASI 75 response after adjustment to every 8 week dosing and this proportion of PASI 75 responders was maintained through Week 52. A similar proportion of patients who were PASI 75 responders at Week 28 and subsequently became partial responders or nonresponders at Week 40 achieved PASI 75 response following a dosing interval adjustment to every 8 weeks.

Quality of Life

In PHOENIX 1 and 2, the mean baseline DLQI scores ranged from 11 to 12. In PHOENIX 1, the mean baseline SF-36 Physical Component ranged from 47-49 and the mean baseline SF-36 Mental Component was approximately 50. Quality of life improved significantly in patients randomized to 45 mg or 90 mg ustekinumab compared with patients randomized to placebo as evaluated by DLQI in PHOENIX 1 and 2 and SF-36 in PHOENIX 1 (Tables 5 and 6). Quality of life improvements were significant as early as 2 weeks in patients treated with ustekinumab and these improvements were maintained over time with continued dosing.

Table 5: Quality of Life endpoints through Week 40 – PHOENIX 1

	Ustekinumab		
	Placebo	45 mg	90 mg
Patients randomized at Week 0	255	255	256
DLQI			
Baseline			
N	254	255	255
Mean ± SD	11.8 ± 7.41	11.1 ± 7.09	11.6 ± 6.92
Median	10.0	10.0	11.0

Change from baseline			
Week 2 [a]			
N	253	255	254
Mean ± SD	-0.9 ± 4.88	-3.6 ± 4.51	-4.5 ± 5.31
Median	-1.0	-3.0	-4.0
Week 12 [a]			
N	252	254	249
Mean ± SD	-0.6 ± 5.97	-8.0 ± 6.87	-8.7 ± 6.47
Median	0.0	-6.0	-7.0
Week 28			
N	NA	249	241
Mean ± SD	NA	-8.1 ± 7.23	-9.6 ± 7.17
Median	NA	-7.0	-8.0
Week 40			
N	NA	246	236
Mean ± SD	NA	-8.2 ± 7.23	-9.5 ± 6.96
Median	NA	-7.0	-9.0
SF-36			
Physical component summary			
Baseline			
N	254	255	255
Mean ± SD	47.22 ± 10.240	48.90 ± 9.555	47.51 ± 9.224
Median	50.70	51.60	49.60
Change from Baseline			
Week 12[a]			
N	250	255	249
Mean ± SD	-0.53± 7.457	1.97 ± 7.422	3.23 ± 7.590
Median	-0.25	1.30	1.50
Week 28			
N	NA	250	239
Mean ± SD	NA	1.86 ± 8.301	3.17 ± 7.855
Median	NA	1.00	1.90
Week 40			
N	NA	246	236
Mean ± SD	NA	1.77 ± 8.402	2.96 ± 8.027
Median	NA	0.80	2.10
Mental component summary			
Baseline			
N	254	255	255
Mean ± SD	49.62 ± 10.582	50.02 ± 10.425	49.86 ± 10.175
Median	53.35	52.90	53.10
Change from Baseline			
Week 12[a]			
N	250	255	249
Mean ± SD	-1.33± 7.473	2.12 ± 9.308	2.54 ± 9.506
Median	-0.60	0.80	1.50
Week 28			
N	NA	250	239
Mean ± SD	NA	1.80 ± 9.578	3.47 ± 9.587
Median	NA	0.40	1.50
Week 40			
N	NA	246	236

Mean ± SD	NA	2.17 ± 9.137	2.91 ± 9.418
Median	NA	0.95	1.10
[a] p < 0.001 for 45 mg or 90 mg comparison with placebo. NA = not applicable			

Table 6: Quality of Life endpoints through Week 24 – PHOENIX 2			
	Ustekinumab		
	Placebo	45 mg	90 mg
Patients randomized at Week 0	410	409	411
DLQI			
Baseline			
N	408	406	408
Mean ± SD	12.3 ± 6.86	12.2 ± 7.07	12.6 ± 7.29
Median	11.0	12.0	12.0
Change from baseline			
Week 4 [a]			
N	405	404	404
Mean ± SD	-1.4 ± 4.68	-6.9 ± 6.07	-7.0 ± 5.86
Median	-1.0	-6.0	-6.0
Week 12[a]			
N	400	401	402
Mean ± SD	-0.5 ± 5.66	-9.3 ± 7.12	-10.0 ± 6.67
Median	-0.5	-8.0	-9.0
Week 24			
N	NA	394	399
Mean ± SD	NA	-9.5 ± 7.26	-10.3 ± 6.96
Median	NA	-8.0	-9.0
[a] p < 0.001 for 45 mg or 90 mg comparison with placebo. NA=not applicable			

Nail Psoriasis

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

Table 7: Summary of percent improvement from baseline in NAPSI at Week 12; patients randomized at Week 0 with nail psoriasis present at Week 0 - PHOENIX 1			
		Ustekinumab	
	Placebo	45 mg	90 mg
Patients randomized at Week 0 with nail psoriasis present at Week 0	176	182	187
Week 12 [a]			
N	174	182	184
Mean ± SD	11.8 ±51.09	26.7 ± 56.80	24.9 ± 48.90
Median	0.0	25.0	25.0

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

Table 8: Summary of percent improvement from baseline in NAPSI at Week 24; patients randomized at Week 0 with nail psoriasis present at Week 0 - PHOENIX 1				
	Ustekinumab			
	Placebo→ 45 mg	Placebo→ 90 mg	45 mg	90 mg

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

Hospital Anxiety and Depression Scale

At baseline in PHOENIX 2, the mean HADS anxiety and depression scores were 6.9 and 5.1, respectively. Both anxiety and depression scores were reduced significantly in patients randomized to 45 mg or 90 mg ustekinumab at Week 12 compared with patients randomized to placebo (Table 9). HADS improvements were maintained through Week 24 (Table 10).

Table 9: Summary of change from baseline in Hospital Anxiety and Depression at Week 12; patients randomized at Week 0 - PHOENIX 2

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

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

Table 10: Summary of change from baseline in Hospital Anxiety and Depression at Week 24; patients randomized at Week 0 – PHOENIX 2

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

Work Limitations Questionnaire

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

Table 11: Summary of change from baseline in Work Limitations Questionnaire at Week 12; patients randomized at Week 0 – PHOENIX 2			
		Ustekinumab	
	Placebo	45 mg	90 mg
Patients randomized at Week 0	410	409	411
Physical Demands score[a]			
n	277	277	281
Mean ± SD	-0.20 ± 30.991	-7.61 ± 30.917	-5.05 ±34.050
Median	0.00	0.00	0.00
Time Management score[b]			
n	259	255	265
Mean ± SD	0.74 ± 18.962	-6.58 ± 21.634	-9.06 ±24.239
Median	0.00	-5.00	-3.30
Mental - Interpersonal score[b]			
n	272	275	276
Mean ± SD	1.11 ± 18.881	-7.82 ± 22.684	-7.51 ±19.366
Median	0.00	-2.80	-1.35
Output Demands score [b]			
n	276	274	279
Mean ± SD	1.08 ± 16.062	-6.82 ± 22.367	-6.98 ± 20.866
Median	0.00	0.00	0.00

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

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

Table 12: Summary of change from baseline in itch VAS at Week 12; patients randomized at Week 0 – PHOENIX 1			
		Ustekinumab	
	Placebo	45 mg	90 mg
Patients randomized at Week 0	255	255	256
Week 12 [a]			
N	252	253	249
Mean ± SD	-0.78 ± 2.538	-4.91 ± 3.142	-5.14 ± 3.020
Median	-0.30	-5.50	-5.50

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

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

The ACCEPT trial compared the efficacy of ustekinumab to etanercept and evaluated the safety of ustekinumab and etanercept in patients with moderate to severe psoriasis. The active-controlled portion of the study was from

Week 0 to Week 12, during which patients were randomized to receive etanercept (50 mg twice a week) ustekinumab 45 mg at Weeks 0 and 4, or ustekinumab 90 mg at Weeks 0 and 4. This trial was powered to test the superiority of each ustekinumab dose to etanercept on the primary endpoint of the proportion of patients who achieved a PASI 75 at week 12.

Significantly greater proportions of subjects treated with ustekinumab 45 mg (67%; p = 0.012) or 90 mg (74%; p < 0.001) were PASI 75 responders at Week 12 compared with the etanercept group (57%). PASI 90 response was observed in 36% and 45 % of patients in the ustekinumab 45 mg and 90 mg groups, respectively, compared with 23% of patients receiving etanercept (p<0.001 for each comparison versus etanercept). PASI 100 response was observed in 12% and 21% of patients in the ustekinumab 45 mg and 90 mg groups, respectively, compared to 6% of patients receiving etanercept (Table 13). In addition, a greater proportion of patients in the ustekinumab 45 mg and 90 mg treatment groups achieved a PGA score of "cleared" or "minimal" (65% and 71%, respectively) compared with patients in the etanercept treatment group (49%) (p<0.001 for each comparison versus etanercept).

In pre-specified analyses of efficacy by body weight in ACCEPT, minimal dose response to ustekinumab was evident in patients ≤ 100 kg. In patients who weighed >100 kg, higher PASI 75 response rates were seen with 90 mg dosing compared with 45 mg dosing, and a higher proportion of patients receiving 90 mg dosing had PGA scores of cleared or minimal compared with patients receiving 45 mg dosing (Table 13).

Table 13: Key psoriasis endpoints at Week 12: ACCEPT

	ACCEPT		
	Etanercept (50 mg twice a week)	Ustekinumab (week 0 and week 4)	
		45 mg	90 mg
Patients randomized	347	209	347
PASI RESPONSE			
PASI 50 response	286 (82%)	181 (87%)	320 (92%)[a]
PASI 75 response	197 (57%)	141 (67%)[b]	256 (74%)[a]
PASI 90 response	80 (23%)	76 (36%)[a]	155 (45%)[a]
PASI 100 response	22 (6%)	25 (12%)[c]	74 (21%)[a]
PGA of Cleared or Minimal	170 (49%)	136 (65%)[a]	245 (71%)[a]
PASI 75 RESPONSE BY WEIGHT			
≤ 100 kg			
N	251	151	244
PASI 75 response	154 (61%)	109 (72%)	189 (77%)
>100 kg			
N	96	58	103
PASI 75 response	43 (45%)	32 (55%)	67 (65%)
PGA OF CLEARED OR MINIMAL BY WEIGHT			
≤ 100 kg			
N	251	151	244
PGA response	131 (52%)	110 (73%)	185 (76%)
>100 kg			
N	96	58	103
PGA response	39 (41%)	26 (45%)	60 (58%)
PASI 75 RESPONSE BY NUMBER OF UNSUITABLE CONVENTIONAL SYSTEMIC AGENTS [g]			
-at least one therapy			
N	347	209	346
PASI 75 Response	197 (57%)	141 (67%) [b]	256 (74%)[a]
-at least two therapies			
N	186	118	185

PASI 75 Response	94 (51%)	79 (67%)[d]	137 (74%)[a]
-at least three therapies			
N	52	31	47
PASI 75 Response	20 (38%)	17 (55%)[e]	34 (72%)[f]

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

Clinical Efficacy – Pediatric Plaque Psoriasis

Adolescent patients (12 to 17 years of age)

The efficacy of ustekinumab was studied in 110 pediatric patients 12 to 17 years of age, in a multicenter, Phase 3, randomized, double blind, placebo controlled study (CADMUS). Patients were randomized to receive either placebo (n=37), or the recommended dose of ustekinumab (n=36) (see Dosage and Administration) or half the recommended dose of ustekinumab (n=37) by subcutaneous injection at Weeks 0 and 4 followed by every 12 week (q12w) dosing. At Week 12, placebo treated patients crossed over to receive ustekinumab. Efficacy observed in patients treated with the recommended dose of ustekinumab is presented below.

The baseline disease characteristics of randomized subjects are summarized in Table 14. Patients with PASI ≥ 12, PGA ≥ 3 and BSA involvement of at least 10%, who were candidates for systemic or phototherapy, were eligible for the study. Approximately half of the patients had prior exposure to conventional systemic or biologic therapy.

Table 14: Baseline Disease Characteristics in pediatric patients 12 to 17 years of age: CADMUS

	Placebo	Ustekinumab*
Patients randomized at Week 0	N= 37	N= 36
Median Age (years)	16.0	15.0
Males	20 (54.1%)	16 (44.4%)
Mean Weight (range; kg)	64.74 (43.8; 107.0)	62.00 (33.8; 109.5)
Median BMI (kg/m^2)	22.70	22.15
Median BSA	21.0	21.5
BSA ≥ 20%	20 (54.1%)	20 (55.6%)
Median PASI	19.6	16.8
Median CDLQI** (0-30)	10.0	9.0
Median PedsQL*** (0-100)	77.17	79.35
PGA of marked or severe	15 (40.5%)	12 (33.3%)
Psoriasis Disease Duration (years)	5.11	5.54
Prior topical therapy	34 (91.9%)	33 (91.7%)
Prior phototherapy	11 (29.7%)	14 (38.9%)
Prior conventional systemic therapy	16 (43.2%)	17 (47.2%)
Prior conventional systemic therapy or phototherapy	22 (59.5%)	22 (61.1%)
Prior biologic therapy	5 (13.5%)	3 (8.3%)
Prior conventional systemic or biologic therapy	18 (48.6%)	17 (47.2%)

* Data presented for the recommended dose of Ustekinumab

** CDLQI: The CDLQI is a dermatology instrument to assess the effect of a skin problem on the health-related quality of life in the pediatric population, with higher scores indicating greater negative effect on health-related quality of life.
*** PedsQL: The PedsQL is a general health-related quality of life measure developed for use in children and adolescent populations.

The primary endpoint was the proportion of patients who achieved a PGA score of cleared (0) or minimal (1) at Week 12. Secondary endpoints included PASI 75, PASI 90, change from baseline in Children's Dermatology Life Quality Index (CDLQI), change from baseline in the total score of PedsQL (Pediatric Quality of Life Inventory) at Week 12. At Week 12, subjects treated with ustekinumab showed significantly greater improvement in their psoriasis and health related quality of life compared with placebo (Table 15).

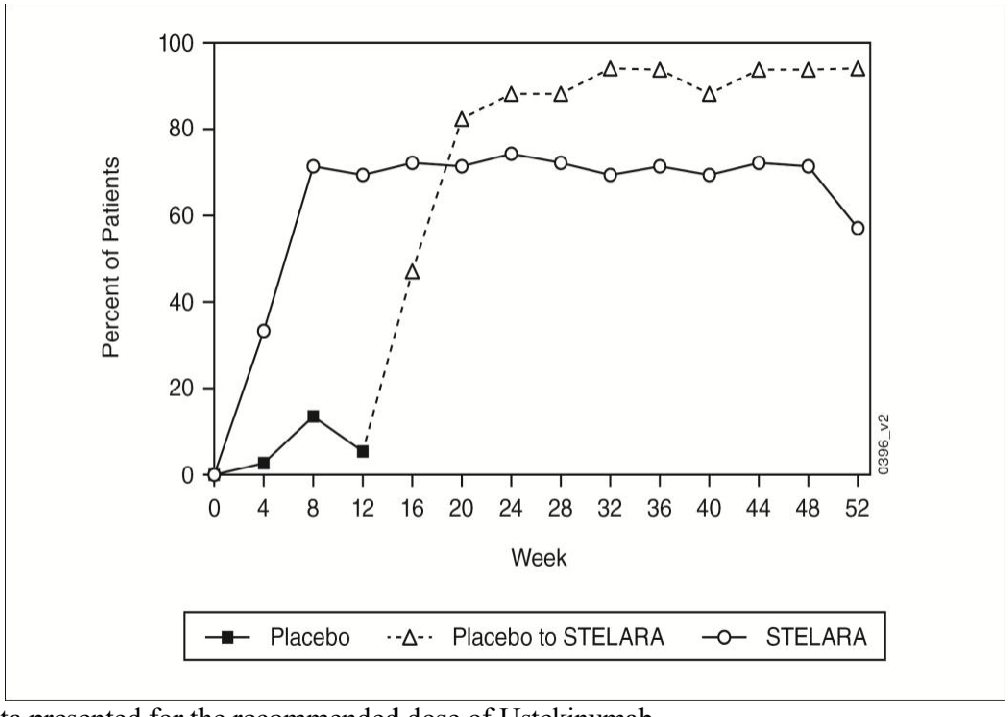
Table 15: Summary of Primary and Secondary End-points at Week 12: CADMUS (Age 12-17)

	Placebo	Ustekinumab*
	N (%)	N (%)
Patients randomized at Week 0	37	36
Number of patients who achieved a PGA score of cleared (0) or minimal (1)	2 (5.4%)	25 (69.4%)[a]
PGA of Cleared (0)	1 (2.7%)	17 (47.2%)[a]
PASI 75 responders	4 (10.8%)	29 (80.6%)[a]
PASI 90 responders	2 (5.4%)	22 (61.1%)[a]
PASI 100 responders	1 (2.7%)	14 (38.9%)[a]
Change from baseline in CDLQI score		
n	32	32
Mean (SD)	-1.5 (3.18)	-6.7 (5.63)
Median	0.0	-5.5
CDLQI of 0 or 1**	4 (13.3%)	17 (56.7%)[a]
Change from baseline in PedsQL Total Scale Score		
n	36	36
Mean (SD)	3.35 (10.04)	8.03 (10.44)[b]

* Data presented for the recommended dose of ustekinumab
a $p<0.001$
b $p=0.028$
** CDLQI of 0 or 1 indicates no effect on child's quality of life.

All patients were followed for efficacy for up to 52 weeks following first administration of study agent. The proportion of patients with a PGA score of cleared (0) or minimal (1) and the proportion achieving PASI 75 showed separation between the ustekinumab treated group and placebo at the first post-baseline visit at Week 4 reaching a maximum at Week 8. Improvements in PGA, PASI, CDLQI and PedsQL were maintained through Week 52. The PGA scores of cleared (0) or minimal (1) over time through Week 52 are summarized in Figure 3 below.

Figure 3: Percent of patients achieving PGA score of cleared (0) or minimal (1) through Week 52 by visit*.



*Data presented for the recommended dose of Ustekinumab

Pediatric Patients (Children 6 to 11 years of age)

The efficacy of ustekinumab was studied in 44 pediatric patients 6 to 11 years of age with moderate to severe plaque psoriasis in an open label, single-arm, multicenter, Phase 3 study (CADMUS Jr.). Patients were treated with the recommended dose of ustekinumab (n=44) (see Dosage and Administration) by subcutaneous injection at Weeks 0 and 4 followed by every 12 week (q12w) dosing.

The baseline disease characteristics of enrolled patients are summarized in Table 16. Patients with PASI $\geqslant$ 12, PGA $\geqslant$ 3 and BSA involvement of at least 10%, who were candidates for systemic therapy or phototherapy, were eligible for the study. Approximately 23% of the patients had prior exposure to conventional systemic therapy or biologic therapy.

Table 16: Baseline Disease Characteristics in pediatric patients 6 to 11 years of age; CADMUS Jr.	
	Ustekinumab*
Patients enrolled at Week 0	N= 44
Median Age (years)	9.5
Males	17 (38.6%)
Mean Weight (range; kg)	38.4 (19; 99)
Median BMI (kg/m^2)	18.0
Median BSA	18.0
BSA ≥ 20%	19 (43.2%)
Median PASI	16.1
Median CDLQI** (0-30)	7.0
PGA of marked or severe	15 (34.1%)
Median Psoriasis Disease Duration (years)	2.9
Prior topical therapy	43 (97.7%)
Prior phototherapy	15 (34.1%)
Prior conventional systemic therapy	8 (18.2%)
Prior conventional systemic therapy or phototherapy	19 (43.2%)
Prior biologic therapy	2 (4.5%)
Prior conventional systemic or biologic therapy	10 (22.7%)

* Data presented for the recommended dose of ustekinumab

** CDLQI: The CDLQI is a dermatology instrument to assess the effect of a skin problem on the health-related quality of life in the pediatric population, with higher scores indicating greater negative effect on health-related quality of life.

The primary endpoint was the proportion of patients who achieved a PGA score of cleared (0) or minimal (1) at Week 12. Secondary endpoints included PASI 75, PASI 90, and change from baseline in Children's Dermatology Life Quality Index (CDLQI) at Week 12. At Week 12, patients treated with ustekinumab showed clinically meaningful improvements in their psoriasis and health related quality of life (Table 17).

Table 17: Summary of Primary and Secondary End-points at Week 12 and 52: CADMUS Jr. (Age 6-11)		
	UstekinumabWeek 12	UstekinumabWeek 52
	N (%)	N (%)
Patients enrolled at Week 0	44	41
Number of patients who achieved a PGA score of cleared (0) or minimal (1)	34 (77.3%)	31 (75.6%)
PGA of cleared (0)	17 (38.6%)	23 (56.1%)
PASI 75 responders	37 (84.1%)	36 (87.8%)
PASI 90 responders	28 (63.6%)	29 (70.7%)

PASI 100 responders	15 (34.1%)	22 (53.7%)
Patients with a CDLQI >1 at baseline	N = 39	N = 36
CDLQI of 0 or 1*	24 (61.5%)	21 (58.3%)

* The CDLQI is a dermatology instrument to assess the effect of a skin problem on the health-related quality of life in the pediatric population. CDLQI of 0 or 1 indicates no effect on child's quality of life.

All patients were followed for efficacy for up to 52 weeks following first administration of study agent. Efficacy measured by PGA score of 0 or 1 was observed as early as the first post-baseline visit at Week 4 and increased through Week 16 and then remained relatively stable through Week 52. Improvements in PGA, PASI, and CDLQI were maintained through Week 52.

Clinical Efficacy – Psoriatic arthritis (PsA)

The safety and efficacy of ustekinumab was assessed in two multicenter, randomized, double-blind, placebo-controlled, Phase 3 studies, PSUMMIT I and PSUMMIT II, in patients with active psoriatic arthritis. Patients were randomized to receive treatment with either ustekinumab 45 mg, 90 mg, or placebo subcutaneous injections at Weeks 0 and 4 followed by every 12 week (q12w) dosing. The primary endpoint in these studies was the reduction in the signs and symptoms of psoriatic arthritis (PsA) as measured by the percentage of ACR 20 responders at Week 24. Secondary endpoints included change from baseline in Disability Index of the Health Assessment Questionnaire (HAQ-DI), PASI 75, ACR 50, ACR 70 and change from baseline in total radiographic scores of the hands and feet, at Week 24. Efficacy data were collected and analyzed through Week 52 for both studies and through Week 100 for PSUMMIT I. These studies included 927 (PSUMMIT I, n=615; PSUMMIT II, n=312) adult patients (≥18 years) who had active psoriatic arthritis (≥5 swollen joints and ≥5 tender joints, despite disease modifying antirheumatic (DMARD) and/or nonsteroidal anti-inflammatory (NSAID) therapy). Methotrexate use was allowed during the studies but was not mandatory. Approximately 50% of patients continued on stable doses of MTX (≤25 mg/week). In PSUMMIT I and PSUMMIT II, 80% and 86% of the patients, respectively, had been previously treated with DMARDs.

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

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

In both studies, a significantly greater proportion of patients achieved ACR 20 and ACR 50 responses at Week 24 in the ustekinumab 45 mg and 90 mg groups compared to placebo (see Table 18). 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 ustekinumab 45 mg and 90 mg groups compared to placebo (see Table 18).

In both studies, the proportion of patients achieving a modified PsA response criteria (PsARC) or a Disease Activity Index Score 28 using C-reactive protein (DAS28-CRP) response was significantly greater in the ustekinumab 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 ustekinumab 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 ustekinumab 90 mg group compared to placebo (see Table 18). DAS28-CRP and PsARC responses were maintained through Week 52 in both studies and through Week 100 in PSUMMIT I.

Table 18: 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		
		Ustekinumab			Ustekinumab	
	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 ustekinumab or placebo are summarized in Figure 4. 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 19). In PSUMMIT I, ACR responses were maintained through Week 100.

Figure 4: Percent of patients achieving ACR 20 response through Week 24

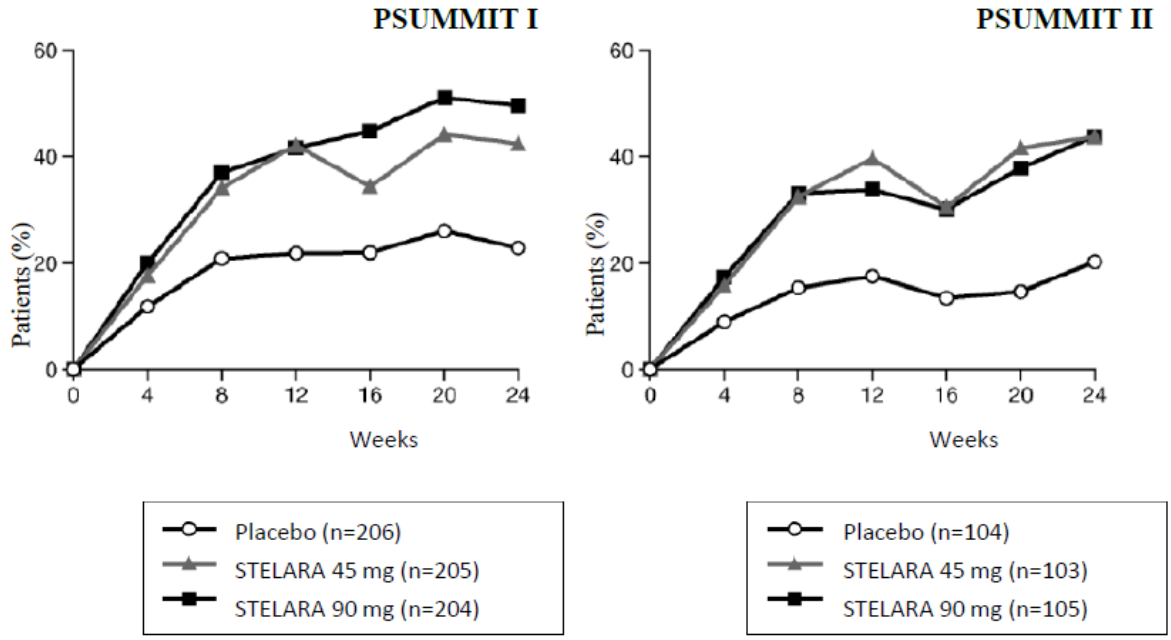


Table 19: Proportion of patients who achieved ACR 20, ACR 50, ACR 70 response at Week 52.				
	PSUMMIT I		**PSUMMIT II**	
	Ustekinumab		**Ustekinumab**	
	45 mg	**90 mg**	**45 mg**	**90 mg**
N	194	189	94	95
ACR response				
ACR 20	55.7%	60.3%	46.8%	48.4%
ACR 50	31.4%	37.0%	27.7%	26.3%
ACR 70	18.0%	21.2%	12.8%	17.9%

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

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

In PSUMMIT II, of 103 subjects randomized to ustekinumab 45 mg, 68 continued the same dose and were available for evaluation at Week 52. Among those, ACR 20, 50, and 70 responses were achieved by 41 (60.3%), 23 (33.8%) and 11 (16.2%) subjects respectively. Of 105 subjects randomized to ustekinumab 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 ustekinumab 45 and 90 mg groups than in the placebo group (see Table 20).

Table 20: Number of patients who achieved ACR 20, ACR 50 and ACR 70 responses by weight through Week 24		
	PSUMMIT I	**PSUMMIT II**

		Ustekinumab			Ustekinumab	
	Placebo (N=206)	**45 mg (N=205)**	**90 mg (N=204)**	**Placebo (N=104)**	**45 mg (N=103)**	**90 mg (N=105)**
Patients randomized with weight ≤100 kg at baseline	154	153	154	74	74	73
ACR 20	39 (25%)	67 (44%)	78 (51%)	17 (23%)	32 (43%)	34 (47%)
ACR 50	14 (9%)	38 (25%)	48 (31%)	6 (8%)	15 (20%)	21 (29%)
ACR 70	5 (3%)	20 (13%)	26 (17%)	3 (4%)	6 (8%)	8 (11%)
Patients randomized with weight >100 kg at baseline	52	52	50	30	29	31
ACR 20	8 (15%)	20 (38%)	23 (46%)	4 (13%)	13 (45%)	12 (39%)
ACR 50	4 (8%)	13 (25%)	9 (18%)	1 (3%)	3 (10%)	3 (10%)
ACR 70	0	5 (10%)	3 (6%)	0	1 (3%)	1 (3%)

Ustekinumab treatment resulted in significantly greater improvement compared with placebo for each ACR component (see Table 21).

Table 21: Summary of percent improvement from baseline in ACR components at Week 24

	PSUMMIT I			**PSUMMIT II**		
		Ustekinumab			Ustekinumab	
	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 ustekinumab than those treated with placebo regardless of concomitant MTX use (see Table 22). Responses observed in the ustekinumab groups were similar in patients receiving or not receiving concomitant MTX. ACR responses were maintained through Week 52 in PSUMMIT I and II and through Week 100 in PSUMMIT I.

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

Prior Anti-TNFα therapy

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

Among patients previously treated with anti-TNFα agents, a significantly greater proportion of ustekinumab-treated patients achieved an ACR 20 response at Week 24 compared to placebo (see Table 23). ACR 20, 50 and 70 responses were generally maintained through Week 52.

Table 23: 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		**Ustekinumab**	
	Placebo (N=104)	**45 mg (N=103)**	**90 mg (N=105)**
Patients randomized	62	60	58
ACR 20	9 (15%)	22 (37%)[a]	20 (34%)[b]
ACR 50	4 (6%)	9 (15%)[c]	9 (16%)[c]
ACR 70	1 (2%)	3 (5%)[c]	3 (5%)[c]

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

Enthesitis and Dactylitis

For patients with enthesitis and/or dactylitis at baseline, in PSUMMIT I, a significant improvement in enthesitis and dactylitis score was observed in the ustekinumab 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 24). In both studies, improvement in enthesitis score and dactylitis score were maintained at Week 52.

In PSUMMIT I, the improvement in enthesitis score and dactylitis score was maintained through Week 100.

Table 24: Summary of percent change in enthesitis and dactylitis scores at Week 24						
	PSUMMIT I			**PSUMMIT II**		
		Ustekinumab			**Ustekinumab**	
	Placebo (N=206)	**45 mg (N=205)**	**90 mg (N=204)**	**Placebo (N= 104)**	**45 mg (N= 103)**	**90 mg (N= 105)**
Enthesitis score [d]						
Patients randomized with enthesitis at baseline	145	142	154	73	72	76
N	137	140	148	68	70	70
Median	0.00	-42.86 [a]	-50.00 [b]	0.00	-33.33 [c]	-48.33[a]
Dactylitis score [e]						
Patients randomized with dactylitis at baseline	96	101	99	38	48	41
N	92	99	95	33	46	38
Median	0.00	-75.00 [b]	-70.83 b	0.00	0.00 [c]	-64.58 [c]

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

A higher proportion of patients treated with ustekinumab, that have spondylitis with peripheral arthritis as their primary presentation, demonstrated Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) 50 and 70 percent improvement in BASDAI scores at Week 24 compared with placebo (see Table 25).

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

[a] p≤0.05
[b] p<0.001
[c] p=NS

[d] p≤0.01
*p value not calculated

PASI Response
In PSUMMIT I and PSUMMIT II, the proportion of patients with psoriasis involvement of ≥3% BSA at baseline who achieved a ≥75% improvement in the PASI assessment at Week 24 was significantly greater in the ustekinumab 45 mg and 90 mg groups compared with the placebo group (see Table 26). In both studies the proportion of patients achieving the PASI 75 response was maintained through Week 52 (PSUMMIT I, ustekinumab 45 mg-70.1% and 90 mg- 68.1%; PSUMMIT II, ustekinumab 45 mg-56.5% and 90 mg- 64.4%). In PSUMMIT I, the PASI 75 response was maintained through Week 100.

The proportion of patients who achieved both a PASI 75 response and an ACR 20 response was evaluated for those patients with ≥3% BSA psoriasis skin involvement at baseline. A significantly higher proportion of patients achieved the combined response in the ustekinumab 45 mg and 90 mg groups compared with the placebo group at Week 24 (see Table 26). In both studies the proportion of patients achieving both a PASI 75 response and an ACR20 response was maintained through Week 52 (PSUMMIT I, ustekinumab 45 mg-44.8% and 90 mg-44.3%; PSUMMIT II, ustekinumab 45 mg-36.8% and 90 mg- 43.1%). In PSUMMIT I, the proportion of patients achieving the combined PASI 75 and ACR20 response was maintained through Week 100.

Table 26: 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**		
		Ustekinumab [a]			**Ustekinumab [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 ustekinumab 45 and 90 mg groups than in the placebo group (see Table 27).

Table 27: Summary of patients who achieved PASI 75, PASI 90 and PASI 100 responses by weight through Week 24

	PSUMMIT I			**PSUMMIT II**		
		Ustekinumab		**Ustekinumab**		
	Placebo (N=206)	**45 mg (N=205)**	**90 mg (N=204)**	**Placebo (N=104)**	**45 mg (N=103)**	**90 mg (N=105)**
Patients randomized with weight ≤100 kg at baseline*	105	105	111	57	54	58

PASI 75	14 (13%)	64 (61%)	73 (66%)	4 (7%)	31 (53%)	32 (56%)
PASI 90	4 (4%)	46 (44%)	48 (43%)	3 (6%)	20 (34%)	27 (47%)
PASI 100	2 (2%)	21 (20%)	30 (27%)	1 (2%)	11 (19%)	13 (23%)
Patients randomized with weight >100 kg at baseline*	41	40	38	26	22	24
PASI 75	2 (5%)	19 (48%)	20 (53%)	0	10 (45%)	13 (54%)
PASI 90	0	14 (35%)	17 (45%)	0	4 (18%)	9 (38%)
PASI 100	0	8 (20%)	11 (29%)	0	2 (9%)	4 (17%)

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

Methotrexate Use

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

Prior Anti-TNFα Therapy

In PSUMMIT II, the proportion of patients who achieved a PASI 75 response at Week 24 was significantly greater in ustekinumab 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 ustekinumab 45 mg or 90 mg treatment significantly inhibited progression of structural damage, when compared to placebo (see Table 28). Beyond Week 24, ustekinumab 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 ustekinumab 45 mg and 90 mg groups respectively) was less than the mean change from Week 0 to 24 (see Table 28). In PSUMMIT I, the effect of ustekinumab on inhibition of structural damage progression was maintained through Week 100. Among subjects treated with ustekinumab 45 mg and 90 mg with no radiographic progression from baseline to Week 52 (n=103, and 113, respectively), 81.5% and 88.8% continued to show no radiographic progression at Week 100.

Table 28: Summary of change from baseline in total modified vdH-S score at Week 24 (Integrated analysis of PSUMMIT I and PSUMMIT II)

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

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

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

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

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

Patients treated with ustekinumab 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 ustekinumab groups when compared with placebo (see Table 29). Improvement was observed at the first assessment (Week 4), reached maximum at Week 12 and was maintained through Week 24. Improvement in HAQ-DI score from baseline was maintained in both studies at Week 52 and through Week 100 in PSUMMIT I.

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

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

Table 29: Improvement in physical function as measured by HAQ-DI at Week 24

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

[a] $p<0.001$
[b] $p<0.01$
*achieving a ≥0.3 improvement from baseline

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

In PSUMMIT II, of 103 subjects randomized to ustekinumab 45 mg, 68 continued the same dose and were available for evaluation at Week 52. Among those, the HAQ-DI response was achieved by 29 (42.6%) subjects. Of 105 subjects randomized to ustekinumab 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 ustekinumab 45 mg and 90 mg groups as compared with placebo (see Table 30) and the improvement was maintained at Week 52. In PSUMMIT I, the improvement from baseline in DLQI scores was maintained through Week 100.

In both PSUMMIT I and PSUMMIT II, at Week 24, the change from baseline in the SF-36 physical component summary (PCS) scores was significantly greater in the ustekinumab 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 ustekinumab groups compared with the placebo group ($p<0.001$ for PSUMMIT I - 90 mg group, p=NS for other groups) (see Table 30). The change from baseline in the SF-36 PCS and MCS scores was maintained at Week 52 in both studies, and at Week 100 in PSUMMIT I.

In PSUMMIT II, a significant change from baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scores was observed at Week 24 in the ustekinumab 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 ustekinumab 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 30: Summary of change from baseline in DLQI and SF-36 and scores at Week 24

	PSUMMIT I			**PSUMMIT II**		
		Ustekinumab			**Ustekinumab**	
	Placebo (N= 206)	**45 mg (N=205)**	**90 mg (N=204)**	**Placebo (N= 104)**	**45 mg (N=103)**	**90 mg (N=105)**
DLQI						
Patients randomized with ≥ 3% BSA psoriasis skin involvement at baseline	146	145	149	80	80	81
Baseline						
N	145	145	149	80	80	81
Mean (SD)	11.68 (7.705)	11.02 (7.308)	10.54 (7.179)	11.93 (7.622)	12.09 (7.667)	11.98 (7.754)
Median	11.00	10.00	9.00	11.00	11.00	10.00
Change from baseline						
N	140	142	146	73	77	75
Mean (SD)	-1.40 (6.177)	-6.63 (6.776)	-7.54 (6.524)	-0.75 (5.666)	-6.95 (7.719)	-7.16 (6.748)
Median	-1.00	-6.00 [a]	-6.00 [a]	0.00	-6.00 [a]	-6.00 [a]
SF-36						
Physical component summary						
Baseline						
N	203	203	204	104	102	104
Mean (SD)	31.39 (8.785)	31.16 (8.511)	31.45 (8.152)	30.28 (9.361)	28.69 (8.501)	28.93 (8.480)
Median	30.40	29.80	29.70	29.35	27.95	28.15
Change from baseline						
N	196	200	197	97	99	97
Mean (SD)	1.4(7.094)	4.89 (9.333)	6.22 (8.747)	1.09 (5.892)	4.29 (8.594)	4.67 (8.758)
Median	1.15	3.90 [a]	5.80 [a]	0.00	2.70[c]	3.50[a]

Mental component summary						
Baseline						
N	203	203	204	104	102	104
Mean (SD)	43.51 (10.848)	42.77 (10.908)	43.48 (11.608)	42.11 (12.507)	43.27 (12.911)	42.81 (11.953)
Median	43.90	42.00	41.65	41.80	43.70	41.40
Change from baseline						
N	196	200	197	97	99	97
Mean (SD)	1.53 (9.582)	3.35 (10.016)	4.79 (10.054)	0.63 (8.238)	3.01 (11.144)	3.52 (11.274)
Median	0.25	2.65[b]	4.40[a]	0.00	0.70[b]	2.20[b]

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

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

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

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

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

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

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

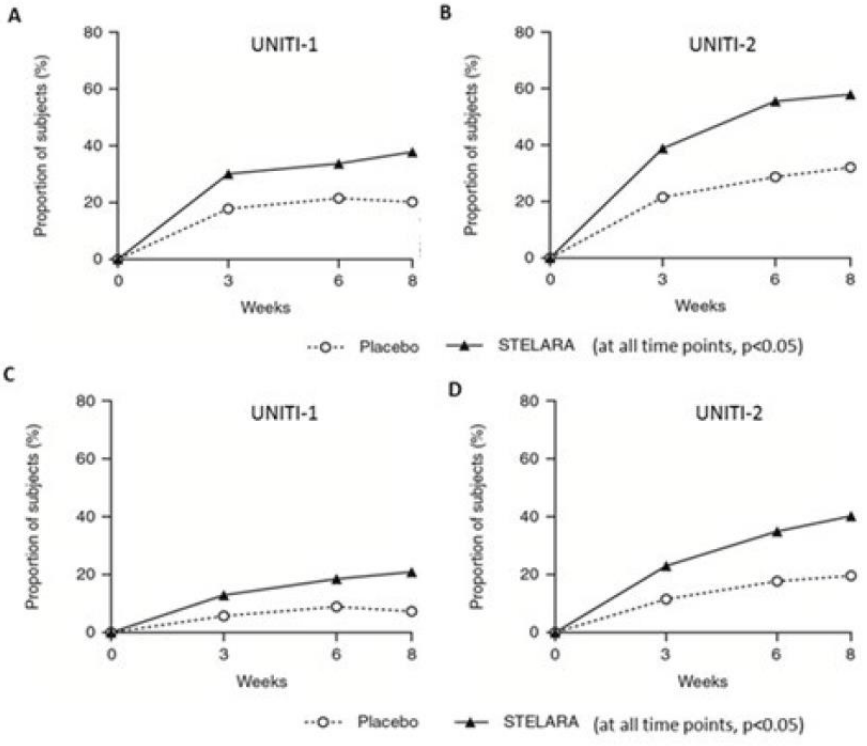
In these induction studies, efficacy was higher and better sustained in the tiered dose group compared to the 130 mg dose group, and tiered dosing is therefore the recommended IV induction dose. In both UNITI-1 and UNITI-2, a significantly greater proportion of patients were in clinical response and remission in the group treated with ustekinumab, compared to placebo (Table 31, Figure 5). Clinical response and remission were significant as early as Week 3 in ustekinumab treated patients and continued to improve through Week 8 (Figure 5).

Table 31: Induction of Clinical Response and Remission in UNITI-1* and UNITI 2**

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

Clinical remission is defined as CDAI score < 150; Clinical response is defined as reduction in CDAI score by at least 100 points or being in clinical remission
70 point response is defined as reduction in CDAI score by at least 70 points
* Anti-TNFα failures
** Conventional therapy failures
[a] $p < 0.001$
[b] $p < 0.01$

Figure 5: Proportion of ustekinumab treated patients in clinical response (A, B) and remission (C, D) through Week 8 in UNITI-1 and UNITI-2 studies



Maintenance of Response and Remission

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

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

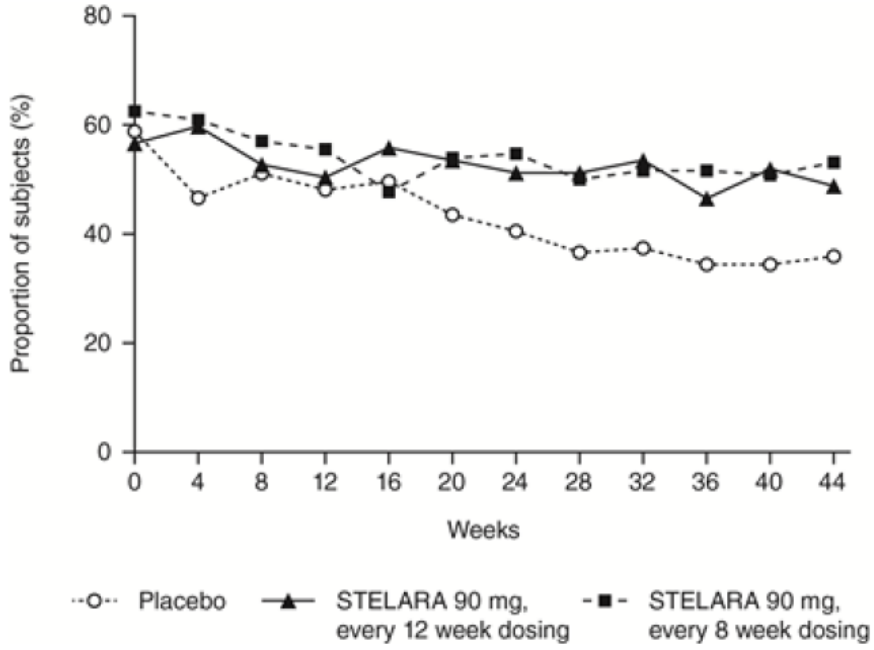
Significantly higher proportions of patients maintained clinical remission and response in the ustekinumab treated groups as compared to placebo at Week 44 (Table 32, Figure 6). A higher proportion of ustekinumab treated patients compared to placebo achieved sustained clinical remission (clinical remission at Week 36, 40 and 44).

Table 32: Maintenance of Clinical Response and Remission in IM-UNITI (Week 44; 52 weeks from initiation of the induction dose)

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

Clinical remission is defined as CDAI score < 150; Clinical response is defined as reduction in CDAI of at least 100 points or being in clinical remission
* The placebo group consisted of patients who were in response to ustekinumab and were randomized to receive placebo at the start of maintenance therapy.
† Patients who achieved a clinical response to ustekinumab at start of maintenance therapy
‡ Defined as clinical remission at Week 36, 40 and 44.
[a] $p < 0.01$
[b] $p < 0.05$
[c] nominally significant ($p<0.05$)

Figure 6: Proportion of patients in clinical remission at each visit through Week 44.



Delayed Response
Patients who were not in clinical response to ustekinumab induction received a 90 mg subcutaneous injection of ustekinumab upon entry into the maintenance study. Eight weeks later, 50.5% of the patients achieved clinical response and continued to receive maintenance dosing every 8 weeks; among these patients with continued maintenance dosing, a majority achieved levels of response (68.1%) and remission (50.2%) similar to the patients who initially responded to ustekinumab induction.

Dosing in Patients with a Lower Inflammatory Burden
In patients with a lower inflammatory burden as reflected by CRP ≤ 10 mg/L at initiation of induction or initiation of maintenance therapy, the efficacy of the every 12 week dosing regimen was similar to that of the every 8 week dosing regimen.

Dosing Frequency Adjustment
In IM-UNITI, patients who did not maintain response to ustekinumab when treated every 12 weeks were allowed to increase the frequency of dosing and receive ustekinumab every 8 weeks. Loss of response was defined as a CDAI score ≥ 220 points and a ≥ 100 point increase from the CDAI score at baseline. In these patients, clinical remission was achieved in 41.4% of patients 16 weeks after dosing frequency adjustment.

Resumption of Treatment
Patients that responded to ustekinumab induction and who were randomized to the placebo group at the start of the maintenance study received 90 mg ustekinumab subcutaneously every 8 weeks at time of loss of response. Of these patients, 70.6% achieved clinical response and 39.2% achieved clinical remission 16 weeks after receiving the first subcutaneous dose of ustekinumab.

Long-Term Maintenance
In IM-UNITI, patients who completed the study through week 44 were eligible to continue treatment in a study extension. Among patients who entered the study extension, clinical remission and response were generally maintained through week 252. Results were consistent between patients who failed TNF-therapies versus those who did not.

No new safety concerns were identified in this study extension with up to 5 years of treatment in patients with Crohn's Disease.

Corticosteroid Use in Maintenance
In patients that were in clinical response to ustekinumab induction therapy, a greater proportion of patients in the ustekinumab treated group were in remission and corticosteroid-free compared to the placebo group after 44 weeks of maintenance treatment (Table 32). In addition, a higher proportion of patients were in clinical response and not receiving corticosteroids in the ustekinumab treated group compared to placebo.

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

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

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

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

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

IBDQ
At Week 8 in UNITI-1 and UNITI-2, significant improvement from baseline in the inflammatory bowel disease questionnaire (IBDQ) total score and all subscales, was observed in the patients treated with ustekinumab compared to placebo. In both studies, a higher proportion of patients with clinically meaningful improvement in IBDQ total scores were observed in patients treated with ustekinumab compared to placebo. These improvements in the IBDQ total scores were maintained in ustekinumab treated patients in the IM-UNITI maintenance study through Week 44.

Long-term Maintenance of Health-related Quality of Life Measures
Improvement in health related quality of life as measured by IBDQ and SF-36 was generally maintained during the extension through week 252.

Clinical Efficacy – Ulcerative Colitis
The safety and efficacy of ustekinumab was assessed in two randomized, double-blind, placebo-controlled, multicenter studies in adult patients with moderately to severely active ulcerative colitis (Mayo score 6 to 12; Endoscopy subscore ≥2 based on central review of the endoscopy). The clinical development program consisted of one intravenous induction study (referred to as UNIFI-induction) with treatment of up to 16 weeks followed by a 44-week subcutaneous randomized withdrawal maintenance study (referred to as UNIFI-maintenance) representing at least 52 weeks of therapy.

Efficacy results presented for UNIFI-induction and UNIFI-maintenance were based on central review of endoscopies.

UNIFI-induction included 961 patients. The primary endpoint for the induction study was the proportion of patients in clinical remission (defined as a Mayo score ≤2 points, with no individual subscore >1) at Week 8. Patients were randomized to receive a single intravenous administration of either the recommended tiered dose of approximately 6 mg/kg (see Table 1; Initial IV dosing of ustekinumab), a fixed dose of 130 mg ustekinumab, or placebo at Week 0.

Concomitant use of oral corticosteroids, immunomodulators, and aminosalicylates were permitted and 90% of patients continued to receive at least one of these medications. Enrolled patients had to have failed conventional therapy (corticosteroids or immunomodulators) or at least one biologic (a TNFα antagonist and/or vedolizumab). 49% of patients had failed conventional therapy, but not a biologic (of which 94% where biological-naïve). 51% of patients had failed or were intolerant to a biologic. Approximately 50% of the patients had failed at least 1 prior anti-TNFα therapy (of which 48% were primary non-responders) and 17% had failed at least 1 anti-TNFα therapy and vedolizumab.

In UNIFI-induction a significantly greater proportion of patients were in clinical response and remission in the ustekinumab treated group compared to placebo (Table 33). As early as Week 2, the earliest scheduled study visit, and at each visit thereafter, a higher proportion of ustekinumab patients had no rectal bleeding or achieved normal stool frequency (defined as a stool frequency subscore of 0 or 1) as compared with placebo patients. Significant differences in partial Mayo score and symptomatic remission were observed between ustekinumab and placebo as early as Week 2. Efficacy was higher in the tiered dose group (6 mg/kg) compared to the 130 mg dose group in select endpoints, and tiered dosing is therefore the recommended intravenous induction dose.

Table 33: Summary of Key Efficacy Measures in UNIFI-Induction (Week 8)

Endpoint	**Placebo N = 319**		**Ustekinumab† N =322**	
	N	%	N	%
Clinical Remission*	17	5%	50	16% a
Biologic-naïve¡	*15/151*	*10%*	*27/147*	*18%*
Not biologic failure	*15/158*	*9%*	*29/156*	*19%*
Prior biological failure	*2/161*	*1%*	*21/166*	*13%*
Clinical Response§	100	31%	199	62%a
Biologic-naïve¡	*54/151*	*36%*	*98/147*	*67%*
Not biologic failure	*56/158*	*35%*	*104/156*	*67%*
Prior biological failure	*44/161*	*27%*	95/166	*57%*
Endoscopic Healing€	44	14%	87	27%a
Biologic-naïve¡	*32/151*	*21%*	*49/147*	*33%*
Not biologic failure	*33/158*	*21%*	*52/156*	*33%*
Prior biologic failure	*11/161*	*7%*	*35/166*	*21%*
Histo-Endoscopic Mucosal Healing‡	28/316	9%	58/315	18% a
Biologic-naïve¡	*21/148*	*14%*	*33/140*	*24%*
Not biologic failure	*22/155*	*14%*	*36/149*	*24%*
Prior biological failure	*6/161*	*4%*	*22/166*	*13%*
Symptomatic Remission£	72	23%	144	45%b
Combined Symptomatic Remission and Endoscopic Healing¡	25	8%	67	21% b

† Infusion dose of ustekinumab using the weight-based dosage regimen specified in Table 1.
¡ An additional 7 patients on placebo and 9 patients on ustekinumab (6mg/kg) had been exposed to, but had not failed, biologics
*Clinical remission is defined as Mayo score ≤2 points, with no individual subscore > 1.

§ Clinical response is defined as a decrease from baseline in the Mayo score by ≥30% and ≥3 points, with either a decrease from baseline in the rectal bleeding subscore ≥1 or a rectal bleeding subscore of 0 or 1.
€ Endoscopic healing is defined as a Mayo endoscopic subscore of 0 or 1 determined by central review of the endoscopy.
‡ Histo-endoscopic mucosal healing is defined as combined endoscopic healing (Mayo endoscopy subscore of 0 or 1) and histologic healing of the colon tissue (neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue).
£ Symptomatic remission is defined as a stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0.
⸸ Combined symptomatic remission and endoscopic healing is defined as remission based on a stool frequency subscore of 0 or 1, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1.
a $p < 0.001$
b Nominally significant ($p < 0.001$)

UNIFI-maintenance evaluated 523 patients who achieved clinical response with single IV administration of ustekinumab in UNIFI-induction. Patients were randomized to receive a subcutaneous maintenance regimen of either 90 mg ustekinumab every 8 weeks, 90 mg ustekinumab every 12 weeks or placebo for 44 weeks.
Significantly greater proportions of patients were in clinical remission at Week 44 and maintained clinical response through Week 44 in both ustekinumab treated groups compared to the placebo group (see Table 34).

Table 34: Summary of Key Efficacy Measures in UNIFI-Maintenance (Week 44; 52 weeks from initiation of the induction dose)

	Placebo* N = 175	**Ustekinumab 90 mg every 8 Weeks N = 176**	**Ustekinumab 90 mg every 12 Weeks N = 172**
Clinical Remission**	24%	44% [a]	38% [b]
Biologic-naïve⸸	*32% (27/84)*	*51% (40/79)*	*47% (45/95)*
Not biologic failure	*31% (27/87)*	*48% (41/85)*	*49% (50/102)*
Prior biologic failure	*17% (15/88)*	*40% (36/91)*	*23% (16/70)*
Maintenance of Clinical Response through Week 44§	45%	71% [a]	68% [a]
Biologic-naïve⸸	*52% (44/84)*	*77% (61/79)*	*77% (73/95)*
Not biologic failure	*51% (44/87)*	*78% (66/85)*	*76% (78/102)*
Prior biologic failure	*39% (34/88)*	*65% (59/91)*	*56% (39/70)*
Corticosteroids Free Clinical Remission‡	23%	42% [a]	38% [b]
Biologic-naïve⸸	*32% (27/84)*	*49% (39/79)*	*46% (44/95)*
Not biologic failure	*31% (27/87)*	*47% (40/85)*	*48% (49/102)*
Prior biologic failure	*16% (14/88)*	*37% (34/91)*	*23% (16/70)*
Endoscopic Healing at Week 44†	29%	51% [a]	44% [b]
Biologic-naïve⸸	*36% (30/84)*	*58% (46/79)*	*55% (52/95)*
Not biologic failure	*34% (30/87)*	*58% (49/85)*	*56% (57/102)*

Prior biologic failure	*23% (20/88)*	*45% (41/91)*	*26% (18/70)*
Maintenance of Clinical Remission through Week 44£	38%	58%	65% [b]
Biologic-naïve⸸	*36% (9/25)*	*75% (12/16)*	*70% (21/30)*
Not biologic failure	*36% (9/25)*	*67% (12/18)*	*72% (23/32)*
Prior biologic failure	*40% (8/20)*	*50% (10/20)*	*38% (3/8)*
Durable Partial Mayo Remission through Week 44‖	35%	57% [c]	48% [c]
Symptomatic Remission at Week 44£	45%	68% [c]	62% [c]
Combined Symptomatic Remission and Endoscopic Healing at Week 44€	28%	48% [c]	41% [c]

* The placebo group consisted of patients who were in response to ustekinumab IV and were randomized to receive placebo at the start of maintenance therapy.
**Clinical remission is defined as Mayo score ≤2 points, with no individual subscore > 1.
§ Clinical response is defined as a decrease from baseline in the Mayo score by ≥30% and ≥3 points, with either a decrease from baseline in the rectal bleeding subscore ≥1 or a rectal bleeding subscore of 0 or 1.
⸸ An additional 3 patients on placebo and 6 patients on Q8W, 7 patients on Q12W ustekinumab had been exposed to, but had not failed, biologics
† Endoscopic healing is defined as a Mayo endoscopic subscore of 0 or 1 determined by central review of the endoscopy
‡ Corticosteroid-free clinical remission is defined as patients in clinical remission and not receiving corticosteroids at Week 44.
£Maintenance of clinical remission is defined as patients in clinical remission at maintenance baseline through Week 44 among patients in clinical remission at maintenance baseline.
‖ Durable partial Mayo remission is defined as partial Mayo remission (i.e. a partial Mayo score of ≤2) at ≥80% of all visits prior to Week 44 and in partial Mayo remission at last visit (Week 44).
£ Symptomatic remission is defined as a stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0.
€Combined symptomatic remission and endoscopic healing is defined as a stool frequency subscore of 0 or 1, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1.
[a] $p < 0.001$
[b] $p<0.05$
[c] Nominally significant ($p<0.05$)

The beneficial effect of ustekinumab on clinical response, mucosal healing and clinical remission was observed in induction and in maintenance both in patients who failed conventional therapy but not a biologic therapy, as well as in those who had failed at least one prior TNFα antagonist therapy, and/or vedolizumab including in patients with a primary non-response to TNFα antagonist therapy.

Delayed Responders to Ustekinumab Induction
Ustekinumab treated patients who were not in response at Week 8 of UNIFI-induction received an administration of 90 mg SC ustekinumab at Week 8 (36% of patients). Of those patients, 9% of patients who were initially randomized to the recommended induction dose achieved clinical remission and 58% achieved clinical response at Week 16. When combining the delayed responders with the initial responders, 80% of subjects randomized to the recommended induction dose in UNIFI-I achieved clinical response and 18% achieved clinical remission within 16 weeks after initiating treatment with Ustekinumab.

Patients who were not in clinical response to ustekinumab induction at Week 8 of the UNIFI-induction study but were in response at Week 16 (157 patients) entered in the non-randomized portion of UNIFI-maintenance and continued to receive maintenance dosing every 8 weeks; among these patients, a majority (62%) maintained response and 30% achieved remission at Week 44.

Long-Term Maintenance
In UNIFI (UCO3001), patients who completed the study through week 44 were eligible to continue treatment in a study extension and were treated with ustekinumab. Among 400 patients who entered in the study extension, symptomatic remission was generally maintained through week 200 for patients who failed conventional therapy (but not a biologic therapy) and those who failed biologic therapy, including those who failed both anti-TNF and vedolizumab. Of those patients who were assessed using the full Mayo score at week 200, mucosal healing and clinical remission were generally maintained.

The safety analysis including 457 patients (1289.9 person-years) followed up to 220 weeks showed a safety profile between week 44 and 220 that was comparable with that observed up to week 44.

No new safety concerns were identified in this study extension with up to 4 years of treatment in patients with ulcerative colitis.

Endoscopic Normalization
Normalization of endoscopic appearance of the mucosa was defined as a Mayo endoscopic subscore of 0 and was observed as early as Week 8 of UNIFI-induction. At Week 44 of UNIFI-maintenance, it was achieved in 24% and 29% of patients treated with ustekinumab every 12 or 8 weeks, respectively, as compared to 18% of patients in the placebo group.

Histologic & Histo-Endoscopic Mucosal Healing
Histologic healing (defined as neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue) was assessed at Week 8 of UNIFI-induction and Week 44 of UNIFI-maintenance. At Week 8, after a single intravenous induction dose, significantly greater proportions of patients in the recommended dose group achieved histologic healing (36%) compared with patients in the placebo group (22%). At Week 44 maintenance of this effect was maintained with significantly more patients in histologic healing in the every 12 week (54%) and every 8 week (59%) ustekinumab groups as compared to placebo (33%).

A combined endpoint of histo-endoscopic mucosal healing defined as subjects having both mucosal healing and histologic healing was evaluated at week 8 of UNIFI-induction and Week 44 of UNIFI-maintenance. Patients receiving ustekinumab at the recommended dose showed significant improvements on the histo-endoscopic mucosal healing endpoint at Week 8 in the ustekinumab group (18%) as compared to the placebo group (9%). At Week 44, maintenance of this effect was observed with significantly more patients in histo-endoscopic mucosal healing in the every 12 week (39%) and every 8 week (46%) ustekinumab groups as compared to placebo (24%).

Health-related quality of life
Health-related quality of life was assessed by Inflammatory Bowel Disease Questionnaire (IBDQ), SF-36 and EuroQoL-5D (EQ-5D) questionnaires. At Week 8 of UNIFI-induction, patients receiving ustekinumab showed significantly greater and clinically meaningful improvements on IBDQ total score, EQ-5D and EQ-5D VAS, and SF-36 Mental Component Summary Score and SF-36 Physical Component Summary Score when compared to placebo. These improvements were maintained in ustekinumab-treated patients in UNIFI-maintenance through Week 44.

Patients receiving ustekinumab experienced significantly more improvements in work productivity as assessed by greater reductions in overall work impairment and in activity impairment as assessed by the WPAI-GH questionnaire than patients receiving placebo.

Long-term maintenance of health-related quality of life measures
Improvement in health-related quality of life as measured by IBDQ and SF-36 was generally maintained during the extension through week 200.

Hospitalizations and Ulcerative Colitis related surgeries

Through Week 8 of UNIFI-induction, the proportions of subjects with ulcerative colitis disease related hospitalizations were significantly lower for subjects in the ustekinumab recommended dose group (1.6%, 5/322) compared with subjects in the placebo group (4.4%, 14/319) and no subjects underwent ulcerative colitis disease related surgeries in subjects receiving ustekinumab at the recommended induction dose compared to 0.6% (2/319) subjects in the placebo group.

Through Week 44 of UNIFI-maintenance, a significantly lower number of ulcerative colitis disease related hospitalizations was observed in subjects in the combined ustekinumab group (2.0%, 7/348) as compared with subjects in the placebo group (5.7%, 10/175). A numerically lower number of subjects in the ustekinumab group (0.6%, 2/348) underwent ulcerative colitis disease related surgeries compared with subjects in the placebo group (1.7%, 3/175) through Week 44.

Pharmacokinetic Properties

Absorption

The median time to reach the maximum serum concentration (tmax) was 8.5 days after a single 90 mg subcutaneous administration in healthy subjects. The median tmax values of ustekinumab following a single subcutaneous administration of either 45 mg or 90 mg in patients with psoriasis were comparable to those 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.

Biotransformation

The exact metabolic pathway for ustekinumab is unknown.

Elimination

Median systemic clearance (CL) following a single intravenous administration to patients with psoriasis ranged from 1.99 to 2.34 mL/day/kg. Median half-life (t1/2) of ustekinumab was approximately 3 weeks in patients with psoriasis, psoriatic arthritis, Crohn's disease or ulcerative colitis, ranging from 15 to 32 days across all psoriasis and psoriatic arthritis studies. In a population pharmacokinetic analysis, the apparent clearance (CL/F) and apparent volume of distribution (V/F) were 0.465 l/day and 15.7 l, respectively, in patients with psoriasis. The CL/F of ustekinumab was not impacted by gender. Population pharmacokinetic analysis showed that there was a trend towards a higher clearance of ustekinumab in patients who tested positive for antibodies to ustekinumab.

Dose linearity

The systemic exposure of ustekinumab (Cmax and AUC) increased in an approximately dose-proportional manner after a single intravenous administration at doses ranging from 0.09 mg/kg to 4.5 mg/kg or following a single subcutaneous administration at doses ranging from approximately 24 mg to 240 mg in patients with psoriasis.

Single dose versus 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 µg/mL to 0.26 µg/mL (45 mg) and from 0.47 µg/mL to 0.49 µg/mL (90 mg). There was no apparent accumulation in serum ustekinumab concentration over time when given subcutaneously every 12 weeks.

In patients with Crohn's disease and ulcerative colitis, following an intravenous dose of ~6 mg/kg, starting at week 8, subcutaneous maintenance dosing of 90 mg ustekinumab was administered every 8 or 12 weeks. Steady state ustekinumab concentration was achieved by the start of the second maintenance dose. In patients with Crohn's disease, median steady-state trough concentrations ranged

from 1.97 μg/mL to 2.24 μg/mL and from 0.61 μg/mL to 0.76 μg/mL for 90 mg ustekinumab every 8 weeks or every 12 weeks respectively. In patients with ulcerative colitis, median steady-state trough concentrations ranged from 2.69 μg/mL to 3.09 μg/mL and from 0.92 μg/mL to 1.19 μg/mL for 90 mg ustekinumab every 8 weeks or every 12 weeks. The steady-state trough ustekinumab levels resulting from 90 mg ustekinumab every 8 weeks were associated with higher clinical remission rates as compared to the steady-state trough levels following 90 mg every 12 weeks.

Impact of weight on pharmacokinetics

In a population pharmacokinetic analysis using data from patients with psoriasis, body weight was found to be the most significant covariate affecting the clearance of ustekinumab. The median CL/F in patients with weight > 100 kg was approximately 55% higher compared to patients with weight ≤ 100 kg. The median V/F in patients with weight > 100 kg was approximately 37% higher as compared to patients with weight ≤ 100 kg. 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. Similar results were obtained from a confirmatory population pharmacokinetic analysis using data from patients with psoriatic arthritis.

Dosing frequency adjustment

In patients with Crohn's disease and ulcerative colitis, based on observed data and population PK analyses, randomised subjects who lost response to treatment had lower serum ustekinumab concentrations over time compared with subjects who did not lose response. In Crohn's disease, dose adjustment from 90 mg every 12 weeks to 90 mg every 8 weeks was associated with an increase in trough serum ustekinumab concentrations and an accompanying increase in efficacy. In ulcerative colitis, population PK model based simulations demonstrated that adjusting dosing from 90 mg every 12 weeks to every 8 weeks would be expected to result in a 3-fold increase in steady-state trough ustekinumab concentrations. Additionally on the basis of clinical trial data in patients with ulcerative colitis, a positive exposure-response relationship was established between trough concentrations, and clinical remission and mucosal healing.

Special populations

No pharmacokinetic data are available in patients with impaired renal or hepatic function. No specific studies have been conducted in elderly patients.
The pharmacokinetics of ustekinumab were generally comparable between Asian and non Asian patients with psoriasis and ulcerative colitis.

In patients with Crohn's disease and ulcerative colitis, variability in ustekinumab clearance was affected by body weight, serum albumin level, sex, and antibody to ustekinumab status while body weight was the main covariate affecting the volume of distribution. Additionally in Crohn's disease, clearance was affected by C-reactive protein, TNF antagonist failure status and race (Asian versus non-Asian). The impact of these covariates was within ±20% of the typical or reference value of the respective PK parameter, thus dose adjustment is not warranted for these covariates. Concomitant use of immunomodulators did not have a significant impact on ustekinumab disposition.

In the population pharmacokinetic analysis, there were no indications of an effect of tobacco or alcohol on the pharmacokinetics of ustekinumab.

The bioavailability of ustekinumab following administration by syringe or pre-filled pen was comparable.

Serum ustekinumab concentrations in paediatric psoriasis patients 6 to 17 years of age, treated with the recommended weight-based dose were generally comparable to those in the adult psoriasis population treated with the adult dose. Serum ustekinumab concentrations in paediatric psoriasis patients 12-17 years of age (CADMUS) treated with half of the recommended weight-based dose were generally lower than those in adults.

Regulation of CYP450 enzymes

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

A phase 1, open-label, drug interaction study, Study CNTO1275CRD1003, was conducted to evaluate the effect of ustekinumab on cytochrome P450 enzyme activities following induction and maintenance dosing in patients with active Crohn's disease (n=18). No clinically significant changes in exposure of caffeine (CYP1A2 substrate), warfarin (CYP2C9 substrate), omeprazole (CYP2C19 substrate), dextromethorphan (CYP2D6 substrate), or midazolam (CYP3A substrate) were observed when used concomitantly with ustekinumab at the approved recommended dosing in patients with Crohn's disease (see section Interaction with other medicinal products and other forms of interaction).

COMPARATIVE CLINICAL TRIALS
Information below refers to biosimilar drug, Steqeyma

Comparative Trial Design and Study Demographics
Clinical studies conducted to support similarity between Steqeyma and the reference biologic drug, Stelara included:

- A comparative pharmacokinetic (PK) clinical Phase I study CT-P43 1.2 in healthy subjects
- A comparative efficacy and safety clinical Phase III study CT-P43 3.1 in patients with moderate to severe plaque psoriasis

An overview of the study design and demographic characteristics of patients enrolled in each clinical study are presented in Table 35.

Table 35 Summary of Trial Design and Patient Demographics (Intent-to-Treat Set)

Study Number	Study Design	Test Product(s); Route of Administration; Dosage Regimen; Duration	Study Subjects (n)	Mean Age (years)	Gender
CT-P43 1.2	Phase 1, randomized, double-blind, 3-arm, parallel group, single dose study to compare the PK and safety of three formulation of ustekinumab (Steqeyma, EU-approved Stelara and US-licensed Stelara) in healthy male subjects	Steqeyma, EU-approved Stelara or US-licensed Stelara 45 mg (45 mg/0.5 ml), a single PFS SC injection of study drug Up to Day 113	Randomized: 331 - Steqeyma: 114 - EU-approved Stelara: 110 - US-licensed Stelara: 107	Overall: 34.8 Steqeyma: 34.6 EU-approved Stelara: 33.5 US-licensed Stelara: 36.3	Overall: M 331 (100%)

CT-P43 3.1	Phase 3, double-blind, randomized, active controlled, parallel group study to compare efficacy and safety of Steqeyma and EU-approved Stelara in patients with moderate to severe plaque psoriasis	Steqeyma or EU-approved Stelara - Patients who weigh ≤100 kg: 45 mg (1 injection of 45 mg/0.5 ml) of study drug by SC injection via PFS - Patients who weigh >100 kg: 90 mg (2 injections of 45 mg/0.5 ml) of study drug by SC injection via PFS Patients receive an initial dose of study drug 45 or 90 mg administered subcutaneously, followed by another dose 4 weeks later, and then every 12 weeks thereafter up to Week 40. Up to Week 52	Randomized: 509 - Steqeyma: 256 - EU-approved Stelara: 253	Overall: 42.4 Steqeyma: 42.6 EU-approved Stelara: 42.2	Overall: M 334 (65.6%) F 175 (34.4%) Steqeyma: M 173 (68.4%) F 80 (31.6%) E-approved Stelara: M 161 (62.9%) F 95 (37.1%)

Comparative Bioavailability Studies
Pharmacokinetics
Comparative Pharmacokinetic Study CT-P43 1.2

Study CT-P43 1.2 is a randomized, double-blind, parallel-group, single-dose phase 1 study to compare the pharmacokinetics, safety and immunogenicity of three subcutaneous injection formulations of ustekinumab (Steqeyma, EU-approved Stelara, and US-licensed Stelara) in healthy male subjects.

A descriptive analysis and statistical analysis of primary serum PK parameters for ustekinumab are summarized for the PK Set in **Table 36.**

Table 36 Statistical Analysis of Primary Serum Pharmacokinetic Parameters for Ustekinumab (ANCOVA) in Study CT-P43 1.2 - PK Set

PK Parameter (unit)	Comparison	Treatment	n	Geometric LS Means[1]	Ratio of Geometric LS Means[1]	90% CI[1]
$AUC_{0\text{-}inf}$ (day*µg/mL)	Steqeyma	Test	109	204.22	108.31	(102.07, 114.94)
	EU-approved Stelara	Reference	105	188.54		
	Steqeyma	Test	109	204.22	100.56	

	US-licensed Stelara	Reference	105	203.09		(94.76, 106.71)
	EU-approved Stelara	Test	105	188.54	92.84	(87.44, 98.57)
	US-licensed Stelara	Reference	105	203.09		
C_{max} (µg/mL)	Steqeyma	Test	110	5.43	101.25	(95.14, 107.76)
	EU-approved Stelara	Reference	105	5.36		
	Steqeyma	Test	110	5.43	95.03	(89.29, 101.13)
	US-licensed Stelara	Reference	105	5.71		
	EU-approved Stelara	Test	105	5.36	93.85	(88.12, 99.96)
	US-licensed Stelara	Reference	105	5.71		

Note: An analysis of covariance (ANCOVA) was performed with the natural log-transformed PK parameters as the dependent variable, treatment as a fixed effect and study center and body weight at Day -1 as covariates.
[1] The least squares mean differences and 90% confidence intervals for the differences were exponentiated to provide estimates of the ratio of geometric least square means (Steqeyma/EU-approved Stelara, Steqeyma/US-licensed Stelara, and EU-approved Stelara/US-licensed Stelara) and 90% CIs for the ratios
CI: Confidence Interval. LS: Least Squares. n: The number of subjects with non-zero PK parameter values.

The 90% CIs for the geometric least square (LS) means ratios of $AUC_{0\text{-inf}}$ and C_{max} were within the pre-defined equivalence margin of 80% to 125% for all treatment comparisons, which indicated that ustekinumab exposure from Steqeyma were similar to those from EU-approved Stelara and US-licensed Stelara.

Comparative Safety and Efficacy
Efficacy
Comparative Efficacy and Safety Study CT-P43 3.1

Study CT-P43 3.1 is a randomized, active-controlled, double-blind, multicenter, Phase 3 study designed to evaluate efficacy, PK, quality of life, and overall safety including immunogenicity and biomarkers of Steqeyma compared with EU-approved Stelara in patients with moderate to severe plaque psoriasis, who are candidates for phototherapy or systemic therapy.

The primary efficacy endpoint was the mean percent improvement from baseline in PASI score at Week 12 and is summarized for the FAS and PPS in **Table 37.** The equivalence test was conducted with patients who were administered at least one 45 mg of study drug and had never received 90 mg of study drug in Treatment Period I. The primary efficacy analysis was conducted on the FAS using an ANCOVA model. A supportive analysis for the primary efficacy endpoint was conducted using the PPS.

The 95% CIs for the point estimate of treatment difference estimated using an ANCOVA model were entirely within the predefined equivalence margin of –15% to 15%. The results demonstrated therapeutic equivalence between the Steqeyma and EU-approved Stelara treatment groups in the mean percent improvement from baseline in PASI score at Week 12 for the FAS (95% CI: [-2.29, 4.16]). A similar result was observed in the PPS (95% CI: [-2.32, 4.07]).

Table 37 Statistical Analysis of Mean Percent Improvement from Baseline in PASI Score at Week 12 (ANCOVA) in Study CT-P43 3.1 (FAS and PPS)

Treatment Group	n	LS Mean (SE)	Estimate of Treatment Difference (%)	95% CI of Treatment Difference (%)

FAS				
Steqeyma	198	78.26 (2.054)	0.94	(-2.29, 4.16)
EU-approved Stelara	194	77.33 (2.049)		
PPS				
Steqeyma	195	78.41 (2.038)	0.87	(-2.32, 4.07)
EU-approved Stelara	193	77.54 (2.025)		

Note: An ANCOVA was performed with the treatment as a fixed effect and country, baseline body weight, prior biologic use approved for psoriasis treatment and baseline PASI score as covariates. Adjusted LS means and SE, estimate of treatment difference [Steqeyma – EU-approved Stelara] and 95% CI calculated from the ANCOVA model. Abbreviation: LS, least squares; n, the number of patients administered each treatment; SE, standard error

Safety

There were no notable differences in the incidence or nature of adverse events between the Steqeyma and EU-/US-Stelara treatment groups across Studies CT-P43 3.1, CT-P43 1.2 and CT-P43 1.1, and the safety profile of each treatment group was in line with the known safety profile of Stelara. As a result, the analysis of adverse events obtained in the clinical studies with Steqeyma illustrated that the benefit-risk profile of Steqeyma is similar to that of Stelara.

Immunogenicity

The immunogenicity of Steqeyma was evaluated in healthy male subjects in Studies CT-P43 1.1 and CT-P43 1.2 and plaque psoriasis patients in Study CT-P43 3.1 using the state-of-the-art and validated immunogenicity assays in accordance with the current international regulatory guidelines.
The proportions of subjects who had at least 1 post-treatment ADA positive result and NAb positive result showed that Steqeyma appeared to be less immunogenic than the reference products in both study with healthy subjects (Study 1.1 and 1.2) and the patients with plaque psoriasis (Study 3.1). Although Steqeyma showed lower immunogenicity results compared to Stelara, the impact of ADA incidence and titer of Steqeyma on the clinical outcome was similar to that of Stelara. Development of antibodies to ustekinumab were associated with reduced serum concentrations but have no significant impact on efficacy and safety.

NON-CLINICAL INFORMATION

Non clinical data reveal no special hazard (e.g. organ toxicity) for humans based on studies of repeated dose toxicity and developmental and reproductive toxicity, including safety pharmacology evaluations. In developmental and reproductive toxicity studies in cynomolgus monkeys, neither adverse effects on male fertility indices nor birth defects or developmental toxicity were observed. No adverse effects on female fertility indices were observed using an analogous antibody to IL 12/23 in mice.

Dose levels in animal studies were up to approximately 45 fold higher than the highest equivalent dose intended to be administered to psoriasis patients and resulted in peak serum concentrations in monkeys that were more than 100 fold higher than observed in humans. Carcinogenicity studies were not performed with ustekinumab due to the lack of appropriate models for an antibody with no cross reactivity to rodent IL 12/23 p40.

PHARMACEUTICAL PARTICULARS

List of Excipients

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

Incompatibilities

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

Shelf life

18 months

Individual vials may be stored at room temperature up to 30 °C for a maximum single period of up to 15 days in the original carton in order to protect from light. Record the date when the vial is first removed from the refrigerator and the discard date in the space provided on the outer carton. The discard date must not exceed the original expiry date printed on the carton. Once a vial has been stored at room temperature (up to 30 °C), it should not be returned to the refrigerator. Discard the vial if not used within 15 days at room temperature storage or by the original expiry date, whichever is earlier.

Special precautions for storage

Store in a refrigerator (2 °C – 8 °C). Do not freeze.
Keep the vial in the outer carton in order to protect from light.
If needed, individual vials may be stored at room temperature up to 30 °C.

Nature and contents of container

0.5 mL solution in a type I glass 3 mL vial closed with a coated butyl rubber stopper.
Steqeyma is available in a pack of 1 vial.

Special precautions for disposal and other handling

The solution in the Steqeyma vial should not be shaken. The solution should be visually inspected for particulate matter or discolouration prior to subcutaneous administration. The solution is clear to slightly opalescent, colourless to pale yellow and may contain a few small translucent or white particles of protein. This appearance is not unusual for proteinaceous solutions. The medicinal product should not be used if the solution is discoloured or cloudy, or if foreign particulate matter is present. Before administration, Steqeyma should be allowed to reach room temperature (approximately half an hour). Detailed instructions for administration are provided in the package leaflet.

Steqeyma does not contain preservatives; therefore any unused medicinal product remaining in the vial should not be used. Steqeyma is supplied as a sterile, single-use vial. The vial must never be re-used. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

When using the single-dose vial, a 1 mL syringe with a 27 gauge, ½ inch (13 mm) needle is recommended.

PRODUCT REGISTRATION HOLDER

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BATCH RELEASER

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