SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

IMULDOSA® 45 mg solution for injection in pre-filled syringe

ustekinumab

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

Excipient with known effect

Each unit volume contains 0.02 mg of polysorbate 80; which is equivalent to 0.02 mg per 45 mg dose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe (solution for injection).

The solution is colourless to slightly yellow and clear to slightly opalescent.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Plaque psoriasis
IMULDOSA 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 section 5.1).

Paediatric plaque psoriasis
IMULDOSA 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 section 5.1).

Psoriatic arthritis (PsA)
IMULDOSA, 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 section 5.1).

Adult Crohn's Disease
IMULDOSA 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

Paediatric Crohn's Disease

IMULDOSA is indicated for the treatment of moderately to severely active Crohn's disease in paediatric patients weighing at least 40 kg, who have had an inadequate response to, or were intolerant to either conventional or biologic therapy.

Ulcerative colitis
IMULDOSA 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.

4.2 Posology and method of administration

IMULDOSA is intended for use under the guidance and supervision of physicians experienced in the diagnosis and treatment of conditions for which IMULDOSA is indicated.

Posology

Plaque psoriasis
The recommended posology of IMULDOSA 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 (see section 5.1, Table 3).

Psoriatic arthritis (PsA)
The recommended posology of IMULDOSA 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.

Elderly (≥ 65 years)
No dose adjustment is needed for elderly patients (see section 4.4).

Renal and hepatic impairment
Ustekinumab has not been studied in these patient populations. No dose recommendations can be made.

Paediatric population
The safety and efficacy of ustekinumab in children with psoriasis less than 6 years of age or in children with psoriatic arthritis less than 18 years of age have not yet been established.

Paediatric plaque psoriasis (6 years and older)
The recommended dose of IMULDOSA for the paediatric population with a body weight over 60 kg is shown below (Table 1). IMULDOSA should be administered at Weeks 0 and 4, then every 12 weeks thereafter.

Table 1: Recommended dose of IMULDOSA for paediatric psoriasis

Body weight at the time of dosing	**Recommended Dose**
< 60 kg*	-
≥ 60 - ≤ 100 kg	45 mg
> 100 kg	90 mg
* IMULDOSA is not available for patients that require less than a full 45 mg dose. If an alternative dose is required, other ustekinumab products offering such an option should be used.	

There is no dose form for IMULDOSA that allows weight-based dosing for paediatric patients below 60 kg. Patients weighing less than 60 kg should be accurately dosed on a mg/kg basis using another ustekinumab product, 45 mg solution for injection in vials offering weight-based dosing instead.

Consideration should be given to discontinuing treatment in patients who have

shown no response up to 28 weeks of treatment.

Adult Crohn’s Disease and Ulcerative Colitis
In the treatment regimen, the first dose of IMULDOSA is administered intravenously. For the posology of the intravenous dosing regimen, see section 4.2 of the IMULDOSA 130 mg concentrate for solution for infusion SmPC.

The first subcutaneous administration of 90 mg IMULDOSA 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 section 5.1).

Patients who lose response on dosing every 12 weeks may benefit from an increase in dosing frequency to every 8 weeks (see section 5.1, section 5.2).

Patients may subsequently be dosed every 8 weeks or every 12 weeks according to clinical judgment (see section 5.1).

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

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

In Crohn’s disease or ulcerative colitis, if therapy 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 (see section 4.4).

Renal and hepatic impairment
Ustekinumab has not been studied in these patient populations. No dose recommendations can be made.

Paediatric population

Paediatric Crohn's disease (patients weighing at least 40 kg)
In the treatment regimen, the first dose of IMULDOSA is administered intravenously. For the posology of the intravenous dosing regimen, see section 4.2 of the IMULDOSA 130 mg Concentrate for solution for infusion SmPC.

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

Patients who lose response on dosing every 12 weeks may benefit from an increase in dosing frequency to every 8 weeks (see section 5.1, section 5.2).

Patients may subsequently be dosed every 8 weeks or every 12 weeks according to clinical judgment (see section 5.1).

Consideration should be given to discontinuing treatment in patients who show no evidence of therapeutic benefit 16 weeks after the IV induction dose or 16 weeks after dose adjustment.

Immunomodulators, 5-aminosalicylate (5-ASA) compounds, antibiotics, and/or corticosteroids may be continued during treatment with IMULDOSA. In patients who have responded to treatment with IMULDOSA, these medications maybe reduced or discontinued in accordance with standard of care.

The safety and efficacy of IMULDOSA in treatment of Crohn's disease for paediatric patients weighing less than 40 kg or ulcerative colitis have not yet been established. No data are available.

Method of administration

IMULDOSA 45 mg pre-filled syringes 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 IMULDOSA 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 IMULDOSA 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 section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Clinically important, active infection (e.g. active tuberculosis; see section 4.4).

4.4 Special warnings and precautions for use

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 4.8).

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 IMULDOSA in patients with a chronic infection or a history of recurrent infection (see section 4.3).

Prior to initiating treatment with IMULDOSA, patients should be evaluated for tuberculosis infection. IMULDOSA must not be given to patients with active tuberculosis (see section 4.3). Treatment of latent tuberculosis infection should be initiated prior to administering IMULDOSA. Anti-tuberculosis therapy should also be considered prior to initiation of IMULDOSA in patients with a history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. Patients receiving IMULDOSA 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 IMULDOSA 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 4.8). 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 IMULDOSA 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 4.8).

Systemic and respiratory hypersensitivity reactions
Systemic
Serious hypersensitivity reactions have been reported in the post-marketing 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 IMULDOSA should be discontinued (see section 4.8).

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 4.8).

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 IMULDOSA.

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 IMULDOSA. 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 IMULDOSA 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 4.5 and 4.6). 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 IMULDOSA may receive concurrent inactivated or non-live vaccinations.

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

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 IMULDOSA or when transitioning from other immunosuppressive biologics (see section 4.5).

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 section 4.8). 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. IMULDOSA 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 aged 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
IMULDOSA contains 0.02 mg polysorbate 80 (E433) in each unit volume, which is equivalent to 0.02 mg per 45 mg dose.

Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Live vaccines should not be given concurrently with IMULDOSA.

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 4.4 and 4.6). 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 5.2).

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 4.4).

4.6 Fertility, pregnancy and lactation

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 IMULDOSA 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 5.3). However, the available clinical experience is limited. As a precautionary measure, it is preferable to avoid the use of IMULDOSA 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 4.4 and 4.5). 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 IMULDOSA must be made taking into account the benefit of breast-feeding to the child and the benefit of IMULDOSA therapy to the woman.

Fertility

The effect of ustekinumab on human fertility has not been evaluated (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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 4.4). 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 ABSIMKY 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 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) and 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 4.4, 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 4.4).

In the controlled and non-controlled periods of psoriasis, psoriatic arthritis and Crohn's disease 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 years 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 ustekinumab exposure in 6,710 patients, the median follow-up was 1.2 years; 1.7 years for psoriatic disease studies, and 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 4.4).

Hypersensitivity reactions
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 4.4).

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.

Paediatric patients weighing at least 40 kg with Crohn's disease
The safety of ustekinumab has been studied in one phase 1 and one phase 3 study of paediatric patients with moderately to severely active Crohn's disease up to week 240 and week 52, respectively. In general, the safety profile in this cohort (n = 71) was similar to that seen in previous studies in adults with Crohn's disease.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, interleukin inhibitors, ATC code:

L04AC05

IMULDOSA is a biosimilar medicinal product. Detailed information is available on the MHRA website.

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-12R 1 receptor protein expressed on the surface of immune cells. Ustekinumab cannot bind to IL-12 or IL-23 that is already bound to IL-12R 1 cell surface receptors. Thus, ustekinumab is not likely to contribute to complement- or antibody-mediated cytotoxicity of cells with IL-12 and/or IL-23 receptors. IL-12 and IL-23 are heterodimeric cytokines secreted by activated antigen presenting cells, such as macrophages and dendritic cells, 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 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 faecal calprotectin during 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 faecal calprotectin during the induction phase, which was 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 adult patients developed protective levels of anti-pneumococcal and anti-tetanus antibodies and antibody titres were similar among ustekinumab-treated and control patients.

Clinical efficacy

Plaque psoriasis (Adults)

The safety and efficacy of ustekinumab was assessed in 1,996 patients in two randomised, double-blind, placebo-controlled studies in patients with moderate to severe plaque psoriasis and who were candidates for phototherapy or systemic therapy. In addition, a randomised, blinded assessor, active-controlled study compared ustekinumab and etanercept in patients with moderate to severe plaque psoriasis who had had an inadequate response to, intolerance to, or contraindication to ciclosporin, MTX, or PUVA.

Psoriasis Study 1 (PHOENIX 1) evaluated 766 patients. 53% of these patients were either non-responsive, intolerant, or had a contraindication to other systemic therapy. Patients randomised to ustekinumab received 45 mg or 90 mg doses at Weeks 0 and 4 and followed by the same dose every 12 weeks. Patients randomised 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 dosing every 12 weeks. Patients originally randomised to ustekinumab who achieved Psoriasis Area and Severity Index 75 response (PASI improvement of at least 75% relative to baseline) at both Weeks 28 and 40 were re-randomised to receive ustekinumab every 12 weeks or to placebo (i.e., withdrawal of therapy). Patients who were re-randomised 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. All patients were followed for up to 76 weeks following first administration of study treatment.

Psoriasis Study 2 (PHOENIX 2) evaluated 1,230 patients. 61% of these patients were either non-responsive, intolerant, or had a contraindication to other systemic therapy. Patients randomised to ustekinumab received 45 mg or 90 mg doses at Weeks 0 and 4 followed by an additional dose at 16 weeks. Patients randomised to receive placebo at Weeks 0 and 4 crossed over to receive ustekinumab (either 45 mg or 90 mg) at Weeks 12 and 16. All patients were followed for up to 52 weeks following first administration of study treatment.

Psoriasis Study 3 (ACCEPT) evaluated 903 patients with moderate to severe psoriasis who inadequately responded to, were intolerant to, or had a contraindication to other systemic therapy and compared the efficacy of ustekinumab to etanercept and evaluated the safety of ustekinumab and etanercept. During the 12-week active-controlled portion of the study, patients were randomised to receive etanercept (50 mg twice a week), ustekinumab 45 mg at Weeks 0 and 4, or ustekinumab 90 mg at Weeks 0 and 4.

Baseline disease characteristics were generally consistent across all treatment groups in Psoriasis Studies 1 and 2 with a median baseline PASI score from 17 to 18, median baseline Body Surface Area (BSA) ≥ 20, and median Dermatology Life Quality Index (DLQI) range from 10 to 12. Approximately one third (Psoriasis Study 1) and one quarter (Psoriasis Study 2) of subjects had Psoriatic Arthritis (PsA). Similar disease severity was also seen in Psoriasis Study 3.

The primary endpoint in these studies was the proportion of patients who achieved PASI 75 response from baseline at week 12 (see Tables 3 and 4).

Table 3: Summary of clinical response in Psoriasis Study 1 (PHOENIX 1) and Psoriasis Study 2 (PHOENIX 2)

	Week 12 2 doses (week 0 and week 4)			Week 28 3 doses (week 0, week 4 and week 16)	
	PBO	45 mg	90 mg	45 mg	90 mg
Psoriasis Study 1					
Number of patients randomised	255	255	256	250	243
PASI 50 response N (%)	26 (10%)	213 (84%)[a]	220 (86%)[a]	228 (91%)	234 (96%)
PASI 75 response N (%)	8 (3%)	171 (67%)[a]	170 (66%)[a]	178 (71%)	191 (79%)
PASI 90 response N (%)	5 (2%)	106 (42%)[a]	94 (37%)[a]	123 (49%)	135 (56%)
PGA[b] of cleared or minimal N (%)	10 (4%)	151 (59%)[a]	156 (61%)[a]	146 (58%)	160 (66%)
Number of patients ≤ 100 kg	166	168	164	164	153
PASI 75 response N (%)	6 (4%)	124 (74%)	107 (65%)	130 (79%)	124 (81%)
Number of patients > 100 kg	89	87	92	86	90
PASI 75 response N (%)	2 (2%)	47 (54%)	63 (68%)	48 (56%)	67 (74%)
Psoriasis Study 2					
Number of patients randomised	410	409	411	397	400
PASI 50 response N (%)	41 (10%)	342 (84%)[a]	367 (89%)[a]	369 (93%)	380 (95%)
PASI 75 response N (%)	15 (4%)	273 (67%)[a]	311 (76%)[a]	276 (70%)	314 (79%)
PASI 90 response N (%)	3 (1%)	173 (42%)[a]	209 (51%)[a]	178 (45%)	217 (54%)
PGA[b] of cleared or minimal N (%)	18 (4%)	277 (68%)[a]	300 (73%)[a]	241 (61%)	279 (70%)
Number of patients ≤ 100 kg	290	297	289	287	280
PASI 75 response N (%)	12 (4%)	218 (73%)	225 (78%)	217 (76%)	226 (81%)
Number of patients > 100 kg	120	112	121	110	119
PASI 75 response N (%)	3 (3%)	55 (49%)	86 (71%)	59 (54%)	88 (74%)

[a] $p < 0.001$ for ustekinumab 45 mg or 90 mg in comparison with placebo (PBO).
[b] PGA = Physician Global Assessment

Table 4: Summary of clinical response at week 12 in Psoriasis Study 3 (ACCEPT)

	Psoriasis Study 3		
	Etanercept 24 doses (50 mg twice a week)	Ustekinumab 2 doses (week 0 and week 4)	
		45 mg	90 mg
Number of patients randomised	347	209	347

PASI 50 response N (%)	286 (82%)	181 (87%)	320 (92%)[a]
PASI 75 response N (%)	197 (57%)	141 (67%)[b]	256 (74%)[a]
PASI 90 response N (%)	80 (23%)	76 (36%)[a]	155 (45%)[a]
PGA of cleared or minimal N (%)	170 (49%)	136 (65%)[a]	245 (71%)[a]
Number of patients ≤ 100 kg	251	151	244
PASI 75 response N (%)	154 (61%)	109 (72%)	189 (77%)
Number of patients > 100 kg	96	58	103
PASI 75 response N (%)	43 (45%)	32 (55%)	67 (65%)

[a] $p < 0.001$ for ustekinumab 45 mg or 90 mg in comparison with etanercept.
[b] $p = 0.012$ for ustekinumab 45 mg in comparison with etanercept.

In Psoriasis Study 1 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. At 1 year (week 52), 89% of patients re-randomised to maintenance treatment were PASI 75 responders compared with 63% of patients re-randomised to placebo (treatment withdrawal) ($p < 0.001$). At 18 months (week 76), 84% of patients re-randomised to maintenance treatment were PASI 75 responders compared with 19% of patients re-randomised to placebo (treatment withdrawal). At 3 years (week 148), 82% of patients re-randomised to maintenance treatment were PASI 75 responders. At 5 years (week 244), 80% of patients re-randomised to maintenance treatment were PASI 75 responders.

In patients re-randomised to placebo, and who reinitiated their original ustekinumab treatment regimen after loss of ≥ 50% of PASI improvement 85% regained PASI 75 response within 12 weeks after re-initiating therapy.

In Psoriasis Study 1, at week 2 and week 12, significantly greater improvements from baseline were demonstrated in the DLQI in each ustekinumab treatment group compared with placebo. The improvement was sustained through week 28. Similarly, significant improvements were seen in Psoriasis Study 2 at week 4 and 12, which were sustained through week 24. In Psoriasis Study 1, improvements in nail psoriasis (Nail Psoriasis Severity Index), in the physical and mental component summary scores of the SF-36 and in the Itch Visual Analogue Scale (VAS) were also significant in each ustekinumab treatment group compared with placebo. In Psoriasis Study 2, the Hospital Anxiety and Depression Scale (HADS) and Work Limitations Questionnaire (WLQ) were also significantly improved in each ustekinumab treatment group compared with placebo.

Psoriatic arthritis (PsA) (Adults)
Ustekinumab has been shown to improve signs and symptoms, physical function and health-related quality of life, and reduce the rate of progression of peripheral joint damage in adult patients with active PsA.

The safety and efficacy of ustekinumab was assessed in 927 patients in two randomised, double-blind, placebo-controlled studies in patients with active PsA (≥ 5 swollen joints and ≥ 5 tender joints) despite non-steroidal anti-inflammatory (NSAID) or disease modifying antirheumatic (DMARD) therapy. Patients in these studies had a diagnosis of PsA for at least 6 months. Patients with each subtype of PsA were enrolled, including polyarticular arthritis with no evidence of rheumatoid nodules (39%), spondylitis with peripheral arthritis (28%), asymmetric peripheral arthritis (21%), distal interphalangeal involvement (12%) and arthritis mutilans (0.5%). Over 70% and 40% of the patients in both studies had enthesitis and dactylitis at baseline, respectively. Patients were randomised to receive treatment with ustekinumab 45 mg, 90 mg, or placebo subcutaneously at Weeks 0 and 4 followed by every 12 weeks (q12w) dosing. Approximately 50% of patients continued on stable doses of MTX (≤ 25 mg/week).

In PsA Study 1 (PSUMMIT I) and PsA Study 2 (PSUMMIT II), 80% and 86% of the patients, respectively, had been previously treated with DMARDs. In Study 1 previous treatment with anti-tumour necrosis factor (TNF)α agent was not allowed. In Study 2, the majority of patients (58%, n = 180) had been previously treated with one or more anti-TNFα agent(s), of whom over 70% had discontinued their anti-TNFα treatment for lack of efficacy or intolerance at any time.

Signs and symptoms
Treatment with ustekinumab resulted in significant improvements in the measures of disease activity compared to placebo at week 24. The primary endpoint was the percentage of patients who achieved American College of Rheumatology (ACR) 20 response at week 24. The key efficacy results are shown in Table 5 below.

Table 5: Number of patients who achieved clinical response in Psoriatic arthritis Study 1 (PSUMMIT I) and Study 2 (PSUMMIT II) at week 24

	Psoriatic arthritis Study 1			**Psoriatic arthritis Study 2**		
	PBO	**45 mg**	**90 mg**	**PBO**	**45 mg**	**90 mg**
Number of patients randomised	**206**	**205**	**204**	**104**	**103**	**105**
ACR 20 response, N (%)	47 (23%)	87 (42%)[a]	101 (50%)[a]	21 (20%)	45 (44%)[a]	46 (44%)[a]
ACR 50 response, N (%)	18 (9%)	51 (25%)[a]	57 (28%)[a]	7 (7%)	18 (17%)[b]	24 (23%)[a]
ACR 70 response, N (%)	5 (2%)	25 (12%)[a]	29 (14%)[a]	3 (3%)	7 (7%)[c]	9 (9%)[c]
Number of patients with ≥ 3% BSA[d]	146	145	149	80	80	81
PASI 75 response, N (%)	16 (11%)	83 (57%)[a]	93 (62%)[a]	4 (5%)	41 (51%)[a]	45 (56%)[a]
PASI 90 response, N (%)	4 (3%)	60 (41%)[a]	65 (44%)[a]	3 (4%)	24 (30%)[a]	36 (44%)[a]
Combined PASI 75 and ACR 20 response, N (%)	8 (5%)	40 (28%)[a]	62 (42%)[a]	2 (3%)	24 (30%)[a]	31 (38%)[a]
Number of patients ≤ 100 kg	154	153	154	74	74	73
ACR 20 response, N (%)	39 (25%)	67 (44%)	78 (51%)	17 (23%)	32 (43%)	34 (47%)
Number of patients with ≥ 3% BSA[d]	105	105	111	54	58	57
PASI 75 response, N (%)	14 (13%)	64 (61%)	73 (66%)	4 (7%)	31 (53%)	32 (56%)
Number of patients > 100 kg	52	52	50	30	29	31
ACR 20 response, N (%)	8 (15%)	20 (38%)	23 (46%)	4 (13%)	13 (45%)	12 (39%)
Number of patients with ≥ 3% BSA[d]	41	40	38	26	22	24
PASI 75 response, N (%)	2 (5%)	19 (48%)	20 (53%)	0	10 (45%)	13 (54%)

[a] $p < 0.001$
[b] $p < 0.05$
[c] p = NS
[d] Number of patients with ≥ 3% BSA psoriasis skin involvement at baseline

ACR 20, 50 and 70 responses continued to improve or were maintained through week 52 (PsA Study 1 and 2) and week 100 (PsA Study 1). In PsA Study 1, ACR 20 responses at week 100 were achieved by 57% and 64%, for 45 mg and 90 mg, respectively. In PsA Study 2, ACR 20 responses at week 52 were achieved by 47% and 48%, for 45 mg and 90 mg, respectively.

The proportion of patients achieving a modified PsA response criteria (PsARC) response was also significantly greater in the ustekinumab groups compared to placebo at week 24. PsARC responses were maintained through weeks 52 and 100. A higher proportion of patients treated with ustekinumab who had spondylitis with peripheral arthritis as their primary presentation, demonstrated 50 and 70 percent improvement in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores compared with placebo at week 24.

Responses observed in the ustekinumab treated groups were similar in patients receiving and not receiving concomitant MTX, and were maintained through weeks 52 and 100. Patients previously treated with anti-TNFα agents who received ustekinumab achieved a greater response at week 24 than patients receiving placebo (ACR 20 response at week 24 for 45 mg and 90 mg was 37% and 34%, respectively, compared with placebo 15%; $p < 0.05$), and responses were maintained through week 52.

For patients with enthesitis and/or dactylitis at baseline, in PsA Study 1 significant improvement in enthesitis and dactylitis score was observed in the ustekinumab groups compared with placebo at week 24. In PsA Study 2 significant improvement in enthesitis score and numerical improvement (not statistically significant) in dactylitis score was observed in the ustekinumab 90 mg group compared with placebo at week 24. Improvements in enthesitis score and dactylitis score were maintained through weeks 52 and 100.

Radiographic Response

Structural damage in both hands and feet was expressed as change in total van der Heijde-Sharp score (vdH-S score), modified for PsA by addition of hand distal interphalangeal joints, compared to baseline. A pre-specified integrated analysis combining data from 927 subjects in both PsA Study 1 and 2 was performed. Ustekinumab demonstrated a statistically significant decrease in the rate of progression of structural damage compared to placebo, as measured by change from baseline to week 24 in the total modified vdH-S score (mean ± SD score was 0.97 ± 3.85 in the placebo group compared with 0.40 ± 2.11 and 0.39 ± 2.40 in the ustekinumab 45 mg ($p < 0.05$) and 90 mg ($p < 0.001$) groups, respectively). This effect was driven by PsA Study 1. The effect is considered demonstrated irrespective of concomitant MTX use, and was maintained through Weeks 52 (integrated analysis) and 100 (PsA Study 1).

Physical function and health-related quality of life

Ustekinumab-treated patients showed significant improvement in physical function as assessed by the Disability Index of the Health Assessment Questionnaire (HAQ-DI) at week 24. The proportion of patients achieving a clinically meaningful ≥ 0.3 improvement in HAQ-DI score from baseline was also significantly greater in the ustekinumab groups when compared with placebo. Improvement in HAQ-DI score from baseline was maintained through Weeks 52 and 100.

There was significant improvement in DLQI scores in the ustekinumab groups as compared with placebo at week 24, which was maintained through weeks 52 and 100. In PsA Study 2 there was a significant improvement in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scores in the ustekinumab groups when compared

with placebo at week 24. The proportion of patients achieving a clinically significant improvement in fatigue (4 points in FACIT-F) was also significantly greater in the ustekinumab groups compared with placebo. Improvements in FACIT scores were maintained through week 52.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with ustekinumab in one or more subsets of the paediatric population with juvenile idiopathic arthritis (see section 4.2 for information on paediatric use).

Paediatric plaque psoriasis

Ustekinumab has been shown to improve signs and symptoms, and health-related quality of life in paediatric patients 6 years and older with plaque psoriasis.

Adolescent patients (12-17 years)

The efficacy of ustekinumab was studied in 110 paediatric patients aged 12 to 17 years with moderate to severe plaque psoriasis in a multicentre, phase 3, randomised, double-blind, placebo-controlled study (CADMUS). Patients were randomised to receive either placebo (n = 37), or the recommended dose of ustekinumab (see section 4.2; n = 36) or half of 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.

Patients with PASI ≥ 12, PGA ≥ 3 and BSA involvement of at least 10%, who were candidates for systemic therapy or phototherapy, were eligible for the study. Approximately 60% of the patients had prior exposure to conventional systemic therapy or phototherapy. Approximately 11% of the patients had prior exposure to biologics.

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 scale score of PedsQL (Paediatric 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 6).

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 by week 12. Improvements in PGA, PASI, CDLQI and PedsQL were maintained through week 52 (Table 6).

Table 6: Summary of primary and secondary endpoints at week 12 and week 52

Paediatric psoriasis study (CADMUS) (Age 12-17)			
	Week 12		**Week 52**
	Placebo	Recommended dose of Ustekinumab	Recommended dose of Ustekinumab
	N (%)	N (%)	N (%)
Patients randomised	37	36	35
PGA			
PGA of cleared (0) or minimal (1)	2 (5.4%)	25 (69.4%)[a]	20 (57.1%)

PGA of Cleared (0)	1 (2.7%)	17 (47.2%)[a]	13 (37.1%)
PASI			
PASI 75 responders	4 (10.8%)	29 (80.6%)[a]	28 (80.0%)
PASI 90 responders	2 (5.4%)	22 (61.1%)[a]	23 (65.7%)
PASI 100 responders	1 (2.7%)	14 (38.9%)[a]	13 (37.1%)
CDLQI			
CDLQI of 0 or 1[b]	6 (16.2%)	18 (50.0%)[c]	20 (57.1%)
PedsQL			
Change from baseline Mean (SD)[d]	3.35 (10.04)	8.03 (10.44)[e]	7.26 (10.92)

[a] $p < 0.001$

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

[c] $p = 0.002$

[d] PedsQL: The PedsQL Total Scale Score is a general health-related quality of life measure developed for use in children and adolescent populations. For the placebo group at week 12, N = 36

[e] $p = 0.028$

During the placebo-controlled period through week 12, the efficacy of both the recommended and half of the recommended dose groups were generally comparable at the primary endpoint (69.4% and 67.6% respectively) although there was evidence of a dose response for higher level efficacy criteria (e.g. PGA of cleared (0), PASI 90). Beyond week 12, efficacy was generally higher and better sustained in the recommended dose group compared with half of the recommended dosage group in which a modest loss of efficacy was more frequently observed toward the end of each 12 week dosing interval. The safety profiles of the recommended dose and half of the recommended dose were comparable.

Children (6-11 years)

The efficacy of ustekinumab was studied in 44 paediatric patients aged 6 to 11 years with moderate to severe plaque psoriasis in an open label, single-arm, multicentre, phase 3, study (CADMUS Jr.). Patients were treated with the recommended dose of ustekinumab (see section 4.2; n = 44) by subcutaneous injection at weeks 0 and 4 followed by every 12 week (q12w) dosing.

Patients with PASI $\geq$ 12, PGA $\geq$ 3 and BSA involvement of at least 10%, who were candidates for systemic therapy or phototherapy, were eligible for the study. Approximately 43% of the patients had prior exposure to conventional systemic therapy or phototherapy. Approximately 5% of the patients had prior exposure to biologics.

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, subjects treated with ustekinumab showed clinically meaningful improvements in their psoriasis and health-related quality of life (Table 7).

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) at week 12 was 77.3%. Efficacy (defined as PGA 0 or 1) was observed as early as the first post-baseline visit at week 4 and the proportion of subjects who achieved a PGA score of 0 or 1 increased through week 16 and then remained relatively stable through week 52. Improvements in PGA, PASI, and CDLQI were maintained through week 52 (Table 7).

Table 7: Summary of primary and secondary endpoints at week 12 and week 52

Paediatric psoriasis study (CADMUS Jr.) (Age 6-11)		
	Week 12	**Week 52**
	Recommended dose of Ustekinumab	Recommended dose of Ustekinumab
	N (%)	N (%)
Patients enrolled	44	41
PGA		
PGA of cleared (0) or minimal (1)	34 (77.3%)	31 (75.6%)
PGA of cleared (0)	17 (38.6%)	23 (56.1%)
PASI		
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%)
CDLQI[a]		
Patients with a CDLQI > 1 at baseline	(N=39)	(N=36)
CDLQI of 0 or 1	24 (61.5%)	21 (58.3%)

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

Crohn's Disease

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

The induction studies included 1409 (UNITI-1, n = 769; UNITI-2 n = 640) patients. The primary endpoint for both induction studies was the proportion of subjects in clinical response (defined as a reduction in CDAI score of ≥ 100 points) at week 6. Efficacy data were collected and analysed through week 8 for both studies. Concomitant doses of oral corticosteroids, immunomodulators, aminosalicylates and antibiotics were permitted and 75% of patients continued to receive at least one of these medications. In both studies, patients were randomised to receive a single intravenous administration of either the recommended tiered dose of approximately 6 mg/kg (see section 4.2 of the IMULDOSA 130 mg concentrate for solution for infusion SmPC), a fixed dose of 130 mg ustekinumab, or placebo at week 0.

Patients in UNITI-1 had failed or were intolerant to prior anti-TNFα therapy. Approximately 48% of the patients had failed 1 prior anti-TNF therapy and 52% had failed 2 or 3 prior anti-TNFα therapies. In this study, 29.1% of the patients had an inadequate initial response (primary non-responders), 69.4% responded but 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, including corticosteroids or immunomodulators, and were either anti-TNF-α naïve (68.6%) or had previously received but not failed anti-TNFα therapy (31.4%).

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

Table 8: Induction of Clinical Response and Remission in UNITI-1 and UNITI 2

	UNITI-1*		**UNITI-2****	
	Placebo N = 247	**Recommended dose of ustekinumab N = 249**	**Placebo N = 209**	**Recommended dose of 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] $p < 0.01$

The maintenance study (IM-UNITI), evaluated 388 patients who achieved 100 point clinical response at week 8 of induction with ustekinumab in studies UNITI-1 and UNITI-2. Patients were randomised 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 (for recommended maintenance posology, see section 4.2).

Significantly higher proportions of patients maintained clinical remission and response in the ustekinumab treated groups compared to the placebo group at week 44 (see Table 9).

Table 9: 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]
Clinical Remission in patients:			
in remission at the start of maintenance therapy	46% (36/79)	67% (52/78)[a]	56% (44/78)
who entered from study CRD3002[‡]	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)
who entered from study CRD3001[§]	26% (16/61)	41% (23/56)	39% (22/57)

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 randomised to receive placebo at the start of maintenance therapy.

† Patients who were in 100 point clinical response to ustekinumab at start of maintenance therapy

‡ Patients who failed conventional therapy but not anti-TNFα therapy

§ Patients who are anti-TNFα refractory/intolerant

[a] $p < 0.01$

[b] $p < 0.05$

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

In IM-UNITI, 29 of 129 patients did not maintain response to ustekinumab when treated every 12 weeks and were allowed to dose adjust to 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 dose adjustment.

Patients who were not in clinical response to ustekinumab induction at week 8 of the UNITI-1 and UNITI-2 induction studies (476 patients) entered into the non-randomised portion of the maintenance study (IM-UNITI) and received a 90 mg subcutaneous injection of ustekinumab at that time. 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 maintained response (68.1%) and achieved remission (50.2%) at week 44, at proportions that were similar to the patients who initially responded to ustekinumab induction.

Of 131 patients who responded to ustekinumab induction, and were randomised to the placebo group at the start of the maintenance study, 51 subsequently lost response and received 90 mg ustekinumab subcutaneously every 8 weeks. The majority of patients who lost response and resumed ustekinumab did so within 24 weeks of the induction infusion. Of these 51 patients, 70.6% achieved clinical response and 39.2% percent achieved clinical remission 16 weeks after receiving the first subcutaneous dose of ustekinumab.

In IM-UNITI, patients who completed the study through week 44 were eligible to continue treatment in a study extension. Among the 567 patients who entered on and were treated with ustekinumab in the study extension, clinical remission and response were generally maintained through week 252 for both patients who failed TNF-therapies and those who failed conventional therapies.

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

Endoscopy

Endoscopic appearance of the mucosa was evaluated in 252 patients with eligible baseline endoscopic disease activity in a substudy. The primary endpoint was change from baseline in Simplified Endoscopic Disease Severity Score for Crohn's Disease (SES-CD), a composite score across 5 ileo-colonic segments of presence/size of ulcers, proportion of mucosal surface covered by ulcers, proportion of mucosal surface affected by any other lesions and presence/type of narrowing/strictures. At week 8, after a single intravenous induction dose, the change in SES-CD score was greater in the ustekinumab group (n = 155, mean change = -2.8) than in the placebo group (n = 97, mean change = -0.7, p = 0.012).

Fistula Response

In a subgroup of patients with draining fistulas at baseline (8.8%; n = 26), 12/15 (80%) of ustekinumab-treated patients achieved a fistula response over 44 weeks (defined as ≥ 50% reduction from baseline of the induction study in the number of draining fistulas) compared to 5/11 (45.5%) exposed to placebo.

Health-related quality of life
Health-related quality of life was assessed by Inflammatory Bowel Disease Questionnaire (IBDQ) and SF-36 questionnaires. At week 8, patients receiving ustekinumab showed statistically significantly greater and clinically meaningful improvements on IBDQ total score and SF-36 Mental Component Summary Score in both UNITI-1 and UNITI-2, and SF-36 Physical Component Summary Score in UNITI-2, when compared to placebo. These improvements were generally better maintained in ustekinumab-treated patients in the IM-UNITI study through week 44 when compared to placebo. Improvement in health-related quality of life was generally maintained during the extension through week 252.

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

Efficacy results presented for UNIFI-I and UNIFI-M were based on central review of endoscopies.

UNIFI-I included 961 patients. The primary endpoint for the induction study was the proportion of subjects in clinical remission at week 8. Patients were randomised to receive a single intravenous administration of either the recommended tiered dose of approximately 6 mg/kg (see Table 1, section 4.2), a fixed dose of 130 mg ustekinumab, or placebo at week 0.

Concomitant doses 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-TNF□ therapy (of which 48% were primary non-responders) and 17% had failed at least 1 anti-TNFα therapy and vedolizumab.

In UNIFI-I a significantly greater proportion of patients were in clinical remission in the ustekinumab treated group compared to placebo at week 8 (Table 10). 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 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 10: Summary of Key Efficacy Outcomes in UNIFI-I (Week 8)

	Placebo N = 319	**Recommended dose of ustekinumab£ N = 322**
Clinical Remission*	5%	16%[a]
In patients who failed conventional therapy, but not a biologic	9% (15/158)	19% (29/156)[c]
In patients who failed biological therapy¥	1% (2/161)	13% (21/166)[b]
In patients who failed both a TNF and vedolizumab	0% (0/47)	10% (6/58%)[c]
Clinical Response§	31%	62%[a]
In patients who failed conventional therapy, but not a biologic	35% (56/158)	67% (104/156)[b]
In patients who failed biological therapy¥	27% (44/161)	57% (95/166)[b]
In patients who failed both a TNF and vedolizumab	28% (13/47)	52% (30/58)[c]
Mucosal Healing†	14%	27%[a]
In patients who failed conventional therapy, but not a biologic	21% (33/158)	33% (52/156)[c]
In patients who failed biological therapy	7% (11/161)	21% (35/166)[b]
Symptomatic Remission‡	23%	45%[b]
Combined Symptomatic Remission and Mucosal Healing	8%	21%[b]

£ Infusion dose of ustekinumab using the weight-based dosage regimen specified in Table 1.

* 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.

¥ A TNFα antagonist and/or vedolizumab.

† Mucosal healing is defined as a Mayo endoscopic subscore of 0 or 1.

‡ Symptomatic remission is defined as a Mayo stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0.

Combined symptomatic remission and mucosal 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] Nominally significant ($p < 0.001$)

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

UNIFI-M, evaluated 523 patients who achieved clinical response with single IV administration of ustekinumab in UNIFI-I. Patients were randomised 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 (for recommended maintenance posology, see section 4.2 of the IMULDOSA solution for injection in pre-filled syringe SmPC).

Significantly greater proportions of patients were in clinical remission in both ustekinumab treated groups compared to the placebo group at week 44 (see Table 11).

Table 11: Summary of Key Efficacy Measures in UNIFI-M (week 44; 52 weeks from initiation of the induction dose)

	Placebo* N = 175	**90 mg ustekinumab every 8 Weeks N = 176**	**90 mg ustekinumab every 12 Weeks N = 172**
Clinical Remission**	24%	44%[a]	38%[b]

In patients who failed conventional therapy, but not a biologic	31% (27/87)	48% (41/85)[d]	49% (50/102)[d]
In patients who failed biological therapy[¥]	17% (15/88)	40% (36/91)[c]	23% (16/70)[d]
In patients who failed both a TNF and vedolizumab	15% (4/27)	33% (7/21)[e]	23% (5/22)[e]
Maintenance of Clinical Response through week 44[§]	45%	71%[a]	68%[a]
In patients who failed conventional therapy, but not a biologic	51% (44/87)	78% (66/85)[c]	77% (78/102)[c]
In patients who failed biological therapy[¥]	39% (34/88)	65% (59/91)[c]	56% (39/70)[d]
In patients who failed both a TNF and vedolizumab	41% (11/27)	67% (14/21)[e]	50% (11/22)[e]
Mucosal Healing[†]	29%	51%[a]	44%[b]
Maintenance of Clinical Remission through week 44[£]	38% (17/45)	58% (22/38)	65% (26/40)[c]
Corticosteroid Free Clinical Remission[€]	23%	42%[a]	38%[b]
Durable Remission[□]	35%	57%[c]	48%[d]
Symptomatic Remission[‡]	45%	68%[c]	62%[d]
Combined Symptomatic Remission and Mucosal Healing[□]	28%	48%[c]	41%[d]

* Following response to IV ustekinumab.

** 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.

¥ A TNFα antagonist and/or vedolizumab.

† Mucosal healing is defined as a Mayo endoscopic sub-score of 0 or 1.

£ Maintenance of clinical remission through Week 44 is defined as patients in clinical remission through Week 44 among patients in clinical remission at maintenance baseline.

€ Corticosteroid-free clinical remission is defined as patients in clinical remission and not receiving corticosteroids at Week 44.

□ Durable Remission is defined as partial Mayo remission 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 Mayo stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0.

□ Combined symptomatic remission and mucosal 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 ($p < 0.001$)

[d] Nominally significant ($p < 0.05$)

[e] Not statistically significant

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 including in patients with a primary non-response to TNFα antagonist therapy. A beneficial effect was also observed in induction in patients who failed at least one prior TNFα antagonist therapy and vedolizumab, however the number of patients in this subgroup was too small to draw definitive conclusions about the beneficial effect in this group during maintenance.

Week 16 Responders to Ustekinumab Induction
Ustekinumab treated patients who were not in response at week 8 of UNIFI-I received an administration of 90 mg SC ustekinumab at week 8 (36% of patients). Of those patients, 9% of patients who were initially randomised to the recommended induction dose achieved clinical remission and 58% achieved clinical response at Week 16.

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

Study Extension
In UNIFI, patients who completed the study through week 44 were eligible to continue treatment in a study extension. Among the 400 patients who entered on and were treated with ustekinumab every 12 or 8 weeks 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. Among patients who received 4 years of ustekinumab treatment and were assessed using the full Mayo score at maintenance week 200, 74.2% (69/93) and 68.3% (41/60) maintained mucosal healing and clinical remission, respectively.

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 2 years of treatment in patients with ulcerative colitis.

Endoscopic Normalisation
Endoscopic normalisation was defined as a Mayo endoscopic subscore of 0 and was observed as early as week 8 of UNIFI-I. At week 44 of UNIFI-M, 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-I and Week 44 of UNIFI-M. 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 observed 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-I and week 44 of UNIFI-M. 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-I, 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-M through week 44. Improvement in health-related quality of life as measured by IBDQ and SF-36 was generally maintained during the extension through week 92.

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.

Hospitalisations and ulcerative colitis (UC) related surgeries
Through week 8 of UNIFI-I, the proportions of subjects with UC disease related hospitalisations 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 UC 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-M, a significantly lower number of UC-related hospitalisations 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 UC disease related surgeries compared with subjects in the placebo group (1.7%, 3/175) through week 44.

Immunogenicity
Antibodies to ustekinumab may develop during ustekinumab treatment and most are neutralising. The formation of anti-ustekinumab antibodies is associated with both increased clearance and reduced efficacy of ustekinumab, except in patients with Crohn’s disease or ulcerative colitis where no reduced efficacy was observed. There is no apparent correlation between the presence of anti-ustekinumab antibodies and the occurrence of injection site reactions.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with ustekinumab in one or more subsets of the paediatric population in Crohn’s Disease and ulcerative colitis (see section 4.2 for information on paediatric use).

Paediatric Crohn’s disease
The safety and efficacy of ustekinumab was evaluated in 48 paediatric patients weighing at least 40 kg, in an interim analysis of a multicentre phase 3 study (UNITI-Jr) for paediatric patients with moderately to severely active Crohn's disease (defined by a Paediatric Crohn’s Disease Activity Index [PCDAI] score >30) through 52 weeks of treatment (8 weeks of induction and 44 weeks of maintenance treatment). Patients included in the study either had not adequately responded to or had not tolerated prior biologic therapy or conventional therapy for Crohn’s disease. The study included an

open-label induction treatment with a single ustekinumab intravenous dose, of approximately 6 mg/kg (see section 4.2), followed by a randomised double-blind subcutaneous maintenance regimen of 90 mg ustekinumab administered either every 8 weeks or every 12 weeks.

Efficacy results
The primary endpoint of the study was clinical remission at induction week 8 (defined as PCDAI score ≤ 10). The proportion of patients who achieved clinical remission was 52.1% (25/48) and is comparable to that observed in the adult ustekinumab phase 3 studies.

Clinical response was observed as early as week 3. The proportion of patients in clinical response at week 8 (defined as a reduction from baseline in the PCDAI score of >12.5 points with a total PCDAI score not more than 30) was 93.8% (45/48).

Table 10 presents the analyses for the secondary endpoints through maintenance week 44.

Table 10: Summary of Secondary endpoints through Maintenance week 44

	90 mg ustekinumab every 8 weeks N = 23	**90 mg ustekinumab every 12 weeks N = 25**	**Total number of patients N = 48**
Clinical Remission [*]	43.5% (10/23)	60.0% (15/25)	52.1% (25/48)
Corticosteroid-free Clinical Remission [§]	43.5% (10/23)	60.0% (15/25)	52.1% (25/48)
Clinical remission for patients who were in clinical remission at induction week 8 [*]	64.3% (9/14)	54.5% (6/11)	60.0% (15/25)
Clinical Response [†]	52.2% (12/23)	60.0% (15/25)	56.3% (27/48)
Endoscopic response [£]	22.7% (5/22)	28.0% (7/25)	25.5% (12/47)

[*] Clinical remission is defined as PCDAI score ≤10 points.

[§] Corticosteroid-free remission is defined as PCDAI score of ≤10 points and not receiving corticosteroids for at least 90 days prior to Week M-44.

[†] Clinical response is defined as a reduction from baseline in the PCDAI score of ≥12.5 points with a total PCDAI score not more than 30.

[£] Endoscopic response is defined as a reduction in the SES-CD score of ≥50% or SES-CD score ≤2, in patients with a baseline SES-CD score of ≥3.

Dosing frequency adjustment
Patients who entered the maintenance regimen and experienced loss of response (LOR) based on PCDAI score were eligible for dose adjustment. Patients were either switched from treatment every 12 weeks to every 8 weeks or stayed on treatment every 8 weeks (sham adjustment). 2 patients were dose adjusted to the shorter dosing interval. In these patients, clinical remission was achieved in 100% (2/2) of patients 8 weeks after dose adjustment.

The safety profile of the induction dose regimen and both maintenance dose regimens in the paediatric population weighing at least 40 kg is comparable with that established in the adult Crohn's disease population (see Section 4.8).

Serum and faecal inflammatory biomarkers

The mean change from baseline at maintenance week 44 in C-Reactive protein (CRP) and faecal calprotectin concentrations were -11.17 mg/L (24.159) and -538.2 mg/kg (1271.33), respectively.

Health-related quality of life
The total IMPACT-III scores and all subdomains (bowel symptoms, fatigue-related systemic symptoms, and well-being) demonstrated clinically meaningful improvements after 52 weeks.

5.2 Pharmacokinetic properties

Absorption
The median time to reach the maximum serum concentration (t_{max}) was 8.5 days after a single 90 mg subcutaneous administration in healthy subjects. The median t_{max} values of ustekinumab following a single subcutaneous administration of either 45 mg or 90 mg in patients with psoriasis were comparable to 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 ($t_{1/2}$) 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 (C_{max} and AUC) increased in an approximately dose-proportional manner after a single intravenous administration at doses ranging from 0.09 mg/kg to 4.5 mg/kg or following a single subcutaneous administration at doses ranging from approximately 24 mg to 240 mg in patients with psoriasis.

Single dose 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 inpatients 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.

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.

The steady-state serum concentration in paediatric patients with Crohn's disease weighing at least 40 kg were comparable to those in the adult Crohn's disease population.

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 4.5). 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 4.5).

5.3 Preclinical safety data

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-histidine

L-histidine hydrochloride monohydrate

Polysorbate 80

Sucrose

Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

3 years.

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

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze.

Keep the pre-filled syringe in the outer carton in order to protect from light.

If needed, individual pre-filled syringes may be stored at room temperature up to 30°C (see section 6.3).

6.5 Nature and contents of container

0.5 mL solution in a type I glass 1 mL syringe with a fixed stainless-steel 29-gauge needle, extended finger flanges and a needle cover with an elastomeric needle shield and a plastic rigid needle shield. The syringe is fitted with an automatic needle guard.

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

6.6 Special precautions for disposal

The solution in the IMULDOSA pre-filled syringe should not be shaken. The solution should be visually inspected for particulate matter or discolouration prior to subcutaneous administration. The solution is colourless to slightly yellow and clear to slightly opalescent. 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, IMULDOSA should be allowed to reach room temperature (approximately half an hour). Detailed instructions for use are provided in the package leaflet.

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

7 MARKETING AUTHORISATION HOLDER

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