J-C Health Care Ltd.

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מאי 2020

רופא/ה נכבד/ה
רוקח/ת נכבד/ה

ברצוננו להביא לידיעתכם את העדכונים בעלון לרופא של התכשיר:

158-52-35072-00 - סטלרה 130 מ"ג/Stelara 130mg
Concentrate for solution for infusion
Ustekinumab 5mg/1ml vial

המאושר להתוויה הבאה:

Crohn's Disease
STELARA 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.

תוספת התוויה:

Ulcerative colitis
STELARA 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).

השינויים המהותיים בעלון לרופא מופיעים בסעיפים הבאים:

4.2 Posology and method of administration

STELARA 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.
STELARA concentrate for solution for infusion should only be used for the intravenous induction dose.

Posology

Crohn's Disease and Ulcerative Colitis
STELARA 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 STELARA 130 mg as specified in Table 1 (see section 6.6 for preparation).

Table ~~1~~1 Initial intravenous dosing of STELARA

Body weight of patient at the time of dosing	**Recommended dose**[a]	**Number of 130 mg STELARA 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 STELARA solution for injection (vial) and solution for injection in pre-filled syringe SmPC.

Elderly (≥ 65 years)
No dose adjustment is needed for elderly patients (see section 4.4).
In Ulcerative Colitis The number of patients aged 65 and over is not sufficient to determine whether they response differently from younger patients. Because there is a higher incidence of infections in

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the elderly population in general, caution should be used in treating the elderly

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

Paediatric population
The safety and efficacy of STELARA 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
STELARA 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.

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4.4 Special warnings and precautions for use

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Respiratory
Cases of allergic alveolitis ~~and~~ 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).

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Concomitant immunosuppressive therapy
In psoriasis studies, the safety and efficacy of STELARA 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 STELARA. In Crohn's disease and ulcerative colitis studies, concomitant use of immunosuppressants or corticosteroids did not appear to influence the safety or efficacy of STELARA. Caution should be exercised when considering concomitant use of other immunosuppressants and STELARA or when transitioning from other immunosuppressive biologics (see section 4.5).

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Special populations
Elderly (≥ 65 years)
No overall differences in efficacy or safety in patients age 65 and older who received STELARA 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
STELARA contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free'.
STELARA is however, diluted in sodium chloride 9 mg/~~ml~~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 STELARA (see section 4.4).

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No interaction studies have been performed in humans. In the population pharmacokinetic analyses of the phase ~~III~~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 STELARA 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 STELARA. In Crohn's disease and ulcerative colitis studies, concomitant use of immunosuppressants or corticosteroids did not appear to influence the safety or efficacy of STELARA. (see section 4.4).

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4.8 Undesirable effects

Summary of the safety profile
The most common adverse reactions (> 5%) in controlled periods of the adult psoriasis, psoriatic arthritis ~~and~~, 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 STELARA is serious hypersensitivity reactions including anaphylaxis (see section 4.4). The overall safety profile was similar for patients with psoriasis, psoriatic arthritis ~~and Crohn's disease. No new safety concerns were identified with up to 2 years of treatment in patients with Crohn's Disease~~, Crohn's disease and ulcerative colitis.

Tabulated list of adverse reactions
The safety data described below reflect exposure in adults to ustekinumab in ~~12~~14 phase 2 and phase 3 studies in ~~5,884~~6,709 patients (4,135 with psoriasis and/or psoriatic arthritis ~~and~~, 1,749 with Crohn's disease and 825 patients with ulcerative colitis). This includes exposure to STELARA in the controlled and non-controlled periods of the clinical studies for at least 6 months or 1 year (4,~~105~~577 and ~~2,846~~3,253 patients respectively with psoriasis, psoriatic arthritis ~~or~~, 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 ~~and~~, 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

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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
Musculoskeletal and connective tissue disorders	Common: Back pain, myalgia, arthralgia
General disorders and administration site conditions	Common: Fatigue, injection site erythema, injection site pain Uncommon: Injection site reactions (including haemorrhage, haematoma, induration, swelling and pruritus), asthenia

* 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 ~~and~~, 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 ~~of patients with psoriasis, patients with psoriatic arthritis and patients with Crohn's disease~~, the rate of infection was 1.~~38~~36 per patient-year of follow-up in ustekinumab-treated patients, and 1.~~35~~34 in placebo-treated patients. Serious infections occurred at the rate of 0.03 per patient-year of follow-up in ustekinumab-treated patients (~~27~~30 serious infections in ~~829~~930 patient-years of follow-up) and 0.03 in placebo-treated patients (~~11~~15 serious infections in ~~385~~434 patient-years of follow-up) (see section 4.4).

In the controlled and non-controlled periods of psoriasis, psoriatic arthritis ~~and~~, Crohn's disease and ulcerative colitis clinical studies, representing ~~10,953~~11,581 patient-years of exposure in ~~5,884~~6,709 patients, the median follow up was 1.0~~.99~~ years; ~~3.2~~1.1 years for ~~psoriasis studies, 1.0 year for~~ psoriatic ~~arthritis~~disease studies ~~and~~, 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 (~~178~~199 serious infections in ~~10,953~~11,581 patient-years of follow-up) and serious infections reported included pneumonia, anal abscess, cellulitis~~, pneumonia~~, 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 ~~and~~, Crohn's disease and ulcerative colitis clinical studies, the incidence of malignancies excluding non-melanoma skin cancer was 0.~~12~~11 per 100 patient-years of follow-up for ustekinumab-treated patients (1 patient in ~~829~~929 patient-years of

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follow-up) compared with 0.2623 for placebo-treated patients (1 patient in 385434 patient-years of follow-up). The incidence of non-melanoma skin cancer was 0.4843 per 100 patient-years of follow-up for ustekinumab-treated patients (4 patients in 829929 patient-years of follow-up) compared to 0.5246 for placebo-treated patients (2 patients in 385433 patient-years of follow-up).

In the controlled and non-controlled periods of psoriasis, psoriatic arthritis and, Crohn's disease and ulcerative colitis clinical studies, representing 10,93511,561 patient-years of exposure in 5,8846,709 patients, the median follow-up was 1.0 years; 3.21.1 years for psoriasis studies, 1.0 year for psoriatic arthritisdisease studies and, 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 5862 patients in 10,93511,561 patient-years of follow-up (incidence of 0.5354 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 = 0.8793 [95% confidence interval: 0.6671, 1.1420], adjusted for age, gender and race). The most frequently observed malignancies, other than non-melanoma skin cancer, were prostate, melanoma, 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 (5356 patients in 10,91911,545 patient-years of follow-up). The ratio of patients with basal versus squamous cell skin cancers (43:1) 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, 2.42% of 466785 placebo treated patients and 2.61.9% of 470790 patients treated with the recommended dose of ustekinumab reported adverse events occurring during or within an hour of the infusion.

Paediatric population
Undesirable effects in paediatric patients 12 years and older with plaque psoriasis
The safety of ustekinumab has been studied in a phase 3 study of 110 patients from 12 to 17 years of age for up to 60 weeks. In this study, the adverse events reported were similar to those seen in previous studies in adults with plaque psoriasis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action
Ustekinumab is a fully human IgG1κ monoclonal antibody that binds with specificity to the shared p40 protein subunit of human cytokines interleukin (IL)-12 and IL-23. Ustekinumab inhibits the bioactivity of human IL-12 and IL-23 by preventing p40 from binding to the IL-12Rβ1 receptor protein expressed on the surface of immune cells. Ustekinumab cannot bind to IL-12 or IL-23 that is already bound to IL-12Rβ1 cell surface receptors. Thus, ustekinumab is not likely to contribute to complement- or antibody-mediated cytotoxicity of cells 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 and, 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 and, Crohn's disease and ulcerative colitis through interruption of the Th1 and Th17 cytokine pathways, which are central to the pathology of these diseases.

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In patients with Crohn's disease and ulcerative colitis, 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.

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Clinical efficacy

Crohn's Disease

The safety and efficacy of ustekinumab was assessed in three randomized, double-blind, ~~placebocontrolled~~placebo-controlled, multicenter 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 randomized withdrawal maintenance study (IM-UNITI) representing 52 weeks of therapy.

The induction studies included 1409 (UNITI-1, n = 769; UNITI-2 n = 640) patients. The primary endpoint for both induction studies was the proportion of subjects in clinical response (defined as a reduction in CDAI score of ≥ 100 points) at week 6. Efficacy data were collected and analyzed 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]
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] $p < 0.01$

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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 randomized to receive a subcutaneous maintenance regimen of either 90 mg ustekinumab every 8 weeks, 90 mg ustekinumab every 12 weeks or placebo for 44 weeks (for recommended maintenance posology, see section 4.2 of the STELARA Solution for injection (vial) and 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*	**90 mg ustekinumab every 8 weeks**	**90 mg ustekinumab every 12 weeks**
	N = 131†	**N = 128†**	**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 randomized 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-randomized 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 randomized 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.

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In IM-UNITI, patients who completed the study through week 44 were eligible to continue treatment in a study extension. Among patients who entered the study extension, clinical remission and response were generally maintained through week 92 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 2 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 92.

Ulcerative colitis
The safety and efficacy of ustekinumab was assessed in two randomized, double-blind, placebo-controlled, multicenter studies in adult patients with moderately to severely active ulcerative colitis (Mayo score 6 to 12; Endoscopy subscore ≥ 2). 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 randomized 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

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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 randomized to receive a subcutaneous maintenance regimen of either 90 mg ustekinumab every 8 weeks, 90 mg ustekinumab every 12 weeks or placebo for 44 weeks (for recommended maintenance posology, see section 4.2 of the STELARA Solution for injection (vial) and 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]

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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 randomized 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-randomized 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.

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Endoscopic Normalization
Endoscopic normalization 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.

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.

Hospitalizations and ulcerative colits (UC) related surgeries
Through week 8 of UNIFI-I, the proportions of subjects with UC disease related hospitalizations were significantly lower for subjects in the ustekinumab recommended dose group (1.6%, 5/322) compared with subjects in the placebo group (4.4%, 14/319) and no subjects underwent 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 hospitalizations was observed in subjects in the combined ustekinumab group (2.0%, 7/348) as compared with subjects in the placebo group (5.7%, 10/175). A numerically lower number of subjects in the ustekinumab group (0.6%, 2/348) underwent 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.

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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

~~In patients with Crohn's disease, following~~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 (Vz) following a single intravenous administration to patients with psoriasis ranged from 57 to 83 mL/kg.

Biotransformation
The exact metabolic pathway for ustekinumab is unknown.

Elimination
Median systemic clearance (CL) following a single intravenous administration to patients with psoriasis ranged from 1.99 to 2.34 mL/day/kg. Median half-life ($t_{1/2}$) of ustekinumab was approximately 3 weeks in patients with 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 ~~CL~~clearance was affected by body weight, serum albumin level, ~~CRP, TNF antagonist failure status,~~ sex, ~~race (Asian versus non-Asian),~~ 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~~. The impact of these statistically significant covariates on the respective PK parameters was within ± 20% when evaluated across a representative range of covariate values or categories in the data which is within the overall variability observed in the PK of ustekinumab~~.

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).

…

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
Do not freeze.

Chemical and physical in-use stability has been demonstrated for ~~4~~8 hours at 15-25°C.

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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.
…

6.6 Special precautions for disposal and other handling

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

Dilution
STELARA 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 STELARA vials needed based on patient weight (see section 4.2, Table 1). Each 26 mL vial of STELARA contains 130 mg of ustekinumab. Only use complete vials ~~ofSTELARA~~of STELARA.
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 STELARA to be added. (discard 26 mL sodium chloride for each vial of STELARA needed, for 2 vials-discard 52 mL, for 3 vials- discard 78 mL, for 4 vials- discard 104 mL)
3. Withdraw 26 mL of STELARA 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, discoloration or foreign particles are observed.
5. Administer the diluted solution over a period of at least one hour. Once diluted, the infusion ~~solution may~~should be ~~stored for up to four~~completed within eight hours ~~prior to~~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.

העלון לרופא והעלון לצרכן נשלחו לפרסום במלואם למאגר התרופות שבאתר משרד הבריאות. כמו כן, ניתן לקבלם מודפסים בפניה אלינו לטלפון 09-9591111 .

בברכה,
צפריר כהן
רוקח ממונה