ANNEX I

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

Qoyvolma 130 mg concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 130 mg ustekinumab in 26 mL (5 mg/mL).

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Crohn's Disease

Qoyvolma is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist or have medical contraindications to such therapies.

Ulcerative colitis

Qoyvolma is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic or have medical contraindications to such therapies (see section 5.1).

4.2 Posology and method of administration

Qoyvolma concentrate for solution for infusion is intended for use under the guidance and supervision of physicians experienced in the diagnosis and treatment of Crohn's disease or ulcerative colitis. Qoyvolma concentrate for solution for infusion should only be used for the intravenous induction dose.

Posology

Crohn's Disease and Ulcerative Colitis

Qoyvolma treatment is to be initiated with a single intravenous dose based on body weight. The infusion solution is to be composed of the number of vials of Qoyvolma 130 mg as specified in Table 1 (see section 6.6 for preparation).

Table 1 Initial intravenous dosing of Qoyvolma

Body weight of patient at the time of dosing	Recommended dose[a]	Number of 130 mg Qoyvolma Vials
≤ 55 kg	260 mg	2
> 55 kg to ≤ 85 kg	390 mg	3
> 85 kg	520 mg	4

[a] Approximately 6 mg/kg

The first subcutaneous dose should be given at week 8 following the intravenous dose. For the posology of the subsequent subcutaneous dosing regimen, see section 4.2 of the Qoyvolma solution for injection in pre-filled syringe SmPC.

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 for the treatment of Crohn's disease or ulcerative colitis in children less than 18 years have not yet been established. No data are available.

Method of administration

Qoyvolma 130 mg is for intravenous use only. It should be administered over at least one hour. For instructions on dilution of the medicinal product before administration, 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 name 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 Qoyvolma in patients with a chronic infection or a history of recurrent infection (see section 4.3).

Prior to initiating treatment with Qoyvolma, patients should be evaluated for tuberculosis infection. Qoyvolma must not be given to patients with active tuberculosis (see section 4.3). Treatment of latent tuberculosis infection should be initiated prior to administering Qoyvolma. Anti-tuberculosis therapy should also be considered prior to initiation of Qoyvolma in patients with a history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. Patients receiving Qoyvolma 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 Qoyvolma 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 Qoyvolma 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 postmarketing setting, in some cases several days after treatment. Anaphylaxis and angioedema have occurred. If an anaphylactic or other serious hypersensitivity reaction occurs, appropriate therapy should be instituted and administration of Qoyvolma should be discontinued (see section 4.8).

Infusion-related reactions
Infusion-related reactions were observed in clinical trials (see section 4.8). Serious infusion-related reactions including anaphylactic reactions to the infusion have been reported in the post-marketing setting. If a serious or life-threatening reaction is observed, appropriate therapy should be instituted and ustekinumab should be discontinued.

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 ustekinumab.

Vaccinations

It is recommended that live viral or live bacterial vaccines (such as Bacillus of Calmette and Guérin (BCG)) should not be given concurrently with Qoyvolma. 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 Qoyvolma 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 Qoyvolma 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 Qoyvolma 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. Qoyvolma should be discontinued if a drug reaction is suspected.

Lupus-related conditions

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

Special populations

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

Sodium content

Qoyvolma contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free'. Qoyvolma is however, diluted in sodium chloride 9 mg/mL (0.9%) solution for infusion. This should be taken into consideration for patients on a controlled sodium diet (see section 6.6).

4.5 Interaction with other medicinal products and other forms of interaction

Live vaccines should not be given concurrently with Qoyvolma.

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.

No interaction studies have been performed in humans. 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 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 ustekinumab with known outcomes, including more than 450 pregnancies exposed during the first trimester, do not indicate an increased risk of major congenital malformations in the newborn.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development (see section 5.3).

However, the available clinical experience is limited. As a precautionary measure, it is preferable to avoid the use of Qoyvolma 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 Qoyvolma must be made taking into account the benefit of breast-feeding to the child and the benefit of Qoyvolma 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

Qoyvolma 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 6 709 patients (4 135 with psoriasis and/or psoriatic arthritis, 1 749 with Crohn's disease and 825 patients with ulcerative colitis). This includes exposure to ustekinumab in the controlled and non-controlled periods of the clinical studies for at least 6 months or 1 year (4 577 and 3 253 patients respectively with psoriasis, psoriatic arthritis, Crohn's disease or ulcerative colitis) and exposure for at least 4 or 5 years (1 482 and 838 patients with psoriasis respectively).

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

Table 2 List of adverse reactions

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

* See section 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, Crohn's disease and ulcerative colitis clinical studies, representing 11 581 patient-years of exposure in 6 709 patients, the median follow-up was 1.0 years; 1.1 years for psoriatic disease studies, 0.6 year for Crohn's disease studies and 1.0 years for ulcerative colitis studies. The rate of infection was 0.91 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 (199 serious infections in 11 581 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 11 561 patient-years of exposure in 6 709 patients, the median follow-up was 1.0 years; 1.1 years for psoriatic disease studies, 0.6 year for Crohn's disease studies and 1.0 years for ulcerative colitis studies. Malignancies excluding non-melanoma skin cancers were reported in 62 patients in 11 561 patient-years of follow-up (incidence of 0.54 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 = 0.93 [95% confidence interval: 0.71, 1.20], adjusted for age, gender and race). The most frequently observed malignancies, other than non-melanoma skin cancer, were prostate, colorectal, melanoma and breast cancers. The incidence of non-melanoma skin cancer was 0.49 per 100 patient-years of follow-up for ustekinumab-treated patients (56 patients in 11 545 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 and infusion reactions

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

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 national reporting system listed in Appendix V.

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.

Qoyvolma is a biosimilar medicinal product. Detailed information is available on the website of the European Medicines Agency https://www.ema.europa.eu.

Mechanism of action

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

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 1 409 (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 Table 1, section 4.2), 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-TNFα 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 3). 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 3 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]

	UNITI-1*		UNITI-2**	
	Placebo N = 247	**Recommended dose of ustekinumab N = 249**	**Placebo N = 209**	**Recommended dose of ustekinumab N = 209**
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 of the Qoyvolma Solution for injection in pre-filled syringe SmPC).

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 4).

Table 4 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-TNFα 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 5). 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 5: 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[ɟ]	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.

[ɟ] 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 Qoyvolma 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 6).

Table 6: 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[l]	35%	57% [c]	48% [d]
Symptomatic Remission[‡]	45%	68% [c]	62% [d]
Combined Symptomatic Remission and Mucosal Healing[ɻ]	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.
l 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.
ɻ 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.

No new safety concerns were identified in this study extension with up to 4 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 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 200.

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 increased clearance of ustekinumab in patients with Crohn's disease or ulcerative colitis. 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).

5.2 Pharmacokinetic properties

Following the recommended intravenous induction dose, median peak serum ustekinumab concentration, observed 1 hour after the infusion, was 126.1 µg/mL in patients with Crohn's disease and 127.0 µg/mL in patients with ulcerative colitis.

Distribution

Median volume of distribution during the terminal phase (V_z) 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 ulcerative colitis, Crohn's disease, psoriasis and/or psoriatic arthritis, ranging from 15 to 32 days across all psoriasis and psoriatic arthritis studies.

Dose linearity

The systemic exposure of ustekinumab (C_{max} and AUC) increased in an approximately dose-proportional manner after a single intravenous administration at doses ranging from 0.09 mg/kg to 4.5 mg/kg.

Special populations

No pharmacokinetic data are available in patients with impaired renal or hepatic function.
No specific studies have been conducted with intravenous ustekinumab in elderly or paediatric patients.

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.

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).

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

EDTA disodium salt dihydrate (E385)
L-histidine
L-histidine monohydrochloride monohydrate

L-methionine
Polysorbate 80 (E433)
Sucrose
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products. Qoyvolma should only be diluted with sodium chloride 9 mg/mL (0.9%) solution. Qoyvolma should not be administered concomitantly in the same intravenous line with other medicinal products.

6.3 Shelf life

3 years
Do not freeze.

Individual vials may be stored at room temperature up to 30 °C for a maximum single period of up to 31 days in the original carton in order to protect from light. Record the date when the vial is first removed from the refrigerator and the discard date in the space provided on the outer carton. The discard date must not exceed the original expiry date printed on the carton. Once a vial has been stored at room temperature (up to 30 °C), it should not be returned to the refrigerator. Discard the vial if not used within 31 days at room temperature storage or by the original expiry date, whichever is earlier.

Chemical and physical in-use stability has been demonstrated for 48 hours at refrigerated condition or room temperature up to 30 °C. From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of user.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C). Do not freeze.
Keep the vial in the outer carton in order to protect from light.
If needed, individual vials may be stored at room temperature up to 30 °C (see section 6.3).

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

26 mL solution in a type I glass 30 mL vial closed with a coated butyl rubber stopper. Qoyvolma is available in a 1 vial pack.

6.6 Special precautions for disposal and other handling

The solution in the Qoyvolma vial should not be shaken. The solution should be visually inspected for particulate matter or discolouration prior to administration. The solution is clear to slightly opalescent, colourless to pale yellow. The medicinal product should not be used if the solution is discoloured or cloudy, or if foreign particulate matter is present.

<u>Dilution</u>

Qoyvolma concentrate for solution for infusion must be diluted and prepared by a healthcare professional using aseptic technique.

1. Calculate the dose and the number of Qoyvolma vials needed based on patient weight (see section 4.2, Table 1). Each 26 mL vial of Qoyvolma contains 130 mg of ustekinumab. Only use complete vials of Qoyvolma.

2. Withdraw and discard a volume of the sodium chloride 9 mg/mL (0.9%) solution from the 250 mL infusion bag equal to the volume of Qoyvolma to be added. (discard 26 mL sodium chloride for each vial of Qoyvolma needed, for 2 vials - discard 52 mL, for 3 vials - discard 78 mL, for 4 vials - discard 104 mL).
3. Withdraw 26 mL of Qoyvolma from each vial needed and add it to the 250 mL infusion bag. The final volume in the infusion bag should be 250 mL. Gently mix.
4. Visually inspect the diluted solution before administration. Do not use if visibly opaque particles, discolouration or foreign particles are observed.
5. Administer the diluted solution over a period of at least one hour. Once diluted, the infusion should be completed within forty-eight hours of the dilution in the infusion bag.
6. Use only an infusion set with an in-line, sterile, non-pyrogenic, low protein-binding filter (pore size 0.2 micrometer).
7. Each vial is for single use only and any unused medicinal product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Celltrion Healthcare Hungary Kft.
1062 Budapest
Váci út 1-3. WestEnd Office Building B torony
Hungary

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1925/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

▼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

Qoyvolma 45 mg solution for injection in pre-filled syringe
Qoyvolma 90 mg solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Qoyvolma 45 mg solution for injection in pre-filled syringe

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

Qoyvolma 90 mg solution for injection in pre-filled syringe

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

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Qoyvolma 45 mg solution for injection in pre-filled syringe

Solution for injection.

Qoyvolma 90 mg solution for injection in pre-filled syringe

Solution for injection.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Plaque psoriasis

Qoyvolma 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

Qoyvolma 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)

Qoyvolma, 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).

Crohn's Disease

Qoyvolma is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist or have medical contraindications to such therapies.

Ulcerative colitis

Qoyvolma is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic or have medical contraindications to such therapies (see section 5.1).

4.2 Posology and method of administration

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

Posology

Plaque psoriasis

The recommended posology of Qoyvolma 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 Qoyvolma 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 Qoyvolma based on body weight is shown below (Table 1). Qoyvolma should be administered at Weeks 0 and 4, then every 12 weeks thereafter.

There is no dose form for Qoyvolma that allows weight-based dosing for paediatric patients below 60 kg. For paediatric plaque psoriasis, Qoyvolma is available only as 45 mg and 90 mg solution for injection in pre-filled syringe.

Table 1 Recommended dose of Qoyvolma for paediatric psoriasis

Body weight at the time of dosing	Recommended dose
< 60 kg*	-
≥ 60 kg to ≤ 100 kg	45 mg
> 100 kg	90 mg

* Qoyvolma 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.

Patients weighing less than 60 kg should be accurately dosed on a mg/kg basis using another ustekinumab product for which a 45 mg solution for injection in vial presentation enabling weight-based dosing is available.

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

Crohn's Disease and Ulcerative Colitis

In the treatment regimen, the first dose of Qoyvolma is administered intravenously. For the posology of the intravenous dosing regimen, see section 4.2 of the Qoyvolma 130 mg Concentrate for solution for infusion SmPC.

The first subcutaneous administration of 90 mg Qoyvolma 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 Qoyvolma. In patients who have responded to treatment with Qoyvolma, 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
The safety and efficacy of ustekinumab in treatment of Crohn's disease or ulcerative colitis in children less than 18 years have not yet been established. No data are available.

Method of administration

Qoyvolma 45 mg and 90 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 Qoyvolma 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 Qoyvolma 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 name 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 Qoyvolma in patients with a chronic infection or a history of recurrent infection (see section 4.3).

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

Qoyvolma 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 Qoyvolma 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 Qoyvolma 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 postmarketing setting, in some cases several days after treatment. Anaphylaxis and angioedema have occurred. If an anaphylactic or other serious hypersensitivity reaction occurs, appropriate therapy should be instituted and administration of Qoyvolma 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 ustekinumab.

Vaccinations

It is recommended that live viral or live bacterial vaccines (such as Bacillus of Calmette and Guérin (BCG)) should not be given concurrently with Qoyvolma. 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 Qoyvolma 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 Qoyvolma 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 Qoyvolma 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. Qoyvolma should be discontinued if a drug reaction is suspected.

Lupus-related conditions

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

Special populations

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

4.5 Interaction with other medicinal products and other forms of interaction

Live vaccines should not be given concurrently with Qoyvolma.

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.

No interaction studies have been performed in humans. 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 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 ustekinumab with known outcomes, including more than 450 pregnancies exposed during the first trimester, do not indicate an increased risk of major congenital malformations in the newborn.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development (see section 5.3).

However, the available clinical experience is limited. As a precautionary measure, it is preferable to avoid the use of Qoyvolma 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 Qoyvolma must be made taking into account the benefit of breast-feeding to the child and the benefit of Qoyvolma 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

Qoyvolma 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 6 709 patients (4 135 with psoriasis and/or psoriatic arthritis, 1 749 with Crohn's disease and 825 patients with ulcerative colitis). This includes exposure to ustekinumab in the controlled and non-controlled periods of the clinical studies for at least 6 months or 1 year (4 577 and 3 253 patients respectively with psoriasis, psoriatic arthritis, Crohn's disease or ulcerative colitis) and exposure for at least 4 or 5 years (1 482 and 838 patients with psoriasis respectively).

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

Table 2 List of adverse reactions

System Organ Class	Frequency: Adverse reaction
Infections and infestations	Common: Upper respiratory tract infection, nasopharyngitis, sinusitis Uncommon: Cellulitis, dental infections, herpes zoster, lower respiratory tract infection, viral upper respiratory tract infection, vulvovaginal mycotic infection
Immune system disorders	Uncommon: Hypersensitivity reactions (including rash, urticaria) Rare: Serious hypersensitivity reactions (including anaphylaxis, angioedema)

Psychiatric disorders	Uncommon: Depression
Nervous system disorders	Common: Dizziness, headache Uncommon: Facial palsy
Respiratory, thoracic and mediastinal disorders	Common: Oropharyngeal pain Uncommon: Nasal congestion Rare: Allergic alveolitis, eosinophilic pneumonia Very rare: Organising pneumonia*
Gastrointestinal disorders	Common: Diarrhoea, nausea, vomiting
Skin and subcutaneous tissue disorders	Common: Pruritus Uncommon: Pustular psoriasis, skin exfoliation, acne Rare: Exfoliative dermatitis, hypersensitivity vasculitis Very rare: Bullous pemphigoid, cutaneous lupus erythematosus
Musculoskeletal and connective tissue disorders	Common: Back pain, myalgia, arthralgia Very rare: Lupus-like syndrome
General disorders and administration site conditions	Common: Fatigue, injection site erythema, injection site pain Uncommon: Injection site reactions (including haemorrhage, haematoma, induration, swelling and pruritus), asthenia

* See section 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, Crohn's disease and ulcerative colitis clinical studies, representing 11 581 patient-years of exposure in 6 709 patients, the median follow-up was 1.0 years; 1.1 years for psoriatic disease studies, 0.6 year for Crohn's disease studies, and 1.0 years for ulcerative colitis studies. The rate of infection was 0.91 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 (199 serious infections in 11 581 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 11 561 patient-years of exposure in 6 709 patients, the median follow-up was 1.0 years; 1.1 years for psoriatic disease studies, 0.6 year for Crohn's disease studies and 1.0 years for ulcerative colitis studies. Malignancies excluding non-melanoma skin cancers were reported in 62 patients in 11 561 patient-years of follow-up (incidence of 0.54 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 = 0.93 [95% confidence interval: 0.71, 1.20], adjusted for age, gender and race). The most frequently observed malignancies, other than non-melanoma skin cancer, were prostate, colorectal, melanoma and breast cancers. The incidence of non-melanoma skin cancer was 0.49 per 100 patient-years of follow-up for ustekinumab-treated patients (56 patients in 11 545 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.

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 national reporting system listed in Appendix V.

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.

Qoyvolma is a biosimilar medicinal product. Detailed information is available on the website of the European Medicines Agency https://www.ema.europa.eu.

Mechanism of action

Ustekinumab is a fully human IgGlκ monoclonal antibody that binds with specificity to the shared p40 protein subunit of human cytokines interleukin (IL)-12 and IL-23. Ustekinumab inhibits the

bioactivity of human IL-12 and IL-23 by preventing p40 from binding to the IL-12Rβ1 receptor protein expressed on the surface of immune cells. Ustekinumab cannot bind to IL-12 or IL-23 that is already bound to IL-12Rβ1 cell surface receptors. Thus, ustekinumab is not likely to contribute to complement- or antibody-mediated cytotoxicity of cells 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 fecal 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 fecal 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 ≥ 12, PGA ≥ 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 1 409 (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 Qoyvolma 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-TNFα 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-TNFα 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[ɻ]	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.

[ɻ] 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 Qoyvolma 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[l]	35%	57% [c]	48% [d]
Symptomatic Remission[‡]	45%	68% [c]	62% [d]
Combined Symptomatic Remission and Mucosal Healing[ɻ]	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.

l 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.

ɻ 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.
No new safety concerns were identified in this study extension with up to 4 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 200.

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).

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 (V_z) 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 in patients with weight > 100 kg was approximately 55% higher compared to patients with weight ≤ 100 kg. The median V/F in patients with weight > 100 kg was approximately 37% higher as compared to patients with weight ≤ 100 kg. The median trough serum concentrations of ustekinumab in patients with higher weight (> 100 kg) in the 90 mg group were comparable to those in patients with lower weight (≤ 100 kg) in the 45 mg group. Similar results were obtained from a confirmatory population pharmacokinetic analysis using data from patients with psoriatic arthritis.

Dosing frequency adjustment

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

Special populations

No pharmacokinetic data are available in patients with impaired renal or hepatic function.
No specific studies have been conducted in elderly patients.

The pharmacokinetics of ustekinumab were generally comparable between Asian and non-Asian patients with psoriasis and ulcerative colitis.

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

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

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

Regulation of CYP450 enzymes

The effects of IL-12 or IL-23 on the regulation of CYP450 enzymes were evaluated in an *in vitro* study using human hepatocytes, which showed that IL-12 and/or IL-23 at levels of 10 ng/mL did not alter human CYP450 enzyme activities (CYP1A2, 2B6, 2C9, 2C19, 2D6, or 3A4; see section 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 monohydrochloride monohydrate
Polysorbate 80 (E433)
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

Qoyvolma 45 mg solution for injection in pre-filled syringe

3 years

Qoyvolma 90 mg solution for injection in pre-filled syringe

3 years

Individual pre-filled syringes may be stored at room temperature up to 30 °C for a maximum single period of up to 31 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 space 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 31 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

Qoyvolma 45 mg solution for injection in pre-filled syringe

0.5 mL solution in a type I glass 1 mL syringe with a staked hypodermic stainless steel needle and a flexible needle shield made of styrene-butadien rubber. The syringe is fitted with a safety guard that automatically shields the needle after dose administration.

Qoyvolma 90 mg solution for injection in pre-filled syringe

1 mL solution in a type I glass 1 mL syringe with a staked hypodermic stainless steel needle and a flexible needle shield made of styrene-butadien rubber. The syringe is fitted with a safety guard that automatically shields the needle after dose administration

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

6.6 Special precautions for disposal and other handling

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

Qoyvolma does not contain preservatives; therefore any unused medicinal product remaining in the syringe should not be used. Qoyvolma is supplied as a sterile, single-use pre-filled syringe. The syringe 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

Celltrion Healthcare Hungary Kft.
1062 Budapest
Váci út 1-3. WestEnd Office Building B torony
Hungary

8. MARKETING AUTHORISATION NUMBER(S)

Qoyvolma 45 mg solution for injection in pre-filled syringe

EU/1/25/1925/001

Qoyvolma 90 mg solution for injection in pre-filled syringe

EU/1/25/1925/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

CELLTRION INC.
20 Academy-ro 51 beon-gil
Yeonsu-gu
22014 Incheon
Republic of Korea

Name and address of the manufacturer responsible for batch release

Nuvisan France SARL
2400, Route des Colles
06410, Biot
France

MIDAS Pharma GmbH
Rheinstrasse 49
55218 West Ingelheim Am Rhein
Rhineland-Palatinate
Germany

Kymos S.L.
Ronda De Can Fatjo 7b
Parc Tecnologic Del Valles
08290 Cerdanyola Del Valles
Barcelona
Spain

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency.
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (130 mg)

1. NAME OF THE MEDICINAL PRODUCT

Qoyvolma 130 mg concentrate for solution for infusion
ustekinumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 130 mg of ustekinumab in 26 mL.

3. LIST OF EXCIPIENTS

Excipients: EDTA disodium salt dihydrate, L-histidine, L-histidine monohydrochloride monohydrate, L-methionine, polysorbate 80, sucrose, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
130 mg/26 mL
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake.
Read the package leaflet before use.
For single use only.
Intravenous use after dilution.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Discard date, if stored at room temperature:_____

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.
Can be stored at room temperature (up to 30 °C) for a single period up to 31 days, but not exceeding the original expiry date.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Celltrion Healthcare Hungary Kft.
1062 Budapest
Váci út 1-3. WestEnd Office Building B torony
Hungary

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1925/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL TEXT (130 mg)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Qoyvolma 130 mg Sterile concentrate
ustekinumab

2. METHOD OF ADMINISTRATION

For IV use after dilution.
Do not shake.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

130 mg/26 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PRE-FILLED SYRINGE CARTON TEXT (45 mg)

1. NAME OF THE MEDICINAL PRODUCT

Qoyvolma 45 mg solution for injection in pre-filled syringe
ustekinumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Excipients: Sucrose, L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe
45 mg/0.5 mL
1 pre-filled syringe with needle guard

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake.
Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Discard date, if stored at room temperature:_____

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the pre-filled syringe in the outer carton in order to protect from light.
Can be stored at room temperature (up to 30 °C) for a single period up to 31 days, but not exceeding the original expiry date.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Celltrion Healthcare Hungary Kft.
1062 Budapest
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Hungary

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1925/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Qoyvolma 45 mg

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE LABEL TEXT (45 mg)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Qoyvolma 45 mg Injection
ustekinumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

45 mg/0.5 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PRE-FILLED SYRINGE CARTON TEXT (90 mg)

1. NAME OF THE MEDICINAL PRODUCT

Qoyvolma 90 mg solution for injection in pre-filled syringe
ustekinumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Excipients: Sucrose, L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe
90 mg/1 mL
1 pre-filled syringe with needle guard

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake.
Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Discard date, if stored at room temperature:_____

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the pre-filled syringe in the outer carton in order to protect from light.
Can be stored at room temperature (up to 30 °C) for a single period up to 31 days, but not exceeding the original expiry date.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Celltrion Healthcare Hungary Kft.
1062 Budapest
Váci út 1-3. WestEnd Office Building B torony
Hungary

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1925/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Qoyvolma 90 mg

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE LABEL TEXT (90 mg)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Qoyvolma 90 mg Injection
ustekinumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

90 mg/1 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Qoyvolma 130 mg concentrate for solution for infusion
ustekinumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

This leaflet has been written for the person taking the medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Qoyvolma is and what it is used for

What Qoyvolma is
Qoyvolma contains the active substance ‘ustekinumab’, a monoclonal antibody. Monoclonal antibodies are proteins that recognise and bind specifically to certain proteins in the body.

Qoyvolma belongs to a group of medicines called ‘immunosuppressants’. These medicines work by weakening part of the immune system.

What Qoyvolma is used for
Qoyvolma is used to treat the following inflammatory diseases:
- Moderate to severe Crohn’s disease - in adults
- Moderate to severe ulcerative colitis - in adults

Crohn’s disease
Crohn’s disease is an inflammatory disease of the bowel. If you have Crohn’s disease you will first be given other medicines. If you do not respond well enough or are intolerant to these medicines, you may be given Qoyvolma to reduce the signs and symptoms of your disease.

Ulcerative colitis
Ulcerative colitis is an inflammatory disease of the bowel. If you have ulcerative colitis you will first be given other medicines. If you do not respond well enough or are intolerant to these medicines, you may be given Qoyvolma to reduce the signs and symptoms of your disease.

2. What you need to know before you use Qoyvolma

Do not use Qoyvolma
- **If you are allergic to ustekinumab** or any of the other ingredients of this medicine (listed in section 6).
- **If you have an active infection** which your doctor thinks is important.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Qoyvolma.

Warnings and precautions
Talk to your doctor or pharmacist before using Qoyvolma. Your doctor will check how well you are before each treatment. Make sure you tell your doctor about any illness you have before each treatment. Also tell your doctor if you have recently been near anyone who might have tuberculosis. Your doctor will examine you and do a test for tuberculosis, before you have Qoyvolma. If your doctor thinks you are at risk of tuberculosis, you may be given medicines to treat it.

Look out for serious side effects
Qoyvolma can cause serious side effects, including allergic reactions and infections. You must look out for certain signs of illness while you are taking Qoyvolma. See 'Serious side effects' in section 4 for a full list of these side effects.

Before you use Qoyvolma tell your doctor:
- **If you ever had an allergic reaction to ustekinumab.** Ask your doctor if you are not sure.
- **If you have ever had any type of cancer** – this is because immunosuppressants like Qoyvolma weaken part of the immune system. This may increase the risk of cancer.
- **If you have been treated for psoriasis with other biologic medicines (a medicine produced from a biological source and usually given by injection)** – the risk of cancer may be higher.
- **If you have or have had a recent infection or if you have any abnormal skin openings (fistulae).**
- **If you have any new or changing lesions** within psoriasis areas or on normal skin.
- **If you are having any other treatment for psoriasis and/or psoriatic arthritis** – such as another immunosuppressant or phototherapy (when your body is treated with a type of ultraviolet (UV) light). These treatments may also weaken part of the immune system. Using these therapies together with ustekinumab has not been studied. However it is possible it may increase the chance of diseases related to a weaker immune system.
- **If you are having or have ever had injections to treat allergies** – it is not known if ustekinumab may affect these.
- **If you are 65 years of age or over** – you may be more likely to get infections.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Qoyvolma.

Some patients have experienced lupus-like reactions including skin lupus or lupus-like syndrome during treatment with ustekinumab. Talk to your doctor right away if you experience a red, raised, scaly rash sometimes with a darker border, in areas of the skin that are exposed to the sun or with joint pains.

Heart attack and strokes
Heart attack and strokes have been observed in a study in patients with psoriasis treated with ustekinumab. Your doctor will regularly check your risk factors for heart disease and stroke in order to ensure that they are appropriately treated. Seek medical attention right away if you develop chest pain, weakness or abnormal sensation on one side of your body, facial droop, or speech or visual abnormalities.

Children and adolescents
Qoyvolma is not recommended for use in children under 18 years of age with Crohn's disease or ulcerative colitis because it has not been studied in this age group.

Other medicines, vaccines and Qoyvolma
Tell your doctor or pharmacist:
- If you are taking, have recently taken or might take any other medicines.
- If you have recently had or are going to have a vaccination. Some types of vaccines (live vaccines) should not be given while using Qoyvolma.
- If you received Qoyvolma while pregnant, tell your baby's doctor about your Qoyvolma treatment before the baby receives any vaccine, including live vaccines, such as the BCG vaccine (used to prevent tuberculosis). Live vaccines are not recommended for your baby in the first twelve months after birth if you received Qoyvolma during the pregnancy unless your baby's doctor recommends otherwise.

Pregnancy and breast-feeding
- If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.
- A higher risk of birth defects has not been seen in babies exposed to ustekinumab in the womb. However, there is limited experience with ustekinumab in pregnant women. It is therefore preferable to avoid the use of Qoyvolma in pregnancy.
- If you are a woman of childbearing potential, you are advised to avoid becoming pregnant and must use adequate contraception while using Qoyvolma and for at least 15 weeks after the last Qoyvolma treatment.
- Ustekinumab can pass across the placenta to the unborn baby. If you received Qoyvolma during your pregnancy, your baby may have a higher risk for getting an infection.
- It is important that you tell your baby's doctors and other health care professionals if you received Qoyvolma during your pregnancy before the baby receives any vaccine. Live vaccines such as the BCG vaccine (used to prevent tuberculosis) are not recommended for your baby in the first twelve months after birth if you received Qoyvolma during the pregnancy unless your baby's doctor recommends otherwise.
- Ustekinumab may pass into breast milk in very small amounts. Talk to your doctor if you are breast-feeding or are planning to breast-feed. You and your doctor should decide if you should breast-feed or use Qoyvolma - do not do both.

Driving and using machines
Qoyvolma has no or negligible influence on the ability to drive and use machines.

Qoyvolma contains sodium
Qoyvolma contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'. However, before Qoyvolma is given to you, it is mixed with a solution that contains sodium. Talk to your doctor if you are on a low salt diet.

3. How Qoyvolma will be given

Qoyvolma is intended for use under the guidance and supervision of a doctor experienced in the diagnosis and treatment of Crohn's disease or ulcerative colitis.

Qoyvolma 130 mg concentrate for solution for infusion will be given to you by your doctor, through a drip in the vein of your arm (intravenous infusion) over at least one hour. Talk to your doctor about when you will have your injections and follow-up appointments.

How much Qoyvolma is given
Your doctor will decide how much Qoyvolma you need to receive and for how long.

Adults aged 18 years or older

- The doctor will work out the recommended intravenous infusion dose for you based on your body weight.

Your body weight	Dose
≤ 55 kg	260 mg
> 55 kg to ≤ 85 kg	390 mg
> 85 kg	520 mg

- After the starting intravenous dose, you will have the next dose of 90 mg Qoyvolma by an injection under your skin (subcutaneous injection) 8 weeks later, and then every 12 weeks thereafter.

How Qoyvolma is given

- The first dose of Qoyvolma for treatment of Crohn's disease or ulcerative colitis is given by a doctor as a drip in the vein of an arm (intravenous infusion).

Talk to your doctor if you have any questions about receiving Qoyvolma.

If you forget to use Qoyvolma

If you forget or miss the appointment for receiving the dose, contact your doctor to reschedule your appointment.

If you stop using Qoyvolma

It is not dangerous to stop using Qoyvolma. However, if you stop, your symptoms may come back.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

Some patients may have serious side effects that may need urgent treatment.

Allergic reactions – these may need urgent treatment. Tell your doctor or get emergency medical help straight away if you notice any of the following signs.

- Serious allergic reactions ('anaphylaxis') are rare in people taking ustekinumab (may affect up to 1 in 1 000 people). Signs include:
  - difficulty breathing or swallowing
  - low blood pressure, which can cause dizziness or light-headedness
  - swelling of the face, lips, mouth or throat.
- Common signs of an allergic reaction include skin rash and hives (these may affect up to 1 in 100 people).

Infusion-related reactions – If you are being treated for Crohn's disease or ulcerative colitis, the first dose of Qoyvolma is given through a drip into a vein (intravenous infusion). Some patients have experienced serious allergic reactions during the infusion.

In rare cases, allergic lung reactions and lung inflammation have been reported in patients who receive ustekinumab. Tell your doctor right away if you develop symptoms such as cough, shortness of breath, and fever.

If you have a serious allergic reaction, your doctor may decide that you should not use Qoyvolma again.

Infections – these may need urgent treatment. Tell your doctor straight away if you notice any of the following signs.

- Infections of the nose or throat and common cold are common (may affect up to 1 in 10 people)
- Infections of the chest are uncommon (may affect up to 1 in 100 people)
- Inflammation of tissue under the skin ('cellulitis') is uncommon (may affect up to 1 in 100 people)
- Shingles (a type of painful rash with blisters) are uncommon (may affect up to 1 in 100 people)

Qoyvolma may make you less able to fight infections. Some infections could become serious and may include infections caused by viruses, fungi, bacteria (including tuberculosis), or parasites, including infections that mainly occur in people with a weakened immune system (opportunistic infections). Opportunistic infections of the brain (encephalitis, meningitis), lungs, and eye have been reported in patients receiving treatment with ustekinumab.

You must look out for signs of infection while you are using Qoyvolma. These include:

- fever, flu-like symptoms, night sweats, weight loss
- feeling tired or short of breath; cough which will not go away
- warm, red and painful skin, or a painful skin rash with blisters
- burning when passing water
- diarrhoea
- visual disturbance or vision loss
- headache, neck stiffness, light sensitivity, nausea or confusion.

Tell your doctor straight away if you notice any of these signs of infection. These may be signs of infections such as chest infections, skin infections, shingles or opportunistic infections that could have serious complications. Tell your doctor if you have any kind of infection that will not go away or keeps coming back. Your doctor may decide that you should not use Qoyvolma until the infection goes away. Also tell your doctor if you have any open cuts or sores as they might get infected.

Shedding of skin – increase in redness and shedding of skin over a larger area of the body may be symptoms of erythrodermic psoriasis or exfoliative dermatitis, which are serious skin conditions. You should tell your doctor straight away if you notice any of these signs.

Other side effects

Common side effects (may affect up to 1 in 10 people):

- Diarrhoea
- Nausea
- Vomiting
- Feeling tired
- Feeling dizzy
- Headache
- Itching ('pruritus')
- Back, muscle or joint pain
- Sore throat
- Redness and pain where the injection is given
- Sinus infection

Uncommon side effects (may affect up to 1 in 100 people):

- Tooth infections
- Vaginal yeast infection
- Depression
- Blocked or stuffy nose
- Bleeding, bruising, hardness, swelling and itching where the injection is given
- Feeling weak

- Drooping eyelid and sagging muscles on one side of the face ('facial palsy' or 'Bell's palsy'), which is usually temporary
- A change in psoriasis with redness and new tiny, yellow or white skin blisters, sometimes accompanied by fever (pustular psoriasis)
- Peeling of the skin (skin exfoliation)
- Acne

Rare side effects (may affect up to 1 in 1 000 people)
- Redness and shedding of skin over a larger area of the body, which may be itchy or painful (exfoliative dermatitis). Similar symptoms sometimes develop as a natural change in the type of psoriasis symptoms (erythrodermic psoriasis)
- Inflammation of small blood vessels, which can lead to a skin rash with small red or purple bumps, fever or joint pain (vasculitis)

Very rare side effects (may affect up to 1 in 10 000 people)
- Blistering of the skin that may be red, itchy, and painful (Bullous pemphigoid).
- Skin lupus or lupus-like syndrome (red, raised scaly rash on areas of the skin exposed to the sun possibly with joint pains).

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Qoyvolma

- Qoyvolma 130 mg concentrate for solution for infusion is given in a hospital or clinic and patients should not need to store or handle it.
- Keep this medicine out of the sight and reach of children.
- Store in a refrigerator (2 °C–8 °C). Do not freeze.
- Keep the vial in the outer carton in order to protect from light.
- If needed, individual Qoyvolma vials may also be stored at room temperature up to 30 °C for a maximum single period of up to 31 days in the original carton in order to protect from light. Record the date when the vial is first removed from the refrigerator and the discard date in the space provided on the outer carton. The discard date must not exceed the original expiry date printed on the carton. Once a vial has been stored at room temperature (up to 30 °C), it should not be returned to the refrigerator. Discard the vial if not used within 31 days at room temperature storage or by the original expiry date, whichever is earlier.
- Do not shake the Qoyvolma vials. Prolonged vigorous shaking may damage the medicine.

Do not use this medicine:
- After the expiry date which is stated on the label and the carton after 'EXP'. The expiry date refers to the last day of that month.
- If the liquid is discoloured, cloudy or you can see other foreign particles floating in it (see section 6 'What Qoyvolma looks like and contents of the pack').
- If you know, or think that it may have been exposed to extreme temperatures (such as accidentally frozen or heated).
- If the product has been shaken vigorously.
- If the seal is broken.

Qoyvolma is for single use only. Any diluted infusion solution or unused product remaining in the vial and the syringe should be thrown away in accordance with local requirements.

6. Contents of the pack and other information

What Qoyvolma contains
- The active substance is ustekinumab. Each vial contains 130 mg ustekinumab in 26 mL.
- The other ingredients are EDTA disodium salt dihydrate (E385), L-histidine, L-histidine monohydrochloride monohydrate, L-methionine, polysorbate 80 (E433), sucrose and water for injections.

What Qoyvolma looks like and contents of the pack
Qoyvolma is a clear to slightly opalescent, colourless to pale yellow concentrate for solution for infusion. It is supplied as a carton pack containing 1 single-dose, glass 30 mL vial. Each vial contains 130 mg ustekinumab in 26 mL of concentrate for solution for infusion.

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This leaflet was last revised in <{MM/YYYY}>.

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

Traceability:

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

Instructions for dilution:

Qoyvolma concentrate for solution for infusion must be diluted, prepared and infused by a healthcare professional using aseptic technique.

1. Calculate the dose and the number of Qoyvolma vials needed based on patient weight (see section 3, Table 1). Each 26 mL vial of Qoyvolma contains 130 mg of ustekinumab.
2. Withdraw and then discard a volume of the sodium chloride 9 mg/mL (0.9%) solution from the 250 mL infusion bag equal to the volume of Qoyvolma to be added (discard 26 mL sodium chloride for each vial of Qoyvolma needed, for 2 vials - discard 52 mL, for 3 vials - discard 78 mL, for 4 vials - discard 104 mL).
3. Withdraw 26 mL of Qoyvolma from each vial needed and add it to the 250 mL infusion bag. The final volume in the infusion bag should be 250 mL. Gently mix.
4. Visually inspect the diluted solution before infusion. Do not use if visibly opaque particles, discolouration or foreign particles are observed.
5. Infuse the diluted solution over a period of at least one hour. Once diluted, the infusion should be completed within forty-eight hours of the dilution in the infusion bag.
6. Use only an infusion set with an in-line, sterile, non-pyrogenic, low protein-binding filter (pore size 0.2 micrometer).
7. Each vial is for single use only and any unused medicinal product should be disposed of in accordance with local requirements.

Storage

If necessary, the diluted infusion solution may be stored at room temperature up to 30 °C. The infusion should be completed within 48 hours of the dilution in the infusion bag. Do not freeze.

Package leaflet: Information for the user

Qoyvolma 45 mg solution for injection in pre-filled syringe
ustekinumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

This leaflet has been written for the person taking the medicine. If you are the parent or caregiver who will give Qoyvolma to a child, please read this information carefully.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Qoyvolma is and what it is used for

What Qoyvolma is
Qoyvolma contains the active substance ‘ustekinumab’, a monoclonal antibody. Monoclonal antibodies are proteins that recognise and bind specifically to certain proteins in the body.

Qoyvolma belongs to a group of medicines called ‘immunosuppressants’. These medicines work by weakening part of the immune system.

What Qoyvolma is used for
Qoyvolma is used to treat the following inflammatory diseases:
- Plaque psoriasis - in adults and children aged 6 years and older
- Psoriatic arthritis - in adults
- Moderate to severe Crohn’s disease - in adults
- Moderate to severe ulcerative colitis - in adults

Plaque psoriasis
Plaque psoriasis is a skin condition that causes inflammation affecting the skin and nails. Qoyvolma will reduce the inflammation and other signs of the disease.

Qoyvolma is used in adults with moderate to severe plaque psoriasis, who cannot use ciclosporin, methotrexate or phototherapy, or where these treatments did not work.

Qoyvolma is used in children and adolescents aged 6 years and older with moderate to severe plaque psoriasis who are unable to tolerate phototherapy or other systemic therapies or where these treatments did not work.

Psoriatic arthritis
Psoriatic arthritis is an inflammatory disease of the joints, usually accompanied by psoriasis. If you have active psoriatic arthritis you will first be given other medicines. If you do not respond well enough to these medicines, you may be given Qoyvolma to:
- Reduce the signs and symptoms of your disease.
- Improve your physical function.
- Slow down the damage to your joints.

Crohn's disease
Crohn's disease is an inflammatory disease of the bowel. If you have Crohn's disease you will first be given other medicines. If you do not respond well enough or are intolerant to these medicines, you may be given Qoyvolma to reduce the signs and symptoms of your disease.

Ulcerative colitis
Ulcerative colitis is an inflammatory disease of the bowel. If you have ulcerative colitis you will first be given other medicines. If you do not respond well enough or are intolerant to these medicines, you may be given Qoyvolma to reduce the signs and symptoms of your disease.

2. What you need to know before you use Qoyvolma

Do not use Qoyvolma
- **If you are allergic to ustekinumab** or any of the other ingredients of this medicine (listed in section 6).
- **If you have an active infection** which your doctor thinks is important.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Qoyvolma.

Warnings and precautions
Talk to your doctor or pharmacist before using Qoyvolma. Your doctor will check how well you are before each treatment. Make sure you tell your doctor about any illness you have before each treatment. Also tell your doctor if you have recently been near anyone who might have tuberculosis. Your doctor will examine you and do a test for tuberculosis, before you have Qoyvolma. If your doctor thinks you are at risk of tuberculosis, you may be given medicines to treat it.

Look out for serious side effects
Qoyvolma can cause serious side effects, including allergic reactions and infections. You must look out for certain signs of illness while you are taking Qoyvolma. See 'Serious side effects' in section 4 for a full list of these side effects.

Before you use Qoyvolma tell your doctor:
- **If you ever had an allergic reaction to ustekinumab.** Ask your doctor if you are not sure.
- **If you have ever had any type of cancer** – this is because immunosuppressants like Qoyvolma weaken part of the immune system. This may increase the risk of cancer.
- **If you have been treated for psoriasis with other biologic medicines (a medicine produced from a biological source and usually given by injection)** – the risk of cancer may be higher.
- **If you have or have had a recent infection.**
- **If you have any new or changing lesions** within psoriasis areas or on normal skin.
- **If you are having any other treatment for psoriasis and/or psoriatic arthritis** – such as another immunosuppressant or phototherapy (when your body is treated with a type of ultraviolet (UV) light). These treatments may also weaken part of the immune system. Using

these therapies together with ustekinumab has not been studied. However it is possible it may increase the chance of diseases related to a weaker immune system.
- **If you are having or have ever had injections to treat allergies** – it is not known if ustekinumab may affect these.
- **If you are 65 years of age or over** – you may be more likely to get infections.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Qoyvolma.

Some patients have experienced lupus-like reactions including skin lupus or lupus-like syndrome during treatment with ustekinumab. Talk to your doctor right away if you experience a red, raised, scaly rash sometimes with a darker border, in areas of the skin that are exposed to the sun or with joint pains.

Heart attack and strokes
Heart attack and strokes have been observed in a study in patients with psoriasis treated with ustekinumab. Your doctor will regularly check your risk factors for heart disease and stroke in order to ensure that they are appropriately treated. Seek medical attention right away if you develop chest pain, weakness or abnormal sensation on one side of your body, facial droop, or speech or visual abnormalities.

Children and adolescents
Qoyvolma is not recommended for use in children with psoriasis under 6 years of age, or for use in children under 18 years of age with psoriatic arthritis, Crohn's disease, or ulcerative colitis because it has not been studied in this age group.

Other medicines, vaccines and Qoyvolma
Tell your doctor or pharmacist:
- If you are taking, have recently taken or might take any other medicines.
- If you have recently had or are going to have a vaccination. Some types of vaccines (live vaccines) should not be given while using Qoyvolma.
- If you received Qoyvolma while pregnant, tell your baby's doctor about your Qoyvolma treatment before the baby receives any vaccine, including live vaccines, such as the BCG vaccine (used to prevent tuberculosis). Live vaccines are not recommended for your baby in the first twelve months after birth if you received Qoyvolma during the pregnancy unless your baby's doctor recommends otherwise.

Pregnancy and breast-feeding
- If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.
- A higher risk of birth defects has not been seen in babies exposed to ustekinumab in the womb. However, there is limited experience with ustekinumab in pregnant women. It is therefore preferable to avoid the use of Qoyvolma in pregnancy.
- If you are a woman of childbearing potential, you are advised to avoid becoming pregnant and must use adequate contraception while using Qoyvolma and for at least 15 weeks after the last Qoyvolma treatment.
- Ustekinumab can pass across the placenta to the unborn baby. If you received Qoyvolma during your pregnancy, your baby may have a higher risk for getting an infection.
- It is important that you tell your baby's doctors and other health care professionals if you received Qoyvolma during your pregnancy before the baby receives any vaccine. Live vaccines such as the BCG vaccine (used to prevent tuberculosis) are not recommended for your baby in the first twelve months after birth if you received Qoyvolma during the pregnancy unless your baby's doctor recommends otherwise.
- Ustekinumab may pass into breast milk in very small amounts. Talk to your doctor if you are breast-feeding or are planning to breast-feed. You and your doctor should decide if you should breast-feed or use Qoyvolma - do not do both.

Driving and using machines
Qoyvolma has no or negligible influence on the ability to drive and use machines.

3. How to use Qoyvolma

Qoyvolma is intended for use under the guidance and supervision of a doctor experienced in treating conditions for which Qoyvolma is intended.

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure. Talk to your doctor about when you will have your injections and follow-up appointments.

How much Qoyvolma is given
Your doctor will decide how much Qoyvolma you need to use and for how long.

Adults aged 18 years or older
Psoriasis or Psoriatic Arthritis
- The recommended starting dose is 45 mg Qoyvolma. Patients who weigh more than 100 kilograms (kg) may start on a dose of 90 mg instead of 45 mg.
- After the starting dose, you will have the next dose 4 weeks later, and then every 12 weeks. The following doses are usually the same as the starting dose.

Crohn's disease or Ulcerative Colitis
- During treatment, the first dose of approximately 6 mg/kg Qoyvolma will be given by your doctor through a drip in a vein in your arm (intravenous infusion). After the starting dose, you will receive the next dose of 90 mg Qoyvolma after 8 weeks, then every 12 weeks thereafter by an injection under the skin ('subcutaneously').
- In some patients, after the first injection under the skin, 90 mg Qoyvolma may be given every 8 weeks. Your doctor will decide when you should receive your next dose.

Children and adolescents aged 6 years or older

Psoriasis
There is no dosage form for Qoyvolma for children with plaque psoriasis below 60 kg body weight and therefore other ustekinumab products should be used.
- The doctor will work out the right dose for you, including the amount (volume) of Qoyvolma to be injected to give the right dose. The right dose for you will depend on your body weight at the time each dose is given.
- If you weigh less than 60 kg, there is no dose form of Qoyvolma available and other ustekinumab products should be used.
- If you weigh 60 kg to 100 kg, the recommended dose is 45 mg Qoyvolma.
- If you weigh more than 100 kg, the recommended dose is 90 mg Qoyvolma.
- After the starting dose, you will have the next dose 4 weeks later, and then every 12 weeks.

How Qoyvolma is given
- Qoyvolma is given as an injection under the skin ('subcutaneously'). At the start of your treatment, medical or nursing staff may inject Qoyvolma.
- However, you and your doctor may decide that you may inject Qoyvolma yourself. In this case you will get training on how to inject Qoyvolma yourself.
- For instructions on how to inject Qoyvolma, see 'Instructions for administration' at the end of this leaflet.

Talk to your doctor if you have any questions about giving yourself an injection.

If you use more Qoyvolma than you should
If you have used or been given too much Qoyvolma, talk to a doctor or pharmacist straight away. Always have the outer carton of the medicine with you, even if it is empty.

If you forget to use Qoyvolma
If you forget a dose, contact your doctor or pharmacist. Do not take a double dose to make up for a forgotten dose.

If you stop using Qoyvolma
It is not dangerous to stop using Qoyvolma. However, if you stop, your symptoms may come back.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Some patients may have serious side effects that may need urgent treatment.

Allergic reactions – these may need urgent treatment. Tell your doctor or get emergency medical help straight away if you notice any of the following signs.

- Serious allergic reactions ('anaphylaxis') are rare in people taking ustekinumab (may affect up to 1 in 1 000 people). Signs include:
  - difficulty breathing or swallowing
  - low blood pressure, which can cause dizziness or light-headedness
  - swelling of the face, lips, mouth or throat.
- Common signs of an allergic reaction include skin rash and hives (these may affect up to 1 in 100 people).

In rare cases, allergic lung reactions and lung inflammation have been reported in patients who receive ustekinumab. Tell your doctor right away if you develop symptoms such as cough, shortness of breath, and fever.

If you have a serious allergic reaction, your doctor may decide that you should not use Qoyvolma again.

Infections – these may need urgent treatment. Tell your doctor straight away if you notice any of the following signs.

- Infections of the nose or throat and common cold are common (may affect up to 1 in 10 people)
- Infections of the chest are uncommon (may affect up to 1 in 100 people)
- Inflammation of tissue under the skin ('cellulitis') is uncommon (may affect up to 1 in 100 people)
- Shingles (a type of painful rash with blisters) are uncommon (may affect up to 1 in 100 people)

Qoyvolma may make you less able to fight infections. Some infections could become serious and may include infections caused by viruses, fungi, bacteria (including tuberculosis), or parasites, including infections that mainly occur in people with a weakened immune system (opportunistic infections). Opportunistic infections of the brain (encephalitis, meningitis), lungs, and eye have been reported in patients receiving treatment with ustekinumab.

You must look out for signs of infection while you are using Qoyvolma. These include:

- fever, flu-like symptoms, night sweats, weight loss
- feeling tired or short of breath; cough which will not go away
- warm, red and painful skin, or a painful skin rash with blisters
- burning when passing water
- diarrhoea
- visual disturbance or vision loss

- headache, neck stiffness, light sensitivity, nausea or confusion.

Tell your doctor straight away if you notice any of these signs of infection. These may be signs of infections such as chest infections, skin infections, shingles or opportunistic infections that could have serious complications. Tell your doctor if you have any kind of infection that will not go away or keeps coming back. Your doctor may decide that you should not use Qoyvolma until the infection goes away. Also tell your doctor if you have any open cuts or sores as they might get infected.

Shedding of skin – increase in redness and shedding of skin over a larger area of the body may be symptoms of erythrodermic psoriasis or exfoliative dermatitis, which are serious skin conditions. You should tell your doctor straight away if you notice any of these signs.

Other side effects

Common side effects (may affect up to 1 in 10 people):
- Diarrhoea
- Nausea
- Vomiting
- Feeling tired
- Feeling dizzy
- Headache
- Itching ('pruritus')
- Back, muscle or joint pain
- Sore throat
- Redness and pain where the injection is given
- Sinus infection

Uncommon side effects (may affect up to 1 in 100 people):
- Tooth infections
- Vaginal yeast infection
- Depression
- Blocked or stuffy nose
- Bleeding, bruising, hardness, swelling and itching where the injection is given
- Feeling weak
- Drooping eyelid and sagging muscles on one side of the face ('facial palsy' or 'Bell's palsy'), which is usually temporary
- A change in psoriasis with redness and new tiny, yellow or white skin blisters, sometimes accompanied by fever (pustular psoriasis)
- Peeling of the skin (skin exfoliation)
- Acne

Rare side effects (may affect up to 1 in 1 000 people)
- Redness and shedding of skin over a larger area of the body, which may be itchy or painful (exfoliative dermatitis). Similar symptoms sometimes develop as a natural change in the type of psoriasis symptoms (erythrodermic psoriasis)
- Inflammation of small blood vessels, which can lead to a skin rash with small red or purple bumps, fever or joint pain (vasculitis)

Very rare side effects (may affect up to 1 in 10 000 people)
- Blistering of the skin that may be red, itchy, and painful (Bullous pemphigoid).
- Skin lupus or lupus-like syndrome (red, raised scaly rash on areas of the skin exposed to the sun possibly with joint pains).

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system

listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Qoyvolma

- Keep this medicine out of the sight and reach of children.
- 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 Qoyvolma pre-filled syringes may also be stored at room temperature up to 30 °C for a maximum single period of up to 31 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 space 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 31 days at room temperature storage or by the original expiry date, whichever is earlier.
- Do not shake Qoyvolma pre-filled syringes. Prolonged vigorous shaking may damage the medicine.

Do not use this medicine:
- After the expiry date which is stated on the label and the carton after 'EXP'. The expiry date refers to the last day of that month.
- If the liquid is discoloured, cloudy or you can see other foreign particles floating in it (see section 6 'What Qoyvolma looks like and contents of the pack').
- If you know, or think that it may have been exposed to extreme temperatures (such as accidentally frozen or heated).
- If the product has been shaken vigorously.

Qoyvolma is for single use only. Any unused product remaining in the syringe should be thrown away. Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Qoyvolma contains
- The active substance is ustekinumab. Each pre-filled syringe contains 45 mg ustekinumab in 0.5 mL.
- The other ingredients are L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80 (E433), sucrose and water for injections.

What Qoyvolma looks like and contents of the pack
Qoyvolma is a clear to slightly opalescent (having a pearl-like shine), colourless to pale yellow solution for injection. The solution may contain a few small translucent or white particles of protein. It is supplied as a carton pack containing 1 single-dose, glass 1 mL pre-filled syringe. Each pre-filled syringe contains 45 mg ustekinumab in 0.5 mL of solution for injection.

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This leaflet was last revised in <{MM/YYYY}>.

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

Instructions for administration

At the start of treatment, your healthcare provider will assist you with your first injection. However, you and your doctor may decide that you may inject Qoyvolma yourself. If this happens, you will get training on how to inject Qoyvolma. Talk to your doctor if you have any questions about giving yourself an injection.

Important Information

- **Do not** open the sealed carton until you are ready to use the pre-filled syringe.
- **Do not** remove the cap until just before you give the injection.
- **Do not** mix Qoyvolma with other liquids for injection.
- The pre-filled syringe cannot be re-used. Dispose of the used pre-filled syringe immediately after use in a sharps disposal container (see **Step 14. Dispose of Qoyvolma**).

Storing Qoyvolma

- **Keep the pre-filled syringe out of the sight and reach of children**. Contains small part.
- Store the pre-filled syringe in a refrigerator between 2 °C and 8 ºC. **Do not** freeze.
- Store this medicine sealed inside its carton to protect it from light.
- If needed, individual Qoyvolma pre-filled syringes may also be stored at room temperature up to 30 °C for a maximum single period of up to 31 days in the original carton in order to protect from light.
- **Do not** shake Qoyvolma pre-filled syringes. Strong shaking may damage the medicine.
- **Do not** use the medicine if it has been shaken strongly.
- **Do not** use the pre-filled syringe if it has been dropped.

Parts of the Pre-filled Syringe (see Figure A)

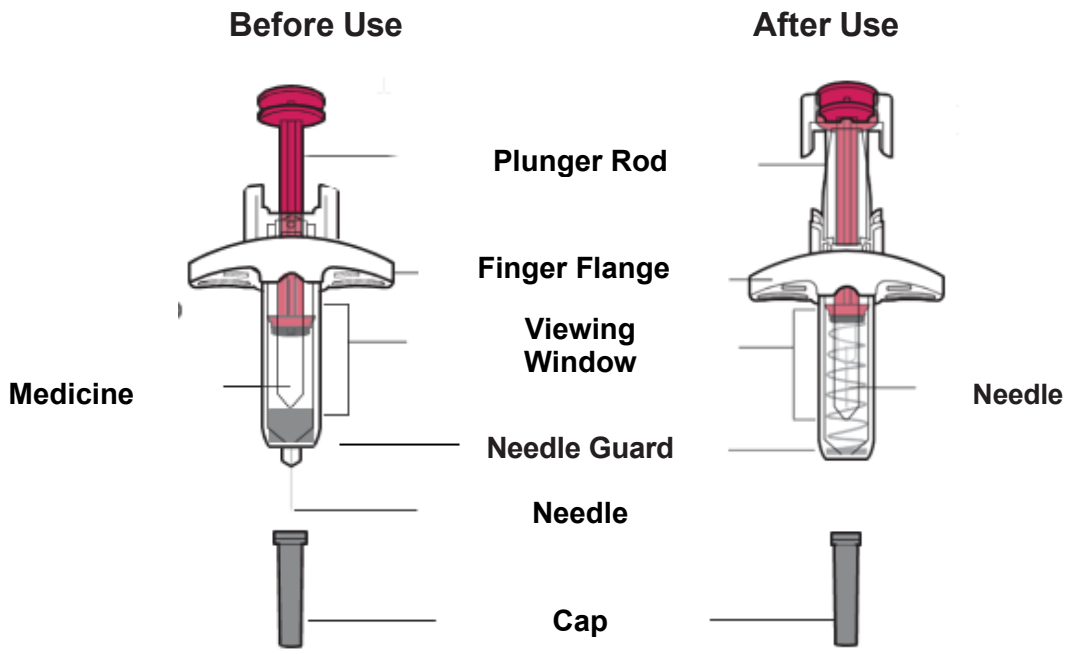

Figure A

Preparing for the Injection

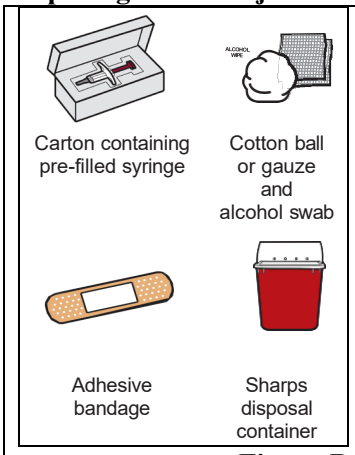

Figure B

1. Gather the supplies for the injection

a. Prepare a clean, flat surface, such as a table or counter top, in a well-lit area.

b. Take the carton(s) containing the pre-filled syringe(s) needed to administer your prescribed dose out of the refrigerator.

c. Make sure you have the following supplies (see Figure B):

- Carton containing pre-filled syringe

Not included in the carton:

- Cotton ball or gauze
- Adhesive bandage
- Sharps disposal container
- Alcohol swab

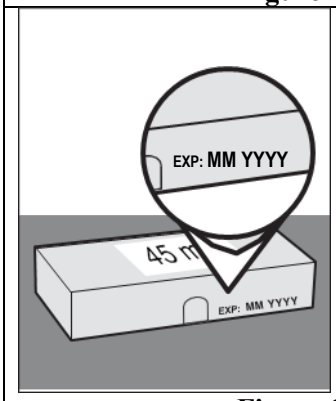

Figure C

2. Check the expiration date on the carton (see Figure C).

- **Do not** use it if the expiration date has passed. If the expiration date has passed, return the entire pack to the pharmacy.

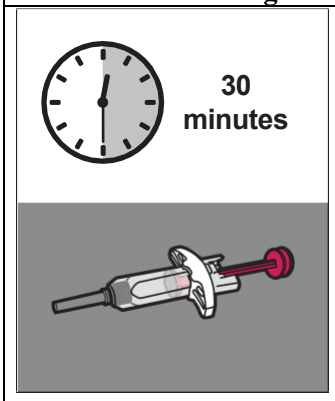

Figure D

3. Wait 30 minutes.

a. Open the carton. Gripping from the syringe body, lift the pre-filled syringe from the carton.

b. Let the pre-filled syringe stand outside the box for about 30 minutes at room temperature (20 °C to 25 °C) to allow it to warm up (see **Figure D**).

- This will let the liquid come to a comfortable temperature for injection (room temperature).
- **Do not** warm the pre-filled syringe using heat sources such as hot water or a microwave.
- **Do not** hold by the plunger head, plunger rod, needle guard wings, or needle cover
- **Do not** pull back on the plunger rod at any time.

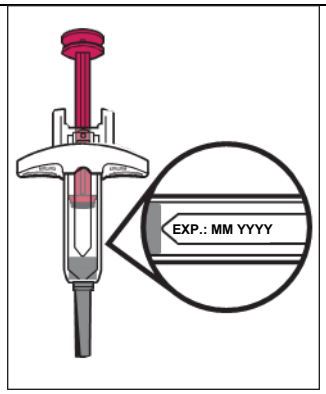

Figure E

4. Inspect the pre-filled syringe.

a. Look at the pre-filled syringe and make sure you have the correct medicine (Qoyvolma) and dosage.

b. Check the pre-filled syringe(s) to make sure the number of pre-filled syringes and strength is correct:

- If your dose is 45 mg you will get one 45 mg pre-filled syringe of Qoyvolma.
- If your dose is 90 mg you will get two 45 mg pre-filled syringes of Qoyvolma and you will need to give yourself two injections. Choose two different sites for these injections (e.g. one injection in the right thigh and the other injection in the left thigh), and give the injections one right after the other.

c. Look at the pre-filled syringe and make sure it is not cracked or damaged.

d. Check the expiration date on the label of the pre-filled syringe (see **Figure E**).

- **Do not** use if the expiration date has passed.
- **Do not** shake the pre-filled syringe.

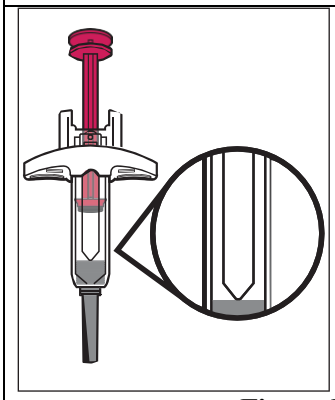

Figure F

5. Inspect the medicine.

a. Look at the medicine and confirm that the liquid is clear to slightly opalescent and colourless to pale yellow. (see **Figure F**).

- **Do not** use the pre-filled syringe if the liquid is discoloured or cloudy.
- You may see air bubbles in the liquid. This is normal.

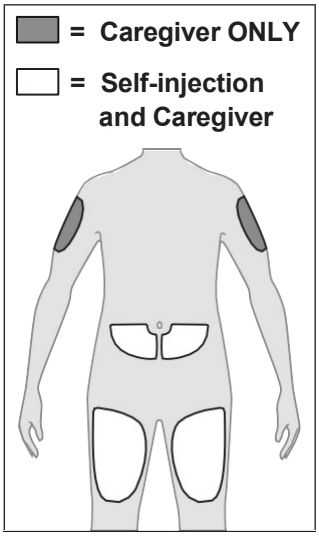

Figure G

6. Choose an appropriate injection site (see Figure G).

a. You may inject into:

- Your upper thighs.
- Your lower abdomen except for the 5 cm around the belly button (navel).
- The outer area of the upper arm if you are a caregiver.

- **Do not** inject into moles, scars, bruises, or areas where the skin is tender, red, hard, or if there are breaks in the skin. If possible, do not use areas of skin that show signs of psoriasis.
- **Do not** inject through your clothes.

b. Choose a different injection site for each new injection at least 2.5 cm away from the area used for the last injection.

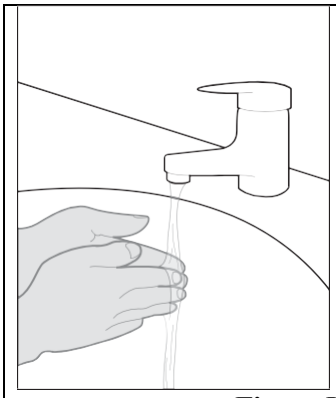

Figure H

7. Wash your hands.

a. Wash your hands with soap and water and dry them thoroughly (see **Figure H**).

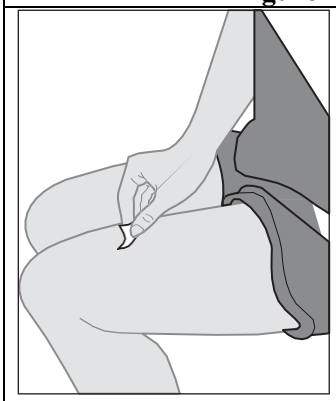

Figure I

8. Clean the injection site.

a. Clean the injection site with an alcohol swab using a circular motion (see **Figure I**).

b. Let the skin dry before injecting.

- **Do not** blow on or touch the injection site again before giving the injection.

Administering the Injection

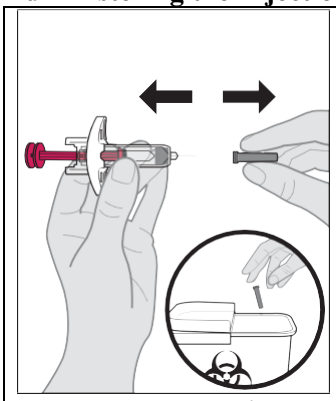

Figure J

9. Remove the cap.

a. Remove the needle cover when you are ready to inject your Qoyvolma by holding the body of the pre-filled syringe in one hand between the thumb and index finger (see **Figure J**).

- **Do not** hold the plunger rod while removing the cap.
- You may notice an air bubble in the pre-filled syringe or a drop of liquid at the tip of needle. This is normal.

b. Dispose of the cap right away in a sharps disposal container (see **Step 14** and **Figure J**).

- **Do not** use the pre-filled syringe if it is dropped without the needle cover in place. If this happens, please contact your doctor or pharmacist.
- Inject the dose promptly after removing the needle cover.
- **Do not** re-cap the pre-filled syringe.
- **Do not** touch the needle. Doing so may result in a needle stick injury.

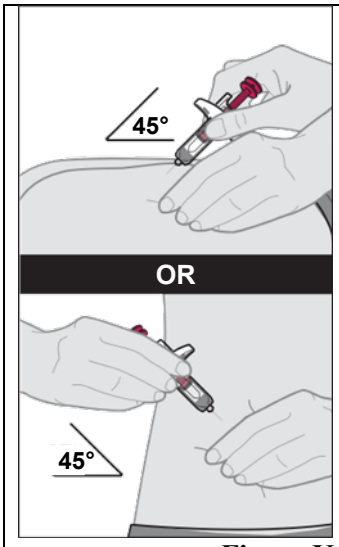

Figure K

10. Insert the pre-filled syringe into the injection site.

a. Hold the body of the pre-filled syringe in one hand between the thumb and index finger.

b. Use the other hand to gently pinch the cleaned skin between your thumb and index finger. **Do not** squeeze it tightly.
Note: Pinching the skin is important to make sure that you inject under the skin (into the fatty area) but not any deeper (into muscle).

c. With a quick and dart-like motion, insert the needle completely into the fold of skin at a 45-degree angle (see Figure K).

- **Do not pull back on the plunger rod at any time.**

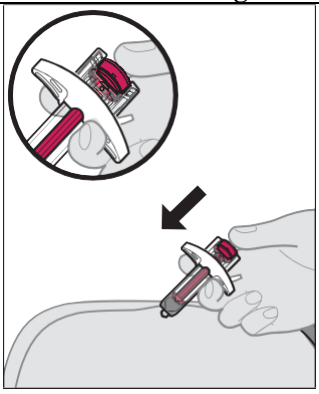

Figure L

11. Give the injection.

a. After the needle is inserted, release the pinch.

b. Slowly push the plunger rod **all the way down** until the full dose of medicine gets injected, and the syringe is empty (see **Figure L**).

- **Do not** change the position of the pre-filled syringe after the injection has started.
- If the plunger rod is not fully pressed, the needle guard will not extend to cover the needle when it is removed.

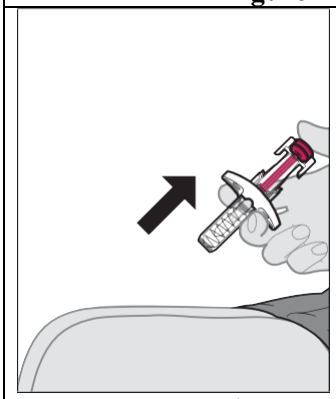

Figure M

12. Remove the pre-filled syringe from the injection site.

a. After the pre-filled syringe is empty, as the needle is being taken out, slowly remove the needle by lifting your thumb from the plunger rod until the needle is completely covered by the needle guard (see **Figure M**).

- If the needle is not covered, proceed carefully to dispose of the syringe (see **Step 14**. **Dispose of Qoyvolma**).
- **Do not** reuse the pre-filled syringe.
- **Do not** rub the injection site.

After the Injection

13. Care for the injection site.

a. If some bleeding occurs, treat the injection site by gently pressing, not rubbing, a cotton ball or gauze to the site and apply an adhesive bandage if needed.

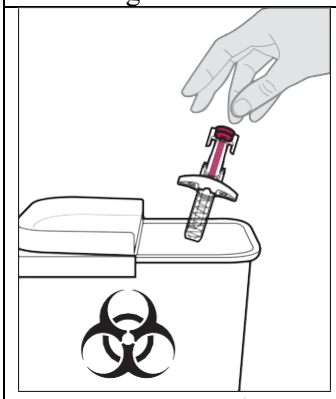

Figure N

14. Dispose of Qoyvolma.

a. Put the used pre-filled syringe in a sharps disposal container right away after use (see **Figure N**).

b. Do not throw away (dispose of) the pre-filled syringe in your household trash.

- If you do not have a sharps disposal container, you may use a household container that is closable and puncture resistant.
- For the safety and health of you and others, needles and used syringes must never be reused. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
- **Do not** throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

Package leaflet: Information for the user

Qoyvolma 90 mg solution for injection in pre-filled syringe
ustekinumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

This leaflet has been written for the person taking the medicine. If you are the parent or caregiver who will give Qoyvolma to a child, please read this information carefully.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Qoyvolma is and what it is used for

What Qoyvolma is
Qoyvolma contains the active substance ‘ustekinumab’, a monoclonal antibody. Monoclonal antibodies are proteins that recognise and bind specifically to certain proteins in the body.

Qoyvolma belongs to a group of medicines called ‘immunosuppressants’. These medicines work by weakening part of the immune system.

What Qoyvolma is used for
Qoyvolma is used to treat the following inflammatory diseases:
- Plaque psoriasis - in adults and children aged 6 years and older
- Psoriatic arthritis - in adults
- Moderate to severe Crohn’s disease - in adults
- Moderate to severe ulcerative colitis - in adults

Plaque psoriasis
Plaque psoriasis is a skin condition that causes inflammation affecting the skin and nails. Qoyvolma will reduce the inflammation and other signs of the disease.

Qoyvolma is used in adults with moderate to severe plaque psoriasis, who cannot use ciclosporin, methotrexate or phototherapy, or where these treatments did not work.

Qoyvolma is used in children and adolescents aged 6 years and older with moderate to severe plaque psoriasis who are unable to tolerate phototherapy or other systemic therapies or where these treatments did not work.

Psoriatic arthritis
Psoriatic arthritis is an inflammatory disease of the joints, usually accompanied by psoriasis. If you have active psoriatic arthritis you will first be given other medicines. If you do not respond well enough to these medicines, you may be given Qoyvolma to:
- Reduce the signs and symptoms of your disease.
- Improve your physical function.
- Slow down the damage to your joints.

Crohn's disease
Crohn's disease is an inflammatory disease of the bowel. If you have Crohn's disease you will first be given other medicines. If you do not respond well enough or are intolerant to these medicines, you may be given Qoyvolma to reduce the signs and symptoms of your disease.

Ulcerative colitis
Ulcerative colitis is an inflammatory disease of the bowel. If you have ulcerative colitis you will first be given other medicines. If you do not respond well enough or are intolerant to these medicines, you may be given Qoyvolma to reduce the signs and symptoms of your disease.

2. What you need to know before you use Qoyvolma

Do not use Qoyvolma
- **If you are allergic to ustekinumab** or any of the other ingredients of this medicine (listed in section 6).
- **If you have an active infection** which your doctor thinks is important.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Qoyvolma.

Warnings and precautions
Talk to your doctor or pharmacist before using Qoyvolma. Your doctor will check how well you are before each treatment. Make sure you tell your doctor about any illness you have before each treatment. Also tell your doctor if you have recently been near anyone who might have tuberculosis. Your doctor will examine you and do a test for tuberculosis, before you have Qoyvolma. If your doctor thinks you are at risk of tuberculosis, you may be given medicines to treat it.

Look out for serious side effects
Qoyvolma can cause serious side effects, including allergic reactions and infections. You must look out for certain signs of illness while you are taking Qoyvolma. See 'Serious side effects' in section 4 for a full list of these side effects.

Before you use Qoyvolma tell your doctor:
- **If you ever had an allergic reaction to ustekinumab.** Ask your doctor if you are not sure.
- **If you have ever had any type of cancer** – this is because immunosuppressants like Qoyvolma weaken part of the immune system. This may increase the risk of cancer.
- **If you have been treated for psoriasis with other biologic medicines (a medicine produced from a biological source and usually given by injection)** – the risk of cancer may be higher.
- **If you have or have had a recent infection.**
- **If you have any new or changing lesions** within psoriasis areas or on normal skin.
- **If you are having any other treatment for psoriasis and/or psoriatic arthritis** – such as another immunosuppressant or phototherapy (when your body is treated with a type of ultraviolet (UV) light). These treatments may also weaken part of the immune system. Using

these therapies together with ustekinumab has not been studied. However it is possible it may increase the chance of diseases related to a weaker immune system.
- **If you are having or have ever had injections to treat allergies** – it is not known if ustekinumab may affect these.
- **If you are 65 years of age or over** – you may be more likely to get infections.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Qoyvolma.

Some patients have experienced lupus-like reactions including skin lupus or lupus-like syndrome during treatment with ustekinumab. Talk to your doctor right away if you experience a red, raised, scaly rash sometimes with a darker border, in areas of the skin that are exposed to the sun or with joint pains.

Heart attack and strokes
Heart attack and strokes have been observed in a study in patients with psoriasis treated with ustekinumab. Your doctor will regularly check your risk factors for heart disease and stroke in order to ensure that they are appropriately treated. Seek medical attention right away if you develop chest pain, weakness or abnormal sensation on one side of your body, facial droop, or speech or visual abnormalities.

Children and adolescents
Qoyvolma is not recommended for use in children with psoriasis under 6 years of age, or for use in children under 18 years of age with psoriatic arthritis, Crohn's disease, or ulcerative colitis because it has not been studied in this age group.

Other medicines, vaccines and Qoyvolma
Tell your doctor or pharmacist:
- If you are taking, have recently taken or might take any other medicines.
- If you have recently had or are going to have a vaccination. Some types of vaccines (live vaccines) should not be given while using Qoyvolma.
- If you received Qoyvolma while pregnant, tell your baby's doctor about your Qoyvolma treatment before the baby receives any vaccine, including live vaccines, such as the BCG vaccine (used to prevent tuberculosis). Live vaccines are not recommended for your baby in the first twelve months after birth if you received Qoyvolma during the pregnancy unless your baby's doctor recommends otherwise.

Pregnancy and breast-feeding
- If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.
- A higher risk of birth defects has not been seen in babies exposed to ustekinumab in the womb. However, there is limited experience with ustekinumab in pregnant women. It is therefore preferable to avoid the use of Qoyvolma in pregnancy.
- If you are a woman of childbearing potential, you are advised to avoid becoming pregnant and must use adequate contraception while using Qoyvolma and for at least 15 weeks after the last Qoyvolma treatment.
- Ustekinumab can pass across the placenta to the unborn baby. If you received Qoyvolma during your pregnancy, your baby may have a higher risk for getting an infection.
- It is important that you tell your baby's doctors and other health care professionals if you received Qoyvolma during your pregnancy before the baby receives any vaccine. Live vaccines such as the BCG vaccine (used to prevent tuberculosis) are not recommended for your baby in the first twelve months after birth if you received Qoyvolma during the pregnancy unless your baby's doctor recommends otherwise.
- Ustekinumab may pass into breast milk in very small amounts. Talk to your doctor if you are breast-feeding or are planning to breast-feed. You and your doctor should decide if you should breast-feed or use Qoyvolma - do not do both.

Driving and using machines
Qoyvolma has no or negligible influence on the ability to drive and use machines.

3. How to use Qoyvolma

Qoyvolma is intended for use under the guidance and supervision of a doctor experienced in treating conditions for which Qoyvolma is intended.

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure. Talk to your doctor about when you will have your injections and follow-up appointments.

How much Qoyvolma is given
Your doctor will decide how much Qoyvolma you need to use and for how long.

Adults aged 18 years or older
Psoriasis or Psoriatic Arthritis
- The recommended starting dose is 45 mg Qoyvolma. Patients who weigh more than 100 kilograms (kg) may start on a dose of 90 mg instead of 45 mg.
- After the starting dose, you will have the next dose 4 weeks later, and then every 12 weeks. The following doses are usually the same as the starting dose.

Crohn's disease or Ulcerative Colitis
- During treatment, the first dose of approximately 6 mg/kg Qoyvolma will be given by your doctor through a drip in a vein in your arm (intravenous infusion). After the starting dose, you will receive the next dose of 90 mg Qoyvolma after 8 weeks, then every 12 weeks thereafter by an injection under the skin ('subcutaneously').
- In some patients, after the first injection under the skin, 90 mg Qoyvolma may be given every 8 weeks. Your doctor will decide when you should receive your next dose.

Children and adolescents aged 6 years or older

Psoriasis
There is no dosage form for Qoyvolma for children with plaque psoriasis below 60 kg body weight and therefore other ustekinumab products should be used.
- The doctor will work out the right dose for you, including the amount (volume) of Qoyvolma to be injected to give the right dose. The right dose for you will depend on your body weight at the time each dose is given.
- If you weigh less than 60 kg, there is no dose form of Qoyvolma available and other ustekinumab products should be used.
- If you weigh 60 kg to 100 kg, the recommended dose is 45 mg Qoyvolma.
- If you weigh more than 100 kg, the recommended dose is 90 mg Qoyvolma.
- After the starting dose, you will have the next dose 4 weeks later, and then every 12 weeks.

How Qoyvolma is given
- Qoyvolma is given as an injection under the skin ('subcutaneously'). At the start of your treatment, medical or nursing staff may inject Qoyvolma.
- However, you and your doctor may decide that you may inject Qoyvolma yourself. In this case you will get training on how to inject Qoyvolma yourself.
- For instructions on how to inject Qoyvolma, see 'Instructions for administration' at the end of this leaflet.

Talk to your doctor if you have any questions about giving yourself an injection.

If you use more Qoyvolma than you should
If you have used or been given too much Qoyvolma, talk to a doctor or pharmacist straight away. Always have the outer carton of the medicine with you, even if it is empty.

If you forget to use Qoyvolma
If you forget a dose, contact your doctor or pharmacist. Do not take a double dose to make up for a forgotten dose.

If you stop using Qoyvolma
It is not dangerous to stop using Qoyvolma. However, if you stop, your symptoms may come back.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Some patients may have serious side effects that may need urgent treatment.

Allergic reactions – these may need urgent treatment. Tell your doctor or get emergency medical help straight away if you notice any of the following signs.
- Serious allergic reactions ('anaphylaxis') are rare in people taking ustekinumab (may affect up to 1 in 1 000 people). Signs include:
  - difficulty breathing or swallowing
  - low blood pressure, which can cause dizziness or light-headedness
  - swelling of the face, lips, mouth or throat.
- Common signs of an allergic reaction include skin rash and hives (these may affect up to 1 in 100 people).

In rare cases, allergic lung reactions and lung inflammation have been reported in patients who receive ustekinumab. Tell your doctor right away if you develop symptoms such as cough, shortness of breath, and fever.

If you have a serious allergic reaction, your doctor may decide that you should not use Qoyvolma again.

Infections – these may need urgent treatment. Tell your doctor straight away if you notice any of the following signs.
- Infections of the nose or throat and common cold are common (may affect up to 1 in 10 people)
- Infections of the chest are uncommon (may affect up to 1 in 100 people)
- Inflammation of tissue under the skin ('cellulitis') is uncommon (may affect up to 1 in 100 people)
- Shingles (a type of painful rash with blisters) are uncommon (may affect up to 1 in 100 people)

Qoyvolma may make you less able to fight infections. Some infections could become serious and may include infections caused by viruses, fungi, bacteria (including tuberculosis), or parasites, including infections that mainly occur in people with a weakened immune system (opportunistic infections). Opportunistic infections of the brain (encephalitis, meningitis), lungs, and eye have been reported in patients receiving treatment with ustekinumab.

You must look out for signs of infection while you are using Qoyvolma. These include:
- fever, flu-like symptoms, night sweats, weight loss
- feeling tired or short of breath; cough which will not go away
- warm, red and painful skin, or a painful skin rash with blisters
- burning when passing water
- diarrhoea
- visual disturbance or vision loss

- headache, neck stiffness, light sensitivity, nausea or confusion.

Tell your doctor straight away if you notice any of these signs of infection. These may be signs of infections such as chest infections, skin infections, shingles or opportunistic infections that could have serious complications. Tell your doctor if you have any kind of infection that will not go away or keeps coming back. Your doctor may decide that you should not use Qoyvolma until the infection goes away. Also tell your doctor if you have any open cuts or sores as they might get infected.

Shedding of skin – increase in redness and shedding of skin over a larger area of the body may be symptoms of erythrodermic psoriasis or exfoliative dermatitis, which are serious skin conditions. You should tell your doctor straight away if you notice any of these signs.

Other side effects

Common side effects (may affect up to 1 in 10 people):
- Diarrhoea
- Nausea
- Vomiting
- Feeling tired
- Feeling dizzy
- Headache
- Itching ('pruritus')
- Back, muscle or joint pain
- Sore throat
- Redness and pain where the injection is given
- Sinus infection

Uncommon side effects (may affect up to 1 in 100 people):
- Tooth infections
- Vaginal yeast infection
- Depression
- Blocked or stuffy nose
- Bleeding, bruising, hardness, swelling and itching where the injection is given
- Feeling weak
- Drooping eyelid and sagging muscles on one side of the face ('facial palsy' or 'Bell's palsy'), which is usually temporary
- A change in psoriasis with redness and new tiny, yellow or white skin blisters, sometimes accompanied by fever (pustular psoriasis)
- Peeling of the skin (skin exfoliation)
- Acne

Rare side effects (may affect up to 1 in 1 000 people)
- Redness and shedding of skin over a larger area of the body, which may be itchy or painful (exfoliative dermatitis). Similar symptoms sometimes develop as a natural change in the type of psoriasis symptoms (erythrodermic psoriasis)
- Inflammation of small blood vessels, which can lead to a skin rash with small red or purple bumps, fever or joint pain (vasculitis)

Very rare side effects (may affect up to 1 in 10 000 people)
- Blistering of the skin that may be red, itchy, and painful (Bullous pemphigoid).
- Skin lupus or lupus-like syndrome (red, raised scaly rash on areas of the skin exposed to the sun possibly with joint pains).

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system

listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Qoyvolma

- Keep this medicine out of the sight and reach of children.
- 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 Qoyvolma pre-filled syringes may also be stored at room temperature up to 30 °C for a maximum single period of up to 31 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 space 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 31 days at room temperature storage or by the original expiry date, whichever is earlier.
- Do not shake Qoyvolma pre-filled syringes. Prolonged vigorous shaking may damage the medicine.

Do not use this medicine:
- After the expiry date which is stated on the label and the carton after 'EXP'. The expiry date refers to the last day of that month.
- If the liquid is discoloured, cloudy or you can see other foreign particles floating in it (see section 6 'What Qoyvolma looks like and contents of the pack').
- If you know, or think that it may have been exposed to extreme temperatures (such as accidentally frozen or heated).
- If the product has been shaken vigorously.

Qoyvolma is for single use only. Any unused product remaining in the syringe should be thrown away. Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Qoyvolma contains
- The active substance is ustekinumab. Each pre-filled syringe contains 90 mg ustekinumab in 1 mL.
- The other ingredients are L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80 (E433), sucrose and water for injections.

What Qoyvolma looks like and contents of the pack
Qoyvolma is a clear to slightly opalescent (having a pearl-like shine), colourless to pale yellow solution for injection. The solution may contain a few small translucent or white particles of protein. It is supplied as a carton pack containing 1 single-dose, glass 1 mL pre-filled syringe. Each pre-filled syringe contains 90 mg ustekinumab in 1 mL of solution for injection.

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Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

Instructions for administration

At the start of treatment, your healthcare provider will assist you with your first injection. However, you and your doctor may decide that you may inject Qoyvolma yourself. If this happens, you will get training on how to inject Qoyvolma. Talk to your doctor if you have any questions about giving yourself an injection.

Important Information

- **Do not** open the sealed carton until you are ready to use the pre-filled syringe.
- **Do not** remove the cap until just before you give the injection.
- **Do not** mix Qoyvolma with other liquids for injection.
- The pre-filled syringe cannot be re-used. Dispose of the used pre-filled syringe immediately after use in a sharps disposal container (see **Step 14. Dispose of Qoyvolma)**.

Storing Qoyvolma

- **Keep the pre-filled syringe out of the sight and reach of children.** Contains small part.
- Store the pre-filled syringe in a refrigerator between 2°C and 8ºC. **Do not** freeze.
- Store this medicine sealed inside its carton to protect it from light.
- If needed, individual Qoyvolma pre-filled syringes may also be stored at room temperature up to 30°C for a maximum single period of up to 31 days in the original carton in order to protect from light.
- **Do not** shake Qoyvolma pre-filled syringes. Strong shaking may damage the medicine.
- **Do not** use the medicine if it has been shaken strongly.
- **Do not** use the pre-filled syringe if it has been dropped.

Parts of the Pre-filled Syringe (see Figure A)

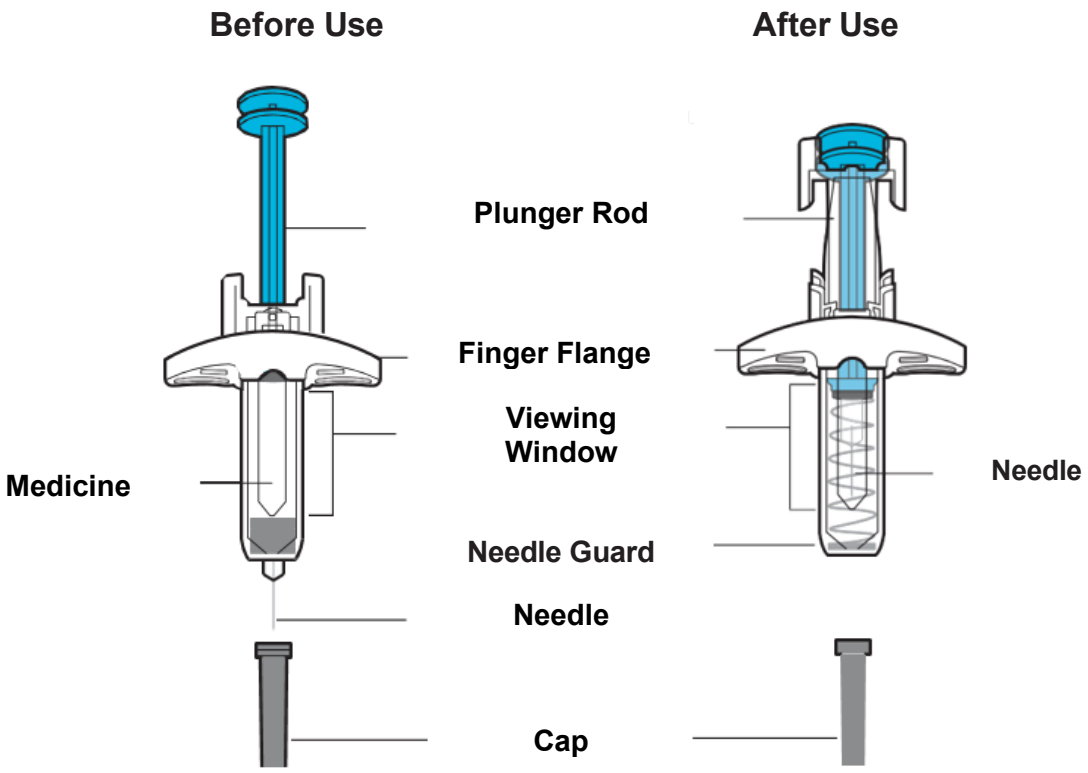

Figure A

Preparing for the Injection

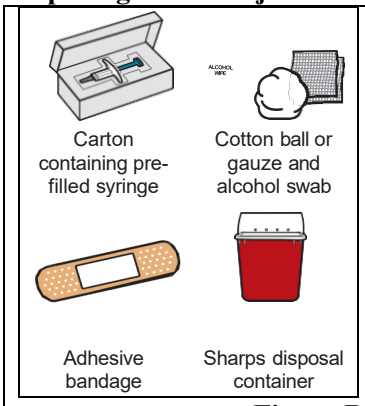

Figure B

1. Gather the supplies for the injection.

a. Prepare a clean, flat surface, such as a table or counter top, in a well-lit area.

b. Take the carton(s) containing the pre-filled syringe(s) needed to administer your prescribed dose out of the refrigerator.

c. Make sure you have the following supplies (see **Figure B**):

- Carton containing pre-filled syringe

Not included in the carton:

- Cotton ball or gauze
- Adhesive bandage
- Sharps disposal container
- Alcohol swab

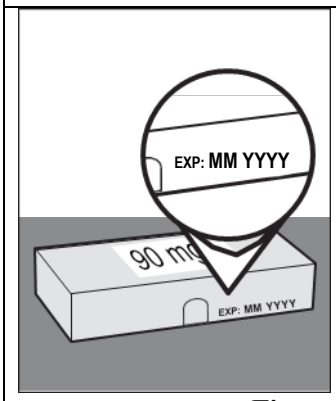

Figure C

2. Check the expiration date on the carton (see Figure C).

- **Do not** use it if the expiration date has passed. If the expiration date has passed, return the entire pack to the pharmacy.

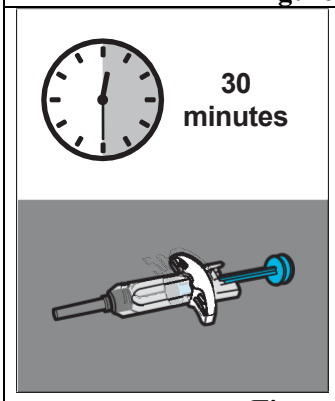

Figure D

3. Wait 30 minutes.

a. Open the carton. Gripping from the syringe body, lift the pre-filled syringe from the carton.

b. Let the pre-filled syringe stand outside the box for about 30 minutes at room temperature (20 °C to 25 °C) to allow it to warm up (see **Figure D**).

- This will let the liquid come to a comfortable temperature for injection (room temperature).
- **Do not** warm the pre-filled syringe using heat sources such as hot water or a microwave.
- **Do not** hold by the plunger head, plunger rod, needle guard wings, or needle cover
- **Do not** pull back on the plunger rod at any time.

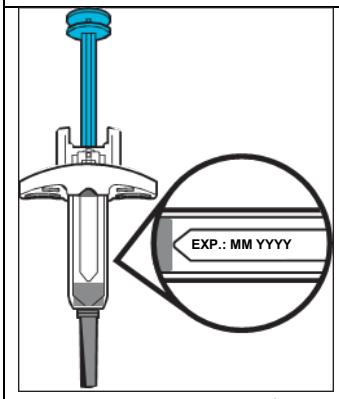

Figure E

4. Inspect the pre-filled syringe.

a. Look at the pre-filled syringe and make sure you have the correct medicine (Qoyvolma) and dosage.

b. Check the pre-filled syringe(s) to make sure the number of pre-filled syringes and strength is correct:

- If your dose is 90 mg you will get one 90 mg pre-filled syringe of Qoyvolma.

c. Look at the pre-filled syringe and make sure it is not cracked or damaged.

d. Check the expiration date on the label of the pre-filled syringe (see **Figure E**).

- **Do not** use if the expiration date has passed.
- **Do not** shake the pre-filled syringe.

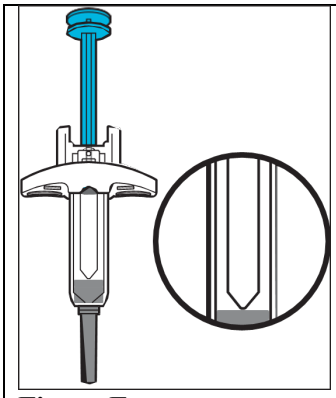

Figure F

5. Inspect the medicine.

a. Look at the medicine and confirm that the liquid is clear to slightly opalescent and colourless to pale yellow. (see **Figure F**).

- **Do not** use the pre-filled syringe if the liquid is discoloured or cloudy.
- You may see air bubbles in the liquid. This is normal.

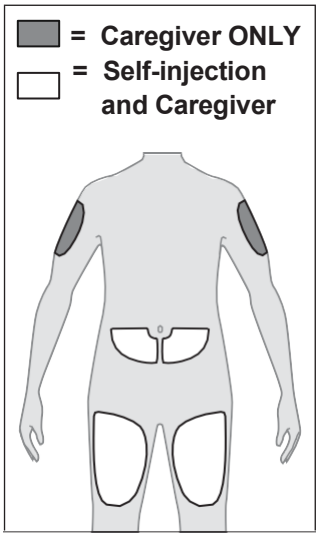

Figure G

6. Choose an appropriate injection site (see Figure G).

a. You may inject into:

- Your upper thighs.
- Your lower abdomen except for the 5 cm around the belly button (navel).
- The outer area of the upper arm if you are a caregiver.

- **Do not** inject into moles, scars, bruises, or areas where the skin is tender, red, hard, or if there are breaks in the skin. If possible, do not use areas of skin that show signs of psoriasis.
- **Do not** inject through your clothes.

b. Choose a different injection site for each new injection at least 2.5 cm away from the area used for the last injection.

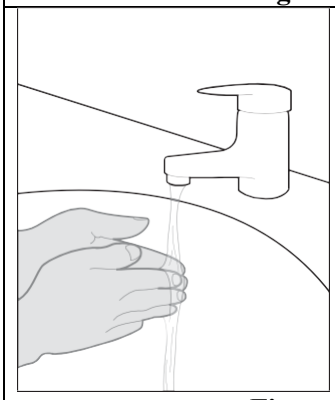

Figure H

7. Wash your hands.

a. Wash your hands with soap and water and dry them thoroughly (see **Figure H**).

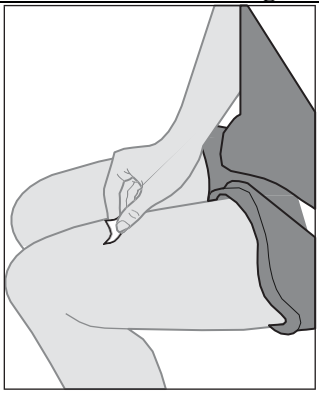

Figure I

8. Clean the injection site.

a. Clean the injection site with an alcohol swab using a circular motion (see **Figure I**).

b. Let the skin dry before injecting.

- **Do not blow on or touch the injection site again before giving the injection.**

Administering the Injection

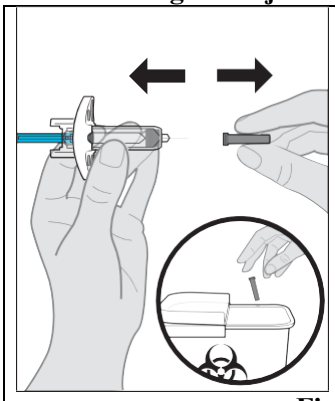

Figure J

9. Remove the cap.

a. Remove the needle cover when you are ready to inject your Qoyvolma by holding the body of the pre-filled syringe in one hand between the thumb and index finger (see **Figure J**).

- **Do not** hold the plunger rod while removing the cap.
- You may notice an air bubble in the pre-filled syringe or a drop of liquid at the tip of needle. This is normal.

b. Dispose of the cap right away in a sharps disposal container (see Step 14 and Figure J).

- **Do not** use the pre-filled syringe if it is dropped without the needle cover in place. If this happens, please contact your doctor or pharmacist.
- Inject the dose promptly after removing the needle cover.
- **Do not** re-cap the pre-filled syringe.
- **Do not** touch the needle. Doing so may result in a needle stick injury.

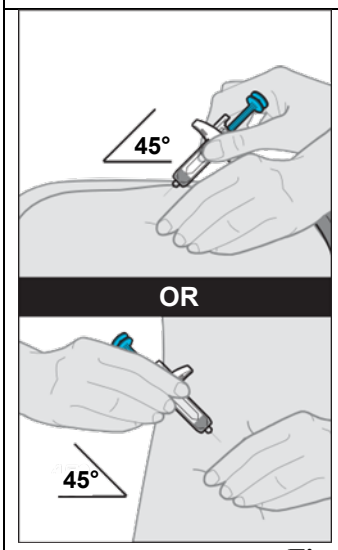

Figure K

10. Insert the pre-filled syringe into the injection site.

a. Hold the body of the pre-filled syringe in one hand between the thumb and index finger.

b. Use the other hand to gently pinch the cleaned skin between your thumb and index finger. **Do not** squeeze it tightly.
Note: Pinching the skin is important to make sure that you inject under the skin (into the fatty area) but not any deeper (into muscle).

c. With a quick and dart-like motion, insert the needle completely into the fold of skin at a 45-degree angle (see **Figure K**).

- **Do not pull back on the plunger rod at any time.**

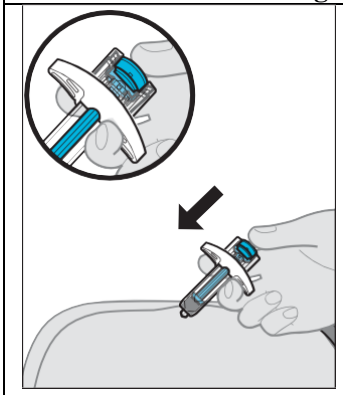

Figure L

11. Give the injection.

a. After the needle is inserted, release the pinch.

b. Slowly push the plunger rod **all the way down** until the full dose of medicine gets injected, and the syringe is empty (see **Figure L**).

- **Do not** change the position of the pre-filled syringe after the injection has started.
- If the plunger rod is not fully pressed, the needle guard will not extend to cover the needle when it is removed.

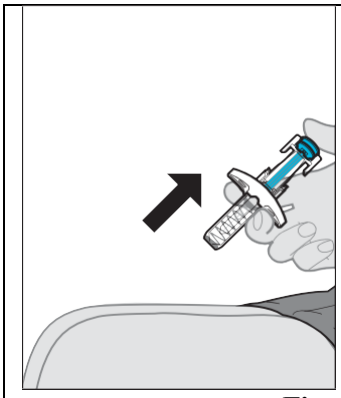

Figure M

12. Remove the pre-filled syringe from the injection site.

a. After the pre-filled syringe is empty, as the needle is being taken out, slowly remove the needle by lifting your thumb from the plunger rod until the needle is completely covered by the needle guard (see **Figure M**).

- If the needle is not covered, proceed carefully to dispose of the syringe (see **Step 14**. **Dispose of Qoyvolma**).
- **Do not** reuse the pre-filled syringe.
- **Do not** rub the injection site.

After the Injection

13. Care for the injection site.

a. If some bleeding occurs, treat the injection site by gently pressing, not rubbing, a cotton ball or gauze to the site and apply an adhesive bandage if needed.

Figure N

14. Dispose of Qoyvolma.

a. Put the used pre-filled syringe in a sharps disposal container right away after use (see **Figure N**).

b. Do not throw away (dispose of) the pre-filled syringe in your household trash.

- If you do not have a sharps disposal container, you may use a household container that is closable and puncture resistant.
- For the safety and health of you and others, needles and used syringes must never be reused. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
- **Do not** throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.