X OMVOSYPN 100 I 01

1. NAME OF THE MEDICINAL PRODUCT

Omvoh 100 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Omvoh 100 mg solution for injection in pre-filled syringe

Each pre-filled syringe contains 100 mg mirikizumab in 1 mL solution.

Omvoh 100 mg solution for injection in pre-filled pen

Each pre-filled pen contains 100 mg mirikizumab in 1 mL solution.

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection)

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

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.
Omvoh 100 mg solution for injection should only be used for the subcutaneous maintenance doses.

Posology

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. (See Summary of Product Characteristics for Omvoh 300 mg concentrate for solution for infusion, section 4.2.)

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

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.

In case of a missed dose, instruct patients to inject as soon as possible. Thereafter, resume dosing every 4 weeks.

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.

Method of administration

For subcutaneous injection only.

Sites for injection include the abdomen, thigh, and back of the upper arm. After training in subcutaneous injection technique, a patient may self-inject with mirikizumab.
Patients should be instructed to inject in a different location every time. For example, if the first injection was in the abdomen, the second injection—to complete a full dose—could be in another area of the abdomen.

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.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per 200 mg dose, that is to say essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.
In ulcerative colitis 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, mercaptopurine, thioguanine, and methotrexate) in patients with ulcerative colitis.

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 (7.9 %, most frequently nasopharyngitis), headache (3.3 %), rash (1.1 %) and injection site reactions (8.7 %, 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 (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000).

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	Common	Injection site reactions[c]
	Uncommon	Infusion site reactions[d]
Investigations	Uncommon	Alanine aminotransferase increased
	Uncommon	Aspartate aminotransferase increased

[a] *Includes: acute sinusitis, 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 in the mirikizumab maintenance study where mirikizumab treatment is administered as subcutaneous injection.*

[d] *Reported in the mirikizumab induction study where mirikizumab treatment is administered as intravenous infusion*.

Description of selected adverse reactions

Infusion-related hypersensitivity reactions (LUCENT-1, weeks 1-12)
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 (LUCENT-2, weeks 12-52)
Injection site reactions were reported in 8.7 % 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.

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increased
In the first 12 weeks (LUCENT-1), ALT increased was reported in 0.4 % mirikizumab-treated patients. AST increased was reported by 0.5 % mirikizumab-treated patients. All adverse reactions were reported as mild to moderate in severity and non-serious.

Over all mirikizumab treatment periods in the ulcerative colitis 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) (2.0 %), ≥ 5 x ULN (0.7 %) and ≥ 10 x ULN (0.2 %) and AST to ≥ 3 x ULN (2.1 %), ≥ 5 x ULN (1.1 %) 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
With 12 months of treatment, up to 23 % of mirikizumab-treated patients 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. No association was found between anti-mirikizumab antibodies and hypersensitivity or injection site reactions.

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 2,400 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 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 through 40 weeks.

Clinical efficacy and safety

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 1 162 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.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Omvoh in one or more subsets of the paediatric population in the treatment of ulcerative colitis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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

Mean (coefficient variation [CV %]) 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 (22.7) µg/mL and 538 (34.4) µg*day/mL, respectively. The mean (CV %) C_{max} and AUC after maintenance dosing (200 mg every 4 weeks by subcutaneous injection) were 10.1 (52.1) µg/mL and 160 (57.6) µg*day/mL, respectively.

Absorption

Following subcutaneous dosing of mirikizumab, peak serum concentrations were achieved 2-3 days post dose with an estimated absolute bioavailability of 44 %.
Injection site location did not significantly influence absorption of mirikizumab.

Distribution

The mean total volume of distribution was 4.83 L.

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, mean apparent clearance was 0.0229 L/hr and the mean elimination half-life is approximately 9.3 days in patients with ulcerative colitis. Clearance is independent of dose.

Dose proportionality

Mirikizumab exhibited linear pharmacokinetics with dose-proportional increase in exposure over a dose range of 5 to 2 400 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 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 1 362 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. 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.

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 30 times the human maintenance dose).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

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

6.4 Special precautions for storage

Store in a refrigerator (2 ºC – 8 ºC).
Do not freeze.
Store in the original package in order to protect from light.

Omvoh may be stored unrefrigerated for up to 2 weeks at a temperature not above 30 ºC.
If these conditions are exceeded, Omvoh must be discarded.

6.5 Nature and contents of container

Omvoh 100 mg solution for injection in pre-filled syringe

1 mL solution in a type I clear glass syringe.
The syringe is encased in a disposable, single-dose syringe with bromobutyl rubber plunger.
Pack size of 2 pre-filled syringes.

Omvoh 100 mg solution for injection in pre-filled pen

1 mL solution in a type I clear glass syringe.
The syringe is encased in a disposable, single-dose pen with bromobutyl rubber plunger.
Pack size of 2 pre-filled pens.

6.6 Special precautions for disposal and other handling

For single use only. Omvoh should not be used if particles appear or if the solution is cloudy and/or distinctly brown.
Do not use Omvoh that has been frozen.

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

7. License Holder

Eli Lilly Israel Limited
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8. Manufacturer

Eli Lilly and Company USA, Lilly Corporate Center, Indianapolis, Indiana (IN) 46285, United States (USA)

9. License Number

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