1. NAME OF THE MEDICINAL PRODUCT

Omvoh 300 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 300 mg mirikizumab in 15 mL solution (20 mg/mL).

After dilution (see section 6.6), the final concentration is approximately 1.1 mg/mL to approximately 4.6 mg/mL for the treatment of ulcerative colitis and approximately 3.6 mg/mL to approximately 9 mg/mL for the treatment of Crohn's disease.

Mirikizumab is a humanised monoclonal antibody produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology.

Excipients with known effect

Each 15 mL vial contains approximately 60 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate)

Clear to opalescent, colourless to slightly yellow to slightly brown solution, free of visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ulcerative colitis

Omvoh 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 treatment.

Crohn's disease

Omvoh 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 biologic treatment.

4.2 Posology and method of administration

This medicinal product is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of ulcerative colitis or Crohn' disease.
Omvoh 300 mg concentrate for solution for infusion should only be used for the induction dose.

Posology

Ulcerative colitis

The recommended mirikizumab dose regimen has 2 parts.

Induction dose
The induction dose is 300 mg by intravenous infusion for at least 30 minutes at weeks 0, 4 and 8.

Maintenance dose
The maintenance dose is 200 mg (i.e. two 100 mg pre-filled syringes or two 100 mg pre-filled pens) by subcutaneous injection every 4 weeks after completion of induction dosing.

For the posology of the subcutaneous dosing regimen, see section 4.2 of the Physician Leaflet for Omvoh 100 mg/mL solution for injection in pre-filled syringe and Omvoh 100 mg/mL solution for injection in pre-filled pen.

Patients should be evaluated after the 12-week induction dosing and if there is adequate therapeutic response, transition to maintenance dosing. For patients who do not achieve adequate therapeutic benefit at week 12 of induction dosing, mirikizumab 300 mg by intravenous infusion may be continued at weeks 12, 16 and 20 (extended induction therapy). If therapeutic benefit is achieved with the additional intravenous therapy, patients may initiate mirikizumab subcutaneous maintenance dosing (200 mg) every 4 weeks, starting at week 24. Mirikizumab should be discontinued in patients who do not show evidence of therapeutic benefit to extended induction therapy by week 24.

Patients with loss of therapeutic response during maintenance treatment may receive 300 mg mirikizumab by intravenous infusion every 4 weeks, for a total of 3 doses (re-induction). If clinical benefit is achieved from this additional intravenous therapy, patients may resume mirikizumab subcutaneous dosing every 4 weeks. The efficacy and safety of repeated re-induction therapy have not been evaluated.

Crohn's disease

The recommended mirikizumab dose regimen has 2 parts.

Induction dose
The induction dose is 900 mg (3 vials of 300 mg each) by intravenous infusion for at least 90 minutes at weeks 0, 4 and 8.

Maintenance dose
The maintenance dose is 300 mg (i.e. one pre-filled syringe or pre-filled pen of 100 mg and one pre-filled syringe or pre-filled pen of 200 mg) by subcutaneous injection every 4 weeks after completion of induction dosing.
The injections may be administered in any order.
The 200 mg pre-filled syringe and 200 mg pre-filled pen are only for the treatment of Crohn's disease.

For the posology of the subcutaneous dosing regimen, see section 4.2 of the Physician Leaflet for Omvoh solutions for injection in pre-filled syringe and pre-filled pen.
Consideration should be given to discontinuing treatment in patients who have shown no evidence of therapeutic benefit by week 24.

Special populations

Elderly
No dose adjustment is required (see section 5.2). There is limited information in subjects aged ≥ 75 years.

Renal or hepatic impairment
Omvoh has not been studied in these patient populations. These conditions are generally not expected to have any significant impact on the pharmacokinetics of monoclonal antibodies and no dose adjustments are considered necessary (see section 5.2).

Paediatric population
The safety and efficacy of Omvoh in children and adolescents aged 2 to less than 18 years have not yet been established. No data are available.
There is no relevant use of Omvoh in children below 2 years for the indication of ulcerative colitis

or Crohn's disease.

Method of administration

Omvoh 300 mg concentrate for solution for infusion is for intravenous use only. Each vial is for single use only.

For instructions on dilution of the medicinal product before administration, see section 6.6.

Administration of the diluted solution

- The intravenous administration set (infusion line) should be connected to the prepared intravenous bag and the line should be primed.
  - For ulcerative colitis the infusion should be administered for at least 30 minutes.
  - For Crohn's disease the infusion should be administered for at least 90 minutes.
- At the end of the infusion, to ensure a full dose is administered, the infusion line should be flushed with sodium chloride 9 mg/mL (0.9 %) solution or 5 % glucose solution for injection. The flush should be administered at the same rate as used for Omvoh administration. The time required to flush Omvoh solution from the infusion line is in addition to the minimum 30 minutes (ulcerative colitis) or 90 minutes (Crohn's disease) infusion time.

4.3 Contraindications

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

Clinically important active infections (active tuberculosis).

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.

Hypersensitivity reactions

In clinical studies, hypersensitivity reactions have been reported. Most were mild or moderate, severe reactions were uncommon (see section 4.8). If a serious hypersensitivity reaction, including anaphylaxis, occurs, mirikizumab must be discontinued immediately and appropriate therapy must be initiated.

Infections

Mirikizumab may increase the risk of severe infection (see section 4.8). Treatment with mirikizumab should not be initiated in patients with a clinically important active infection until the infection resolves or is adequately treated (see section 4.3). The risks and benefits of treatment should be considered prior to initiating use of mirikizumab in patients with a chronic infection or a history of recurrent infection. Patients should be instructed to seek medical advice if signs or symptoms of clinically important acute or chronic infection occur. If a serious infection develops, discontinuation of mirikizumab should be considered until the infection resolves.

Pre-treatment evaluation for tuberculosis

Prior to initiating treatment, patients should be evaluated for tuberculosis (TB) infection. Patients receiving mirikizumab should be monitored for signs and symptoms of active TB during and after treatment. Anti-TB therapy should be considered prior to initiating treatment in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed.

Hepatic enzyme elevations

Cases of drug-induced liver injury (including one case meeting Hy's Law criteria) occurred in patients receiving mirikizumab in clinical trials. Liver enzymes and bilirubin should be evaluated at baseline and monthly during induction (including extended induction period, if applicable). Thereafter, liver enzymes and bilirubin should be monitored (every 1 - 4 months) according to standard practice for patient management and as clinically indicated. If increases in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) are observed and drug-induced liver injury is suspected, mirikizumab must be discontinued until this diagnosis is excluded.

Immunisations

Prior to initiating therapy with mirikizumab, completion of all appropriate immunisations should be considered according to current immunisation guidelines. Avoid use of live vaccines in patients treated with mirikizumab. No data are available on the response to live or non-live vaccines.

Excipients with known effect

Sodium

Ulcerative colitis
This medicinal product contains 60 mg sodium per 300 mg dose, equivalent to 3 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

If prepared with sodium chloride 9 mg/mL (0.9 %) solution for injection, the amount of sodium contributed by the sodium chloride diluent will range from 177 mg (for a 50 mL bag) to 885 mg (for a 250 mL bag), equivalent to 9-44 % of the WHO recommended maximum daily intake. This is in addition to the amount contributed by the medicinal product.

Crohn's disease
This medicinal product contains 180 mg sodium per 900 mg dose, equivalent to 9 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

If prepared with sodium chloride 9 mg/mL (0.9 %) solution for injection, the amount of sodium contributed by the sodium chloride diluent will range from 195 mg (for a 100 mL bag) to 726 mg (for a 250 mL bag), equivalent to 10-36 % of the WHO recommended maximum daily intake. This is in addition to the amount contributed by the medicinal product.

Polysorbate

This medicinal product contains 0.5 mg/mL of polysorbate 80 in each vial which is equivalent to 7.5 mg for the induction dose to treat ulcerative colitis and equivalent to 22.5 mg for the induction dose to treat Crohn's disease. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.
In clinical studies, concomitant use of corticosteroids or oral immunomodulators did not influence the safety of mirikizumab.
Population pharmacokinetic data analyses indicated that the clearance of mirikizumab was not impacted by concomitant administration of 5-ASAs (5-aminosalicylic acid), corticosteroids or oral immunomodulators (azathioprine, 6-mercaptopurine, thioguanine, and methotrexate).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should use an effective method of contraception during treatment and for at least 10 weeks after treatment.

Pregnancy

There is a limited amount of data from the use of mirikizumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Omvoh during pregnancy.

Breast-feeding

It is unknown whether mirikizumab is excreted in human milk. Human IgGs are known to be excreted in breast milk during the first few days after birth, which is decreasing to low concentrations soon afterwards; consequently, a risk to the breast-fed infant cannot be excluded during this short period. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Omvoh therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions are upper respiratory tract infections (9.8 %, most frequently nasopharyngitis), headache (3.2 %), rash (1.3 %) and injection site reactions (10.8 %, maintenance period).

Tabulated list of adverse reactions

Adverse reactions from clinical studies (Table 1) are listed by MedDRA system organ class. The frequency category for each reaction is based on the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10000 to < 1/1000); very rare (< 1/10000).

Table 1: Adverse reactions

MedDRA System organ class	Frequency	Adverse reaction
Infections and infestations	Common	Upper respiratory tract infections[a]
	Uncommon	Herpes zoster
Immune system disorders	Uncommon	Infusion-related hypersensitivity reactions
Musculoskeletal and Connective Tissue Disorders	Common	Arthralgia
Nervous system disorders	Common	Headache
Skin and subcutaneous tissue disorders	Common	Rash[b]
General disorders and administration site conditions	Very common	Injection site reactions[c]
	Uncommon	Infusion site reactions[d]
Investigations	Uncommon	Alanine aminotransferase increased
	Uncommon	Aspartate aminotransferase increased

[a] *Includes: acute sinusitis, COVID-19, nasopharyngitis, oropharyngeal discomfort, oropharyngeal pain, pharyngitis, rhinitis, sinusitis, tonsillitis, upper respiratory tract infection, and viral upper respiratory tract infection.*

[b] *Includes: rash, rash macular, rash maculo-papular, and rash papular and rash pruritic.*
[c] *Reported during mirikizumab maintenance therapy where mirikizumab treatment is administered as subcutaneous injection.*
[d] *Reported during mirikizumab induction therapy where mirikizumab treatment is administered as intravenous infusion.*

Description of selected adverse reactions

Infusion-related hypersensitivity reactions (induction therapy)
Infusion-related hypersensitivity reactions were reported in 0.4 % of mirikizumab-treated patients. All infusion-related hypersensitivity reactions were reported as non-serious.

Injection site reactions (maintenance therapy)
Injection site reactions were reported in 10.8 % of mirikizumab-treated patients. The most frequent reactions were injection site pain, injection site reaction and injection site erythema. These symptoms were reported as non-serious, mild and transient in nature.
The results described above were obtained with the original formulation of Omvoh. In a double blind, 2-arm, randomised, single-dose, parallel design study in 60 healthy subjects comparing 200 mg mirikizumab (2 injections of 100 mg in a pre-filled syringe) of the original formulation with the revised formulation statistically significantly lower VAS pain scores were obtained with the revised (12.6) vs. the original formulation (26.1) 1 minute after injection.

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increased
In the first 12 weeks, ALT increased was reported in 0.6 % mirikizumab-treated patients. AST increased was reported by 0.4 % mirikizumab-treated patients. All adverse reactions were reported as mild to moderate in severity and non-serious.

Overall mirikizumab treatment periods in the ulcerative colitis and Crohn's disease clinical development program (including the placebo-controlled and open label induction and maintenance periods), there have been elevations of ALT to ≥ 3 x upper limit of normal (ULN) (2.3 %), ≥ 5 x ULN (0.7 %) and ≥ 10 x ULN (0.2 %) and AST to ≥ 3 x ULN (2.2 %), ≥ 5 x ULN (0.8 %) and ≥ 10 x ULN (0.1 %) in patients receiving mirikizumab (see section 4.4). These elevations have been noted with and without concomitant elevations in total bilirubin.

Immunogenicity
In the ulcerative colitis studies, up to 23 % of mirikizumab-treated patients with 12 months of treatment developed anti-drug antibodies, most of which were of low titer and tested positive for neutralising activity. Higher antibody titers in approximately 2 % of subjects treated with mirikizumab were associated with lower serum mirikizumab concentrations and reduced clinical response.

In the Crohn's disease study, 12.7% of mirikizumab-treated patients with 12 months of treatment developed anti-drug antibodies, most of which were of low titer and tested positive for neutralising activity. There was no identified clinically significant effect of anti-drug antibodies on pharmacokinetics or effectiveness of mirikizumab.

No association was found between anti-mirikizumab antibodies and hypersensitivity or injection-related events in the ulcerative colitis or the Crohn's disease studies.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il

4.9 Overdose

Mirikizumab doses up to 2400 mg intravenously and up to 500 mg subcutaneously have been administered in clinical trials without dose-limiting toxicity. In the event of overdose, the patient must be monitored for signs or symptoms of adverse reactions and appropriate symptomatic treatment must be started immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, interleukin inhibitors, ATC code: L04AC24

Mechanism of action

Mirikizumab is a humanised IgG4 monoclonal, anti-interleukin-23 (anti-IL-23) antibody that selectively binds to the p19 subunit of human IL-23 cytokine and inhibits its interaction with the IL-23 receptor.

IL-23, a regulatory cytokine, affects the differentiation, expansion, and survival of T cell subsets, (e.g., Th17 cells and Tc17 cells) and innate immune cell subsets, which represent sources of effector cytokines, including IL-17A, IL-17F and IL-22 that drive inflammatory disease. In humans, selective blockade of IL-23 was shown to normalise production of these cytokines.

Pharmacodynamic effects

Inflammatory biomarkers were measured in the phase 3 ulcerative colitis and Crohn's disease studies. Mirikizumab administered intravenously every 4 weeks during induction dosing significantly reduced levels of fecal calprotectin and C-reactive protein from baseline to week 12. Also, mirikizumab administered subcutaneously every 4 weeks during maintenance dosing sustained significantly reduced levels of fecal calprotectin and C-reactive protein up to 52 weeks.

Clinical efficacy and safety

Ulcerative colitis

The efficacy and safety of mirikizumab was evaluated in adult patients with moderately to severely active ulcerative colitis in two randomised, double-blind, placebo-controlled, multicentre studies. Enrolled patients had a confirmed diagnosis of ulcerative colitis for at least 3 months and moderately to severely active disease, defined as a modified Mayo score of 4 to 9, including a Mayo endoscopy subscore ≥ 2. Patients had to have failed (defined as loss of response, inadequate response or intolerance) corticosteroids or immunomodulators (6-mercaptopurine, azathioprine) or at least one biologic (a TNFα antagonist and/or vedolizumab) or tofacitinib.

LUCENT-1 was an intravenous induction study with treatment of up to 12 weeks, followed by a 40 week subcutaneous randomised withdrawal maintenance study (LUCENT-2), representing at least 52 weeks of therapy. Mean age was 42.5 years. 7.8 % of patients were ≥ 65 of age and 1.0 % of patients ≥ 75 of age. 59.8 % were men; 40.2 % were women. 53.2 % had severely active disease with a modified Mayo score 7 to 9.

Efficacy results presented for LUCENT-1 and LUCENT-2 were based on central reading of endoscopies and histology.

LUCENT-1
LUCENT-1 included 1162 patients in the primary efficacy population. Patients were randomised to receive a dose of 300 mg mirikizumab via intravenous infusion or placebo, at week 0, week 4 and week 8 with a 3:1 treatment allocation ratio. The primary endpoint for the induction study was the

proportion of subjects in clinical remission [modified Mayo score (MMS) defined as: Stool frequency (SF) subscore = 0 or 1 with a ≥ 1-point decrease from baseline, and rectal bleeding (RB) subscore = 0, and Endoscopic subscore (ES) = 0 or 1 (excluding friability)] at week 12.

Patients in these studies may have received other concomitant therapies including aminosalicylates (74.3 %), immunomodulatory agents (24.1 % such as azathioprine, 6-mercaptopurine or methotrexate), and oral corticosteroids (39.9 %; prednisone daily dose up to 20 mg or equivalent) at a stable dose prior to and during the induction period. Per protocol oral corticosteroids were tapered after induction.

Of the primary efficacy population, 57.1 % were biologic-naive and tofacitinib-naive. 41.2 % of patients had failed a biologic or tofacitinib. 36.3 % of the patients had failed at least 1 prior anti-TNF therapy, 18.8 % had failed vedolizumab and 3.4 % of patients had failed tofacitinib. 20.1 % had failed more than one biologic or tofacitinib. An additional 1.7 % had previously received but had not failed a biologic or tofacitinib.

In LUCENT-1 a significantly greater proportion of patients were in clinical remission in the mirikizumab treated group compared to placebo at week 12 (Table 2). As early as week 2, mirikizumab-treated patients achieved a greater reduction in RB subscores and decreases in SF subscores.

Table 2: Summary of key efficacy outcomes in LUCENT-1 (week 12 unless indicated otherwise)

	Placebo n = 294		**Mirikizumab IV n = 868**		**Treatment difference and 99.875 % CI**
	n	**%**	**n**	**%**	
Clinical remission*[1]	39	13.3 %	210	24.2 %	11.1 % (3.2 %, 19.1 %)[c]
Patients who were biologic and JAK-inhibitor naïve [a]	27/171	15.8 %	152/492	30.9 %	- - -
Patients who failed [b] at least one biologic or JAK-inhibitor [d]	10/118	8.5 %	55/361	15.2 %	- - -
Alternate clinical remission*[2]	43	14.6 %	222	25.6 %	11.1 % (3.0 %, 19.3 %)[c]
Patients who were biologic and JAK-inhibitor naïve [a]	31/171	18.1 %	160/492	32.5 %	- - -
Patients who failed [b] at least one biologic or JAK-inhibitor [d]	10/118	8.5 %	59/361	16.3 %	- - -
Clinical response*[3]	124	42.2 %	551	63.5 %	21.4 % (10.8 %, 32.0 %)[c]
Patients who were biologic and JAK-inhibitor naïve [a]	86/171	50.3 %	345/492	70.1 %	- - -
Patients who failed [b] at least one biologic or JAK-inhibitor [d]	35/118	29.7 %	197/361	54.6 %	- - -
Endoscopic improvement*[4]	62	21.1 %	315	36.3 %	15.4 % (6.3 %, 24.5 %)[c]
Patients who were biologic and JAK-inhibitor naïve [a]	48/171	28.1 %	226/492	45.9 %	- - -
Patients who failed [b] at least one biologic or JAK-inhibitor [d]	12/118	10.2 %	85/361	23.5 %	- - -
Symptomatic remission (week 4)*[5]	38	12.9 %	189	21.8 %	9.2 % (1.4 %, 16.9 %)[c]
Patients who were biologic and JAK-inhibitor naïve [a]	26/171	15.2 %	120/492	24.4 %	- - -
Patients who failed [b] at least one biologic or JAK-inhibitor [d]	10/118	8.5 %	67/361	18.6 %	- - -

Symptomatic remission*[5]	82	27.9 %	395	45.5 %	17.5 % (7.5 %, 27.6 %)[c]
Patients who were biologic and JAK-inhibitor naïve [a]	57/171	33.3 %	248/492	50.4 %	- - -
Patients who failed [b] at least one biologic or JAK-inhibitor [d]	22/118	18.6 %	139/361	38.5 %	- - -
Histo-endoscopic mucosal improvement*[6]	41	13.9 %	235	27.1 %	13.4 % (5.5 %, 21.4 %)[c]
Patients who were biologic and JAK-inhibitor naïve [a]	32/171	18.7 %	176/492	35.8 %	- - -
Patients who failed [b] at least one biologic or JAK-inhibitor [d]	8/118	6.8 %	56/361	15.5 %	- - -

	Placebo n = 294		**Mirikizumab IV n = 868**		**Treatment difference and 99.875 % CI**
	LS mean	**Standard error**	**LS mean**	**Standard error**	
Bowel urgency severity*[7]	-1.63	0.141	-2.59	0.083	-0.95 (-1.47, -0.44)[c]
Patients who were biologic and JAK-inhibitor naïve [a]	-2.08	0.174	-2.72	0.101	- - -
Patients who failed [b] at least one biologic or JAK-inhibitor [d]	-0.95	0.227	-2.46	0.126	- - -

Abbreviations: CI = confidence interval; IV = intravenous; LS = least square

*[1] *Clinical remission is based on the modified Mayo score (MMS) and is defined as: Stool frequency (SF) subscore = 0 or 1 with a ≥ 1-point decrease from baseline, and Rectal bleeding (RB) subscore = 0, and Endoscopic subscore (ES) = 0 or 1 (excluding friability)*

*[2] *Alternate clinical remission is based on the modified Mayo score (MMS) and is defined as: Stool frequency (SF) subscore = 0 or 1, and Rectal bleeding (RB) subscore = 0, and Endoscopic subscore (ES) = 0 or 1 (excluding friability)*

*[3] *Clinical response based on the MMS and is defined as: A decrease in the MMS of ≥ 2 points and ≥ 30 % decrease from baseline, and a decrease of ≥ 1 point in the RB subscore from baseline or a RB score of 0 or 1*

*[4] *Endoscopic improvement defined as: ES = 0 or 1 (excluding friability)*

*[5] *Symptomatic remission defined as: SF = 0, or SF = 1 with a ≥ 1-point decrease from baseline, and RB = 0*

*[6] *Histo-endoscopic mucosal improvement defined as achieving both: 1. Histologic improvement, defined using Geboes scoring system with neutrophil infiltration in < 5 % of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue. 2. Endoscopic improvement, defined as ES = 0 or 1 (excluding friability).*

*[7] *Change from baseline in the Urgency Numeric Rating Scale score*

a) An additional 5 patients on placebo and 15 patients on mirikizumab where previously exposed to but did not fail a biologic or JAK-inhibitor.

b) Loss of response, inadequate response or intolerance.

c) $p < 0.001$

d) Mirikizumab results in the subgroup of patients who failed more than one biologic or JAK-inhibitor were consistent with results in the overall population.

LUCENT-2

LUCENT-2 evaluated 544 patients out of the 551 patients who achieved clinical response with mirikizumab in LUCENT-1 at week 12 (see Table 2). Patients were re-randomised in a 2:1 treatment allocation ratio to receive a subcutaneous maintenance regimen of 200 mg mirikizumab or placebo every 4 weeks for 40 weeks (which is 52 weeks from initiation of the induction dose). The primary endpoint for the maintenance study was the proportion of subjects in clinical remission (same definition as in LUCENT-1) at week 40. Corticosteroid tapering was required upon entrance into

LUCENT-2 for patients who were receiving corticosteroids during LUCENT-1. Significantly greater proportions of patients were in clinical remission in the mirikizumab-treated group compared to the placebo group at week 40 (see Table 3).

Table 3: Summary of key efficacy measures in LUCENT-2 (week 40; 52 weeks from initiation of the induction dose)

	Placebo n = 179		**Mirikizumab SC n = 365**		**Treatment difference and 95 % CI**
	n	**%**	**n**	**%**	
Clinical remission*[1]	45	25.1 %	182	49.9 %	23.2 % (15.2 %, 31.2 %)[c]
Patients who were biologic and JAK-inhibitor naïve [a]	35/114	30.7 %	118/229	51.5 %	- - -
Patients who failed [b] at least one biologic or JAK-inhibitor [d]	10/64	15.6 %	59/128	46.1 %	- - -
Alternate clinical remission*[2]	47	26.3 %	189	51.8 %	24.1 % (16.0 %, 32.2 %)[c]
Patients who were biologic and JAK-inhibitor naïve [a]	37/114	32.5 %	124/229	54.1 %	- - -
Patients who failed [b] at least one biologic or JAK-inhibitor [d]	10/64	15.6 %	60/128	46.9 %	- - -
Maintenance of clinical remission through week 40*[3]	24/65	36.9 %	91/143	63.6 %	24.8 % (10.4 %, 39.2 %)[c]
Patients who were biologic and JAK-inhibitor naïve [a]	22/47	46.8 %	65/104	62.5 %	- - -
Patients who failed [b] at least one biologic or JAK-inhibitor [d]	2/18	11.1 %	24/36	66.7 %	- - -
Corticosteroid-free remission*[4]	39	21.8 %	164	44.9 %	21.3 % (13.5 %, 29.1 %)[c]
Patients who were biologic and JAK-inhibitor naïve [a]	30/114	26.3 %	107/229	46.7 %	- - -
Patients who failed [b] at least one biologic or JAK-inhibitor [d]	9/64	14.1 %	52/128	40.6 %	- - -
Endoscopic improvement*[5]	52	29.1 %	214	58.6 %	28.5 % (20.2 %, 36.8 %)[c]
Patients who were biologic and JAK-inhibitor naïve [a]	39/114	34.2 %	143/229	62.4 %	**- - -**
Patients who failed [b] at least one biologic or JAK-inhibitor [d]	13/64	20.3 %	65/128	50.8 %	**- - -**
Histo-endoscopic mucosal remission*[6]	39	21.8 %	158	43.3 %	19.9 % (12.1 %, 27.6 %)[c]
Patients who were biologic and JAK-inhibitor naïve [a]	30/114	26.3 %	108/229	47.2 %	**- - -**
Patients who failed [b] at least one biologic or JAK-inhibitor [d]	9/64	14.1 %	46/128	35.9 %	**- - -**

Bowel urgency remission[*7]	43/172	25.0 %	144/336	42.9 %	18.1 % (9.8 %, 26.4 %)[c]
Patients who were biologic and JAK-inhibitor naïve [a]	31/108	28.7 %	96/206	46.6 %	- - -
Patients who failed [b] at least one biologic or JAK-inhibitor [d]	12/63	19.0 %	43/122	35.2 %	- - -
	Placebo n = 179		**Mirikizumab SC n = 365**		**Treatment difference and 95 % CI**
	LS mean	**Standard error**	**LS mean**	**Standard error**	
Bowel urgency severity[*8]	-2.74	0.202	-3.80	0.139	-1.06 (-1.51, -0.61)[c]
Patients who were biologic and JAK-inhibitor naïve [a]	-2.69	0.233	-3.82	0.153	- - -
Patients who failed [b] at least one biologic or JAK-inhibitor [d]	-2.66	0.346	-3.60	0.228	- - -

Abbreviations: CI = confidence interval; SC = subcutaneous; LS = least square

*[1, 2] *See footnotes on Table 2*

*[3] *The proportion of patients who were in clinical remission at week 40 among patients in clinical remission at week 12, with clinical remission defined as: Stool frequency (SF) subscore = 0 or SF = 1 with a ≥ 1-point decrease from induction baseline, and Rectal bleeding (RB) subscore = 0, and Endoscopic subscore (ES) = 0 or 1 (excluding friability)*

*[4] *Corticosteroid-free remission without surgery, defined as: Clinical remission at week 40, and Symptomatic remission at week 28, and no corticosteroid use for ≥ 12 weeks prior to week 40*

*[5] *Endoscopic improvement defined as: ES = 0 or 1 (excluding friability)*

*[6] *Histo-endoscopic mucosal remission, defined as achieving both: 1. Histologic remission, defined as Geboes subscores of 0 for grades: 2b (lamina propria neutrophils), and 3 (neutrophils in epithelium), and 4 (crypt destruction), and 5 (erosion or ulceration) and 2. Mayo endoscopic score 0 or 1 (excluding friability)*

*[7] *Numeric Rating Scale (NRS) 0 or 1 in patients with urgency NRS ≥ 3 at baseline in LUCENT-1*

*[8] *Change from baseline in the Urgency NRS score*

a) An additional 1 patient on placebo and 8 patients on mirikizumab where previously exposed to but did not fail a biologic or JAK-inhibitor.

b) Loss of response, inadequate response or intolerance.

c) p < 0.001

d) Mirikizumab results in the subgroup of patients who failed more than one biologic or JAK-inhibitor were consistent with results in the overall population.

The efficacy and safety profile of mirikizumab was consistent across subgroups, i.e. age, gender, body weight, disease activity severity at baseline and region. The effect size may vary.

At week 40, a greater proportion of patients were in clinical response (defined as decrease in the MMS of ≥ 2 points and ≥ 30 % decrease from baseline, and a decrease of ≥ 1 point in the RB subscore from baseline or a RB score of 0 or 1) in the mirikizumab responder group re-randomised to mirikizumab (80 %) compared to the mirikizumab responder group re-randomised to placebo (49 %).

Week 24 responders to mirikizumab extended induction (LUCENT-2)

For the mirikizumab patients who were not in response at week 12 of LUCENT-1 and received open-label additional 3 doses of 300 mg mirikizumab IV every 4 weeks (Q4W) 53.7 % achieved clinical response at week 12 of LUCENT-2 and 52.9 % mirikizumab patients continued to maintenance receiving 200 mg mirikizumab Q4W SC, and among these patients 72.2 % achieved

clinical response and 36.1 % achieved clinical remission at week 40.

Recapture of efficacy after loss of response to mirikizumab maintenance (LUCENT-2)
19 patients who experienced a first loss of response (5.2 %) between week 12 and 28 of LUCENT-2 received open-label mirikizumab rescue dosing with 300 mg mirikizumab Q4W IV for 3 doses and 12 of these patients (63.2 %) achieved symptomatic response and 7 patients (36.8 %) achieved symptomatic remission after 12 weeks.

Endoscopic normalisation at week 40
Normalisation of endoscopic appearance of the mucosa was defined as a Mayo endoscopic subscore of 0. At week 40 of LUCENT-2, endoscopic normalisation was achieved in 81/365 (22.2 %) of patients treated with mirikizumab and in 24/179 (13.4 %) of patients in placebo group.

Histologic outcomes
At week 12 greater proportions of patients in the mirikizumab group achieved histologic improvement (39.2 %) compared with patients in the placebo group (20.7 %). At week 40 histologic remission was observed with more patients in the mirikizumab group (48.5 %) as compared to placebo (24.6 %).

Stable maintenance of symptomatic remission
Stable maintenance of symptomatic remission was defined as the proportion of patients in symptomatic remission for at least 7 out of 9 visits from week 4 to week 36 and in symptomatic remission at week 40 among patients in symptomatic remission and clinical response at week 12 of LUCENT-1. At week 40 of LUCENT-2, the proportion of patients achieving stable maintenance of symptomatic remission was greater in patients treated with mirikizumab (69.7 %) versus placebo (38.4 %).

Health-related quality of life
At week 12 of LUCENT-1, patients receiving mirikizumab showed significantly greater clinically relevant improvements on the Inflammatory Bowel Disease Questionnaire (IBDQ) total score ($p \leq 0.001$) when compared to placebo. IBDQ response was defined as at least a 16-point improvement from baseline in IBDQ score and IBDQ remission was defined as a score of at least 170. At week 12 of LUCENT-1, 57.5 % of mirikizumab-treated patients achieved IBDQ remission versus 39.8 % with placebo ($p < 0.001$) and 72.7 % of mirikizumab-treated patients achieved IBDQ response versus 55.8 % in placebo. In LUCENT-2 at week 40, 72.3 % of mirikizumab-treated patients achieved maintenance of IBDQ remission versus 43.0 % placebo treated patients and 79.2 % mirikizumab treated patients achieved IBDQ response versus 49.2 % of placebo treated patients.

Patient reported outcomes
Decreases in bowel urgency severity were observed as early as week 2 in patients treated with mirikizumab in LUCENT-1. Patients receiving mirikizumab achieved significant bowel urgency remission compared with patients in the placebo group at week 12 in LUCENT-1 (22.1 % vs 12.3 %), and week 40 in LUCENT-2 (42.9 % vs 25 %). Patients receiving mirikizumab showed significant improvements in fatigue as early as week 2 of LUCENT-1 and the improvements were maintained at week 40 of LUCENT-2. As early as week 4 there was also a significantly greater reduction in abdominal pain.

Hospitalisations and ulcerative colitis related surgeries
Through week 12 of LUCENT-1, the proportion of patients with UC-related hospitalisations were 0.3 % (3/868) in the mirikizumab and 3.4 % (10/294) in the placebo group. UC-related surgeries were reported in 0.3 % (3/868) patients receiving mirikizumab and 0.7 % (2/294) patients in the placebo group. There were no UC-related hospitalisations and no UC-related surgeries in LUCENT-2 in the mirikizumab arm.

Crohn's disease

The efficacy and safety of mirikizumab was evaluated in a randomized, double-blind, placebo- and active controlled treat-through designed clinical study VIVID-1 in adult patients with moderately to severely active Crohn's disease who had an inadequate response with, loss of response, or intolerance to corticosteroids, immunomodulators (e.g. azathioprine, 6-mercaptopurine), or a biologic treatment (e.g. TNFα antagonist or integrin receptor antagonist). This study included a mirikizumab 12-week intravenous infusion induction period followed by a 40-week subcutaneous injection maintenance period. This study also included an ustekinumab comparator arm in the induction and maintenance periods.

VIVID-1
In VIVID-1, efficacy was evaluated in 1065 patients who were randomized 6:3:2 to receive mirikizumab 900 mg by intravenous infusion (IV) at week 0, week 4, and week 8 followed by a maintenance dose of 300 mg by subcutaneous injection (SC) at week 12 and then every 4 weeks (Q4W) for 40 weeks, ustekinumab approximately 6 mg/kg by IV administration at week 0 followed by 90 mg SC administration every 8 weeks (Q8W) starting at week 8, or placebo. Patients randomised to placebo at baseline who achieved clinical response by Patient-Reported Outcome (PRO) at week 12 (defined as at least a 30% decrease in stool frequency (SF) and/or abdominal pain (AP) with neither score worse than baseline) remained on placebo. Patients randomized to placebo at baseline who did not achieve clinical response by PRO at week 12 received mirikizumab 900 mg by IV infusion at week 12, week 16, and week 20 followed by a maintenance dose of 300 mg Q4W SC at week 24 through week 48.

Disease activity at baseline was assessed by (1) the unweighted daily average of SF (2), the unweighted daily average AP (ranging from 0 to 3) and (3) Simple Endoscopic Score for Crohn's disease (SES-CD) (ranging from 0 to 56).

Moderately to severely active CD was defined by SF ≥4 and/or AP ≥2 and SES-CD ≥7 (centrally read) for patients with ileal-colonic and isolated colonic disease or ≥4 for patients with isolated ileal disease. At baseline patients had a median SF of 6, AP of 2 and SES-CD of 12.

Patients had a mean age of 36 years (range 18 to 76 years); 45 % were female; and 72 % identified as White, 25 % as Asian, 2 % as Black, and 1 % as another racial group. Patients were permitted to use stable doses of corticosteroids, immunomodulators (e.g., 6-mercatopurine, azathioprine or methotrexate) and/or aminosalicylates. At baseline, 31 % of patients were receiving oral corticosteroids, 27 % were receiving immunomodulators, and 44 % were receiving aminosalicylates.

At baseline, 49 % had a loss of response, inadequate response, or intolerance to one or more biologic therapy (prior biologic failure); 46 % of patients had failed TNFα inhibitors and 11 % had failed vedolizumab therapy.

The co-primary endpoints of VIVID-1 were (1) clinical response by PRO at week 12 and endoscopic response at week 52 versus placebo and (2) clinical response by PRO at week 12 and clinical remission by Crohn's Disease Activity Index (CDAI) at week 52; the results for the co-primary endpoints and the major secondary endpoints at week 52 versus placebo are provided in table 4.
The major secondary endpoints at week 12 versus placebo are provided in table 5.

Table 4. Proportion of patients with Crohn's disease meeting efficacy endpoints in VIVID-1 at week 52

	Placebo n=199		**Mirikizumab 300 mg SC injection[a] n=579**		**Treatment Difference from Placebo[b] (99.5% CI)**
	n	**%**	**n**	**%**	
Co-primary endpoints					
Clinical response by PRO[c] at week 12 and endoscopic response[d] at week 52	18/199	9 %	220/579	38 %	29%[e] (21 %, 37 %)
Without prior biologic failure	12/102	12 %	117/298	39 %	
Prior biologic failure[f]	6/97	6 %	103/281	37 %	
Clinical response by PRO[c] at week 12 and	39/199	20 %	263/579	45 %	26 %[e] (16 %, 36 %)

clinical remission by CDAI[g] at week 52					
Without prior biologic failure	27/102	27 %	141/298	47 %	
Prior biologic failure[f]	12/97	12 %	122/281	43 %	
Additional endpoints					
Endoscopic response[d] at week 52	18/199[h]	9 %	280/579	48 %	39 %[e] (31 %, 47 %)
Without prior biologic failure	12/102[h]	12 %	154/298	52 %	
Prior biologic failure[f]	6/97[h]	6 %	126/281	45 %	
Clinical remission by CDAI[h] at week 52	39/199[h]	20 %	313/579	54 %	35 %[e] (25 %, 44 %)
Without prior biologic failure	27/102[h]	27 %	169/298	57 %	
Prior biologic failure[f]	12/97[h]	12 %	144/281	51 %	
Clinical response by PRO[c] at week 12 and clinical remission by PRO[i] at week 52	39/199	20 %	263/579	45 %	26 %[e] (16 %, 36 %)
Clinical response by PRO[c] at week 12 and endoscopic remission[j] at week 52	8/199	4 %	136/579	24 %	19 %[e] (13 %, 26 %)
Clinical response by PRO[c] at week 12 and corticosteroid-free clinical remission by CDAI[g, k] at Week 52	37/199	19 %	253/579	44 %	25 %[e] (15 %, 35 %)

Abbreviations: AP = abdominal pain; CDAI = Crohn's Disease Activity Index; CI = confidence interval; PRO = 2 of the patient-reported items of the CDAI (SF and AP); SES-CD = Simple Endoscopic Score for Crohn's Disease; SF = stool frequency.

a Following mirikizumab 900 mg as an IV infusion at week 0, week 4, and week 8 patients received mirikizumab 300 mg as a SC injection at week 12 and every 4 weeks thereafter for up to an additional 40 weeks.
b For binary endpoints adjusted treatment difference was based on Cochran-Mantel-Haenszel method adjusted for baseline covariates.
c Clinical response by PRO is defined as at least a 30% decrease in SF and/or AP and neither score worse than baseline.
d Endoscopic response is defined as ≥50% reduction from baseline in SES-CD total score, based on central reading.
e $p < 0.000001$
f Prior biologic failure includes loss of response, inadequate response, or intolerance to one or more biologic therapy (e.g. TNFα antagonist or integrin receptor antagonist).
g Clinical remission by CDAI is defined as CDAI total score < 150.
h Placebo sample size includes all patients randomized to placebo at baseline. Placebo patients that did not achieve clinical response by PRO at week 12 were considered non-responders at week 52.
i Clinical remission by PRO is defined as SF ≤3 and not worse than baseline (according to the Bristol Stool Scale Category 6 or 7) and AP ≤1 and not worse than baseline.
j Endoscopic remission is defined as SES-CD Total Score ≤4 and at least a 2-point reduction versus baseline and no subscore >1 in any individual variable, based on central reading.
k Corticosteroid-free is defined as patients who were corticosteroid-free from week 40 to week 52.

Bowel urgency remission

Bowel urgency remission was assessed during VIVID-1 with an urgency numeric rating scale (NRS) of 0 to 10. A greater proportion of patients with a baseline urgency NRS weekly average score ≥3 treated with mirikizumab compared to placebo achieved clinical response by PRO at week 12 and an urgency NRS weekly average score of ≤ 2 at week 52 (33 % versus 11 %).

Table 5. Proportion of patients with Crohn's disease meeting efficacy endpoints in VIVID -1 at week 12

Endpoint	**Placebo n=199**		**Mirikizumab 900 mg IV infusion[a] n=579**		**Treatment Difference from Placebo[b] (99.5% CI)**
	n	**%**	**n**	**%**	
Clinical response by PRO[c]	103/199	52 %	409/579	71 %	19 %[e] (8 %, 30 %)
Clinical remission by CDAI[g]	50/199	25 %	218/579	38 %	12 %[f] (2 %, 23 %)
Endoscopic response[d]	25/199	13 %	188/579	32 %	20 %[e] (11 %, 28 %)

Endoscopic remission[j]	14/199	7 %	102/579	18 %	11 %[f](4 %, 17 %)
Change from baseline in FACIT-fatigue[h]	**LS Mean**	**SE**	**LS Mean**	**SE**	
	2.6	0.61	5.9	0.36	3.2[f](1.2, 5.2)

Abbreviations: FACIT-fatigue = Functional Assessment of Chronic Illness Therapy – fatigue; LS Mean = Least Square Mean; SE = Standard Error; others see above table 4.

a Weeks 0, 4, 8

b see table 4. Also see footnote h below.

c, d, e, g, j see table 4

f p-value <0.005

h For change from baseline in FACIT-fatigue, the LS means and treatment difference were based on ANCOVA model adjusted for baseline FACIT-fatigue and other covariates. At baseline, mean FACIT-fatigue values were similar across treatment groups and ranged from 32.3-31.5.

Improvements in clinical remission by CDAI were observed as early as week 4 in a greater proportion of patients treated with mirikizumab compared to placebo.
Reductions in abdominal pain were observed as early as week 4 and in stool frequency as early as week 6 in patients treated with mirikizumab compared to placebo.

The efficacy and safety profile of mirikizumab was consistent across subgroups, i.e. age, gender, body weight, disease activity severity at baseline and region. The effect size may vary.

Active comparator arm
At week 52, mirikizumab demonstrated non-inferiority (pre-specified margin of -10%) to ustekinumab on clinical remission by CDAI (mirikizumab 54 %; ustekinumab 48 %). Superiority over ustekinumab in week 52 endoscopic response was not achieved (mirikizumab 48 %, ustekinumab 46 %).

Histologic outcome
Across all five intestinal segments 44 % of patients on mirikizumab achieved the composite endpoint of clinical response by PRO at week 12 and histologic response at week 52 compared to 16 % of patients on placebo. Histologic response at week 52 was achieved by 58 % of patients compared to 49% on ustekinumab.

Health-related quality of life
At week 12, change in the Inflammatory Bowel Disease Questionnaire (IBDQ) score was 36.9 for mirikizumab and 17.4 for placebo; IBDQ response and remission were achieved in 69 % and 52 % of mirikizumab-treated patients versus 45 % and 28 % in placebo patients respectively. These improvements were maintained at week 52.

5.2 Pharmacokinetic properties

There was no apparent accumulation in serum mirikizumab concentration over time when given subcutaneously every 4 weeks.

Exposure

Ulcerative colitis

Mean (coefficient of variation in %) C_{max} and area under the curve (AUC) after induction dosing (300 mg every 4 weeks administered by intravenous infusion) in patients with ulcerative colitis were 99.7 µg/mL (22.7 %) and 538 µg*day/mL (34.4 %), respectively. The mean (CV %) C_{max} and AUC after maintenance dosing (200 mg every 4 weeks by subcutaneous injection) were 10.1 µg/mL (52.1 %) and 160 µg*day/mL (57.6 %), respectively.

Crohn's disease

Mean (coefficient of variation in %) C_{max} and area under the curve (AUC) after induction dosing (900 mg every 4 weeks administered by intravenous infusion) in patients with Crohn's disease were 332 µg/mL

(20.6 %) and 1820 µg*day/mL (38.1 %), respectively. The mean (CV %) C_{max} and AUC after maintenance dosing (300 mg every 4 weeks by subcutaneous injection) were 13.6 µg/mL (48.1 %) and 220 µg*day/mL (55.9 %), respectively.

Absorption

Following subcutaneous dosing of mirikizumab for ulcerative colitis, median (range) Tmax was 5 (3.08-6.75) days post dose and geometric mean (CV%) absolute bioavailability was 44 % (34%). Following subcutaneous dosing of mirikizumab for Crohn's disease, median (range) Tmax was 5 (3 to 6.83) days post dose and geometric mean (CV%) absolute bioavailability was 36.3% (31%).

Injection site location did not significantly influence absorption of mirikizumab.

Distribution

The geometric mean total volume of distribution was 4.83 L (21 %) in patients with ulcerative colitis and 4.40 L (14 %) in patients with Crohn's disease.

Biotransformation

Mirikizumab is a humanised IgG4 monoclonal antibody and is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgGs.

Elimination

In the population PK analysis, geometric mean (CV %) clearance was 0.0229 L/hr (34 %) and the geometric mean half-life is approximately 9.3 days (40 %) in patients with ulcerative colitis. The geometric mean (CV%) clearance was 0.0202 L/hr (38 %) and the geometric mean (CV %) half-life is also approximately 9.3 days (26 %) in patients with Crohn's disease. Clearance is independent of dose.

Dose proportionality

Mirikizumab exhibited linear pharmacokinetics with dose-proportional increase in exposure over a dose range of 5 to 2400 mg given as an intravenous infusion or over a dose range of 120 to 400 mg given as a subcutaneous injection in patients with ulcerative colitis or Crohn's disease or in healthy volunteers.

Special populations

Population pharmacokinetic analysis showed that age, sex, weight, or race/ethnicity did not have a clinically meaningful effect on the pharmacokinetics of mirikizumab (see also section 4.8, "immunogenicity"). Among the 1362 subjects with ulcerative colitis exposed to mirikizumab in Phase 2 and Phase 3 studies, 99 (7.3 %) patients were 65 years or older and 11 (0.8 %) patients were 75 years or older.

Renal or hepatic impairment
Specific clinical pharmacology studies to evaluate the effects of renal impairment and hepatic impairment on the pharmacokinetics of mirikizumab have not been conducted.

In patients with ulcerative colitis, population pharmacokinetic analysis showed that creatinine clearance (range of 36.2 to 291 mL/min) or total bilirubin (range of 1.5 to 29 µmol/L) did not affect mirikizumab pharmacokinetics.

In patients with Crohn's disease, population pharmacokinetic analysis showed that creatinine clearance (range of 26.5 to 269 mL/min) or total bilirubin (range of 1.5 to 36 µmol/L) did not affect mirikizumab pharmacokinetics.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, toxicity to reproduction and development.

Carcinogenesis / mutagenesis

Non-clinical studies have not been conducted to evaluate the carcinogenic or mutagenic potential of mirikizumab.

Impairment of fertility

No reproductive organ weight or histopathology effects were observed in sexually mature cynomolgus monkeys that received mirikizumab once weekly for 26 weeks, at a dose of 100 mg/kg (at least 20 times the human maintenance dose).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium citrate dihydrate
Polysorbate 80
Citric acid, anhydrous
Water for injection

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Omvoh should not be administered concomitantly in the same intravenous line with other medicinal products.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

After dilution

Chemical and physical in-use stability has been demonstrated for diluted infusion solution prepared with sodium chloride 9 mg/mL (0.9 %) solution for 96 hours at 2 °C to 8 °C of which not more than 10 hours are permitted at non-refrigerated temperatures not to exceed 25 ºC, starting from the time of vial puncture.

Chemical and physical in-use stability has been demonstrated for diluted infusion solution prepared with 5 % glucose for 48 hours at 2 °C to 8 °C of which not more than 5 hours are permitted at non-refrigerated temperatures not to exceed 25 °C, starting from the time of vial puncture.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

Keep the diluted solution away from direct heat or light.
Do not freeze the diluted solution.

6.4 Special precautions for storage

Unopened vial

Store in a refrigerator (2 ºC – 8 ºC).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

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

6.5 Nature and contents of container

15 mL concentrate in a type I clear glass vial with a chlorobutyl rubber stopper, an aluminium seal and polypropylene flip top.

Pack size of 1 vial.

6.6 Special precautions for disposal and other handling

Do not use Omvoh that has been frozen.

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

Dilution prior to intravenous infusion

1. Each vial is for single use only.
2. Prepare the infusion solution using aseptic technique to ensure the sterility of the prepared solution.
3. Inspect the content of the vial. The concentrate should be clear, colourless to slightly yellow to slightly brown and free of visible particles. Otherwise, it should be discarded.
4. Prepare the infusion bag for treatment of either ulcerative colitis or Crohn's disease as specified below. Note that there are unique instructions and volumes specified for each indication.

   Ulcerative colitis: one 15 mL vial (300 mg)
   Withdraw 15 mL of the mirikizumab vial (300 mg) using an appropriately sized needle (18 to 21 gauge is recommended) and transfer to the infusion bag. If administered for the treatment of ulcerative colitis, the concentrate should be diluted only in infusion bags (bag size ranging from 50 - 250 mL) containing either sodium chloride 9 mg/mL (0.9 %) solution for injection or 5 % glucose solution for injection. The final concentration after dilution is approximately 1.1 mg/mL to approximately 4.6 mg/mL.

   Crohn's disease: three 15 mL vials; total volume = 45 mL (900 mg)
   First, withdraw and discard 45 mL of diluent from the infusion bag. Next, withdraw 15 mL from each of the three mirikizumab vials (900 mg) and transfer to the infusion bag, using an appropriately sized syringe and needle (18 to 21 gauge is recommended). If administered for the treatment of Crohn's disease, the concentrate should be diluted only in infusion bags (bag size ranging from 100-250 mL) containing either sodium chloride 9 mg/mL (0.9 %) solution for injection or 5 % glucose solution for injection.
   The final concentration after dilution is approximately 3.6 mg/mL to approximately 9 mg/mL.

5. Gently invert the infusion bag to mix. Do not shake the prepared bag.

7. License Holder

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8. Manufacturer

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9. License Number

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