▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – OMVOH (MIRIKIZUMAB) SOLUTION FOR INJECTION

1 NAME OF THE MEDICINE

Mirikizumab

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Intravenous Infusion

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

Subcutaneous

Each autoinjector (pre-filled pen) or pre-filled syringe contains 100 mg/mL mirikizumab.

Mirikizumab is a humanised immunoglobulin G4 (IgG4) variant monoclonal antibody that is directed against the p19 subunit of IL-23 and does not bind IL-12. Mirikizumab is produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology and it is composed of two identical light chain polypeptides and two identical heavy chain polypeptides with an overall molecular weight of approximately 147 kDa.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Intravenous Infusion

Concentrate for solution for infusion.

Sterile, non-pyrogenic, preservative free, clear colourless to slightly yellow solution free of visible particles.

Subcutaneous

Solution for subcutaneous injection.

Sterile, non-pyrogenic, preservative free, clear colourless to slightly yellow solution free of visible particles.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

OMVOH is indicated for the treatment of moderately to severely active ulcerative colitis (UC) in adult patients who have had an inadequate response with, lost response to, or were intolerant to conventional therapy or a biological medicine, or have medical contraindications to such therapies.

4.2 DOSE AND METHOD OF ADMINISTRATION

Therapy with OMVOH is intended for use under the guidance and supervision of a healthcare professional experienced in the diagnosis and treatment of ulcerative colitis.

Prior to Administration of OMVOH

Consider completion of all immunisations according to current immunisation guidelines (see Section 4.4 Special warnings and precautions for use).

Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with OMVOH (see Section 4.4 Special warnings and precautions for use).

Recommended Dose for Ulcerative Colitis

OMVOH is single use only. Use in one patient on one occasion only. It contains no antimicrobial preservative.

Induction Dose

The recommended induction dosage regimen of OMVOH is 300 mg infused intravenously for at least 30 minutes at Week 0, Week 4, and Week 8 (see Section 4.2 Dose and method of administration).

Evaluate patients after the 12-week induction dosing, and if there is adequate therapeutic response, transition to maintenance dosing. If patients do not have adequate therapeutic response at Week 12 after induction dosing, consider extended induction dosing by administering 300 mg OMVOH by intravenous infusion at Weeks 12, 16, and 20 (see Section 5 Pharmacological properties, Clinical trials). If therapeutic benefit is achieved with the additional intravenous therapy, patients may initiate OMVOH subcutaneous maintenance dosing every 4 weeks. Discontinue OMVOH in patients who do not show evidence of therapeutic benefit to extended induction therapy by Week 24.

Maintenance Dose

The recommended maintenance dosage regimen of OMVOH is 200 mg (given as two consecutive subcutaneous injections of 100 mg each) every 4 weeks after completion of induction dosing (see Section 4.2 Dose and method of administration) starting at week 12. A full maintenance dose is two 100 mg pre-filled syringes or two 100 mg autoinjectors (pre-filled pens). If a dose is missed, administer the dose as soon as possible. Thereafter, resume monthly dosing.

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. If therapeutic benefit

is achieved with the additional intravenous therapy, patients may resume OMVOH subcutaneous maintenance dosing every 4 weeks (see Section 5 Pharmacological properties, Clinical trials).

No dose adjustment is required in the elderly (65 years and older) (see Section 5.2 Pharmacokinetic properties).

OMVOH has not been studied in patients with renal or hepatic impairment. No dose recommendations can be made.

Preparation and Administration for Intravenous Infusion (Induction Dose)

OMVOH solution for intravenous infusion must be diluted, prepared and infused by a healthcare professional.

Dilution of OMVOH to prepare solution for infusion

- Each vial is for single use only.
- Prepare the infusion solution using aseptic technique to ensure the sterility of the prepared solution.
- Inspect the content of the vial. The solution should be a clear, colourless to slightly yellow solution and free of visible particles.
- Withdraw 15 mL from the OMVOH vial (300 mg) using an appropriately sized needle (18 to 21 gauge is recommended) and transfer to the infusion bag. OMVOH should be diluted only in intravenous infusion bags (bag size ranging from 50 - 250 mL) containing EITHER 0.9% sodium chloride solution for injection OR 5% dextrose (or glucose) solution for injection. Do not dilute the infusion solution with other solutions or co-infuse with other electrolytes or medications.
- Gently invert the infusion bag to mix the contents. Do not shake the prepared bag.

Administration of OMVOH solution for infusion

- Connect the intravenous administration set (infusion line) to the prepared infusion bag and prime the line. Administer the infusion for at least 30 minutes.
- At the end of the infusion, to ensure a full dose is administered, the infusion line should be flushed with 0.9% sodium chloride solution for injection or 5% dextrose (or glucose) solution for injection. The flush should be administered at the same infusion rate as used for OMVOH administration. The time required to flush OMVOH solution from the infusion line is in addition to the minimum 30-minute infusion time.

General Considerations for Administration for Subcutaneous Injection by Autoinjector (Pre-filled Pen) or Pre-filled Syringe (Maintenance Dose)

- A full maintenance dose will require 2 autoinjectors (pre-filled pens) or 2 pre-filled syringes injected subcutaneously every 4 weeks after completion of induction dosing.
- OMVOH is intended for use under the guidance and supervision of a healthcare professional. Patients may self-inject OMVOH after training in subcutaneous injection technique. Provide proper training to patients and/or caregivers on the subcutaneous injection technique of OMVOH according to the "Instructions for Use", included with the packaged product.
- Sites for injection include the abdomen, thigh, and back of the upper arm. Instruct patients 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.
- Do not inject into areas where the skin is tender, bruised, erythematous or indurated.
- Before injection, remove OMVOH autoinjector (pre-filled pen) or OMVOH pre-filled syringe from the refrigerator and leave at room temperature for 30 minutes.
- Inspect OMVOH visually for particulate matter and discolouration prior to administration. Do not use OMVOH if it is cloudy or there are visible particles.
- OMVOH does not contain preservatives, therefore discard any unused product. Do not reuse.

4.3 CONTRAINDICATIONS

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

Clinically important active infections.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity reactions

Serious hypersensitivity reactions, including anaphylaxis, may occur with OMVOH administration. If serious hypersensitivity reactions occur, discontinue OMVOH immediately and initiate appropriate treatment (see Section 4.8 Adverse effects (Undesirable effects)).

Infections

OMVOH may increase the risk of infection. Treatment with OMVOH should not be initiated in patients with a clinically important active infection until the infection resolves or is adequately treated. Consider the risks and benefits of treatment prior to initiating use of OMVOH in patients with a chronic infection or a history of recurrent infection. Instruct patients to seek medical advice if signs or symptoms of clinically important acute or chronic infection occur. If a serious infection develops, consider discontinuation of OMVOH until the infection resolves.

No safety data are available in patients with HIV, hepatitis B or hepatitis C, as they were excluded from clinical trials.

OMVOH should not be given to patients with active tuberculosis (TB). Consider anti-TB therapy prior to initiation of OMVOH in patients with latent TB.

During the induction study (LUCENT-1), 0.5% of subjects in the mirikizumab arm experienced opportunistic infections (oesophageal candidiasis, cytomegalovirus colitis, herpes zoster, intestinal tuberculosis) and 0.3% in the placebo arm (herpes zoster). During the placebo-controlled maintenance study (LUCENT-2), 1.3% in the mirikizumab arm (oral candidiasis, herpes zoster) and 0 in the placebo arm experienced opportunistic infections.

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. Elevations of aminotransferases have been reported in patients receiving OMVOH. 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-associated liver injury is suspected, mirikizumab must be discontinued until this diagnosis is excluded (see Section 4.8 Adverse effects (Undesirable effects)).

Immunisations

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

Malignancy

The risk of malignancy is increased in patients with ulcerative colitis. Immunomodulatory medicinal products may increase the risk of malignancy.

Among all patients treated with mirikizumab in the ulcerative colitis clinical trials, the incidence rate of malignancies (excluding basal cell carcinomas and squamous cell carcinomas) was 0.5 per 100 patient-years of exposure, In the induction study, there were 2 reported malignancies in the mirikizumab arm and 0 in the placebo arm, and in the maintenance study, there was 1 reported malignancy in the mirikizumab arm and 0 in the placebo arm. The incidence rate of non-melanoma skin cancers (basal cell carcinomas and squamous cell carcinomas) was 0.2 per 100 patient-years of exposure.

Use in hepatic impairment

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

Population pharmacokinetic analysis showed that total bilirubin (range of 1.5 to 29 µmol/L) did not affect mirikizumab pharmacokinetics.

Use in renal impairment

Specific clinical pharmacology studies to evaluate the effects of renal 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) did not affect mirikizumab pharmacokinetics.

Use in the elderly

There is limited information in this age group, especially in those aged 75 years or older. Of the 1362 subjects with ulcerative colitis exposed to OMVOH in Phase 2 and Phase 3 studies, 99 subjects were 65 years or older and 11 subjects were 75 years or older. Population pharmacokinetic analysis showed no overall differences in OMVOH exposure between older and younger subjects.

Paediatric use

The safety and efficacy of OMVOH in patients less than 18 years of age has not been established.

Effects on laboratory tests

For hepatic enzyme elevation information in the clinical trial development programmes see Section 4.4 Special warnings and precautions for use.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

In ulcerative colitis studies, concomitant use of corticosteroids or oral immunomodulators (azathioprine, mercaptopurine, tioguanine, and methotrexate) were not found to affect the safety of OMVOH.

Population pharmacokinetic data analyses indicated that the clearance of mirikizumab was not impacted by concomitant administration of 5-ASAs, corticosteroids, or oral immunomodulators in patients with ulcerative colitis.

Based on a clinical drug interaction study conducted in patients with moderate-to-severe psoriasis, multiple subcutaneous doses of 250 mg every 4 weeks of mirikizumab (a dosage 1.25-times the recommended maintenance dosage) did not result in changes in the exposure of CYP3A, CYP2C9, CYP2D6, CYP2C19, or CYP1A2 substrates. Based on this study, mirikizumab is not expected to affect the metabolism by these five CYP enzymes. No drug interaction study was conducted in patients with ulcerative colitis at the recommended dosage.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

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

The effect of mirikizumab on human fertility has not been evaluated.

No dedicated animal fertility studies have been conducted with mirikizumab. In a repeat-dose toxicity study, no organ weight or histopathology effects were observed in the male or female reproductive tract in sexually mature cynomolgus monkeys that received mirikizumab once

weekly for 26 weeks via the subcutaneous (SC) route, at a dose of 100 mg/kg (7 times the exposure (AUC) at the maximum recommended human dose (MRHD)).

Use in pregnancy – Pregnancy Category B1

There are no available data on mirikizumab use in pregnant women to inform any drug associated risks. Human IgG is known to cross the placental barrier; therefore, mirikizumab may be transmitted from the mother to the developing fetus. As a precautionary measure, it is preferable to avoid the use of OMVOH during pregnancy.

An enhanced pre- and postnatal development study was conducted in cynomolgus monkeys administered mirikizumab by intravenous injection during organogenesis to parturition at a twice weekly dose of 300 mg/kg (79 times the exposure (AUC) at the MRHD). Mirikizumab crossed the placenta in monkeys. No mirikizumab related toxicity or effects on morphological, functional or immunological development were observed in infant monkeys from birth through 6 months of age.

Use in lactation

There are no data on the presence of mirikizumab in human milk, the effects on the breastfed infant, or the effects on milk production. However, IgG antibodies are known to be present in human milk. Risk to the breast-fed child cannot be excluded. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for OMVOH and any potential adverse effects on the breastfed infant from OMVOH or from the underlying maternal condition.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There are no known effects on the ability to drive or use machines associated with the use of mirikizumab.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

A total of 1442 adult subjects were treated with OMVOH in clinical development trials in ulcerative colitis with 1208 subjects being exposed for at least 6 months, 926 exposed for at least 1 year, and 450 exposed for at least 2 years.

Table 1: Treatment-Emergent Adverse Events Occurring in at least 2% of Mirikizumab-treated Participants by Decreasing Frequency in the UC Placebo-Controlled (LUCENT-1) Induction Period

Event	UC Placebo-controlled Induction Period	
	Placebo, N=321 n (%)	Mirikizumab 300 mg IV Q4W, N=958 n (%)
Participants with at least 1 TEAE	148 (46.1)	426 (44.5)
Nasopharyngitis	10 (3.1)	29 (4.1)
Anaemia	19 (5.9)	32 (3.3)
Headache	9 (2.8)	32 (3.3)
Arthralgia	4 (1.2)	20 (2.1)

Abbreviations: N = number of participants in the safety analysis set; n = number of participants in specified category; TEAE = treatment-emergent adverse event; UC = ulcerative colitis.

Table 2: Treatment-Emergent Adverse Events Occurring in at least 2% of Mirikizumab-treated Participants by Decreasing Frequency in the UC Mirikizumab-Responder Placebo-Controlled (LUCENT-2) Maintenance Period

Event	UC Placebo-controlled Maintenance Period	
	Placebo (mirikizumab responder), N=192 n (%)	Mirikizumab responder 200 mg SC Q4W, N=389 n (%)
Participants with at least 1 TEAE	132 (68.8)	251 (64.5)
Nasopharyngitis	11 (5.7)	28 (7.2)
Arthralgia	8 (4.2)	26 (6.7)
Colitis ulcerative	40 (20.8)	26 (6.7)
Injection site pain	6 (3.1)	17 (4.4)
Headache	2 (1.0)	16 (4.1)
Rash	0	14 (3.6)
Pyrexia	5 (2.6)	13 (3.3)
Abdominal pain	4 (2.1)	11 (2.8)
Blood creatine phosphokinase increased	5 (2.6)	10 (2.6)
Diarrhoea	1 (0.5)	10 (2.6)
Fatigue	4 (2.1)	10 (2.6)
Gastroesophageal reflux disease	1 (0.5)	10 (2.6)
Injection site reaction	1 (0.5)	10 (2.6)
Hypertension	1 (0.5)	9 (2.3)
Anaemia	9 (4.7)	8 (2.1)
COVID-19	4 (2.1)	8 (2.1)
Injection site erythema	2 (1.0)	8 (2.1)

Abbreviations: COVID-19 = coronavirus disease 2019; N = number of participants in the safety analysis set; n = number of participants in specified category; TEAE = treatment-emergent adverse event; UC = ulcerative colitis.

Tabulated list of adverse reactions
The most frequently reported adverse reactions were injection site reactions (maintenance period), upper respiratory tract infections (most frequently nasopharyngitis), headache and rash.

Adverse reactions from clinical studies (Table 3) are listed by MedDRA system organ class. Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. In addition, the corresponding 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 3: Patients with moderately to severely active ulcerative colitis

System organ class	Frequency	Adverse reaction
Infections and infestations	Common	Upper respiratory tract infections[a]
Immune system disorders	Uncommon	Infusion-related hypersensitivity reaction
Nervous system disorders	Common	Headache
Skin and subcutaneous tissue disorders	Common	Rash[b]
General disorders and administration site conditions	Common	Injection site reactions[c]
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.

Description of selected adverse reactions
Upper respiratory tract infections

In the first 12 weeks (LUCENT-1), Upper respiratory tract infections were reported in 76 (7.9%) mirikizumab treated patients compared to 19 (5.9%) patients in the placebo group.

Infusion-related hypersensitivity reactions

In the first 12 weeks (LUCENT-1), all infusion related hypersensitivity reactions were reported as non-serious in 4 (0.4%) mirikizumab treated patients compared to 1 (0.3%) patient in the placebo group.

Injection site reactions (LUCENT-2, weeks 12-52)

Injection site reactions were reported in 8.7% mirikizumab treated patients compared to 4.2% patients in the placebo group. The most frequent events were injection site pain, injection site reaction and injection site erythema. These symptoms were usually reported as non-serious, mild and transient in nature.

Hepatic enzyme elevations

In the first 12 weeks (LUCENT-1), ALT increased was reported in 4 (0.4%) mirikizumab treated patients compared to 1 (0.3%) in the placebo group. AST increased was reported by 5 (0.5%) mirikizumab treated patients compared to 1 (0.3%) in the placebo group. All events were reported as mild to moderate in severity and non-serious.

Across 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 Special warnings and precautions for use). These elevations have been noted with and without concomitant elevations in total bilirubin.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

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, monitor the patient for signs or symptoms of adverse reactions and start appropriate symptomatic treatment immediately.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Mirikizumab is a humanised IgG4 monoclonal antibody that binds with high affinity and specificity to the p19 subunit of human IL-23 cytokine and inhibits its interaction with the IL-23 receptor. It has no observed cross-reactivity to other members of the IL-12 cytokine family (that is, IL-12, IL-27, and IL-35).

IL-23 is an important driver of mucosal inflammation in ulcerative colitis and affects the differentiation, expansion, and survival of T cell subsets, and innate immune cell subsets, which represent sources of pro-inflammatory cytokines. Research in animal models has shown that genetic deletion or pharmacological inhibition of IL-23p19 can ameliorate or prevent intestinal inflammation.

Biomarkers of inflammation

Levels of inflammatory biomarkers were measured in the Phase 3 ulcerative colitis studies. OMVOH administered intravenously every 4 weeks during induction dosing significantly reduced levels of faecal calprotectin and C-reactive protein from baseline through 12 weeks. Additionally, OMVOH administered subcutaneously every 4 weeks during maintenance dosing sustained significantly reduced levels of faecal calprotectin and C-reactive protein through 40 weeks.

Faecal calprotectin, a marker of mucosal inflammation, was reduced significantly from baseline during the induction period and maintained throughout the maintenance period. At baseline 90.4% of mirikizumab treated patients and 88.9% of placebo treated patients had faecal calprotectin levels greater than 250 µg/g. Among these patients, 34.3% of those in the mirikizumab group had a faecal calprotectin level at week 12 of 250 µg/g or less compared with 20.1% in the placebo group.

Clinical trials

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. 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.

Induction Study (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, immunomodulatory agents (azathioprine, 6 mercaptopurine or methotrexate), and oral corticosteroids (prednisone daily dose up to 20 mg or equivalent). At induction baseline, 39.9% of patients were receiving oral corticosteroids, 24.1% were receiving immunomodulators and 74.3% were receiving aminosalicylates.

Of the primary efficacy population, 57.1% were biologic naive and tofacitinib naive. 41.2% of patients had failed (inadequate response, loss of response, or intolerance) 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, and an additional 1.7% had previously received but not failed a biologic or tofacitinib. 23.5% of patients had an inadequate response to a biologic or tofacitinib.

The mean age was 42.5 years (range 18-79 years). 59.8% of subjects were male. Subjects had median MMS of 7.0 and 53.2% had severely active disease (MMS of 7-9).

In LUCENT-1 a significantly greater proportion of patients were in clinical remission (primary outcome) in the mirikizumab treated group compared to placebo at week 12 (Table 4). Key secondary outcomes showed that, as early as week 4 and at each visit thereafter, a higher proportion of mirikizumab patients had both no rectal bleeding and normal stool frequency (symptomatic remission) as compared with placebo patients ($p \leq 0.001$). Other secondary outcomes showed that as early as week 2, mirikizumab treated patients achieved a significantly greater reduction in RB subscores ($p=0.001$) and significant decreases in SF subscores ($p=0.035$).

Table 4: 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	%	
Primary outcome					
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%	- - -
Key secondary outcomes					
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 were 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.

Maintenance Study (LUCENT-2)

LUCENT-2 evaluated 544 patients who achieved clinical response in LUCENT-1 at week 12. 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). 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 5).

Table 5: 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	%	
Primary outcome					
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%	- - -
Key secondary outcomes					
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
	mean	Standard error	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 3

*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 NRS 0 or 1 in patients with urgency NRS ≥ 3 at baseline in LUCENT-1

*8 Change from baseline in the Urgency Numeric Rating Scale score

a) An additional 1 patient on placebo and 8 patients on mirikizumab were 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 beneficial effect of mirikizumab on symptomatic, endoscopic and histologic outcomes was observed in induction and in maintenance both in patients who failed conventional therapy (but had not failed a biologic or JAK inhibitor therapy) as well as in those who had failed at least one or more biologic or JAK inhibitor. At week 12, 50.2% of patients who were inadequate responders to a biologic or JAK inhibitor therapy achieved clinical response with mirikizumab and of those who were re-randomised to mirikizumab for maintenance treatment 45.9% were in clinical remission at week 40.

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

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

Patients who were non responders at week 12 of LUCENT-1 were eligible to receive extended open label induction therapy in LUCENT-2 (300 mg mirikizumab IV at weeks 0, 4 and 8). Of those 272 patients, 146 (53.7%) achieved clinical response at week 12 (24 weeks after the first induction dose), and 144 patients received the maintenance dose of 200 mg mirikizumab Q4W SC; among these patients, a majority (72.2%) maintained clinical response and 36.1% achieved clinical remission at week 40.

Recapture of efficacy after loss of response to mirikizumab maintenance (LUCENT-2)

Patients who developed symptomatic and confirmatory endoscopic loss of response (5.2%) between week 12 and 28 of LUCENT-2 while on maintenance therapy with mirikizumab,

received open label mirikizumab re-induction therapy with 300 mg mirikizumab Q4W IV for 3 doses (referred to as rescue dosing). Of these, 63.2% (12/19) patients achieved symptomatic response and 36.8% (7/19) achieved symptomatic remission after 12 weeks rescue dosing.

Other secondary outcomes (LUCENT-1 and LUCENT-2)

Histologic results

At week 12 significantly 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 significantly 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

Health-related quality of life was assessed by Inflammatory Bowel Disease Questionnaire (IBDQ). IBDQ response was defined as a ≥16 point improvement from baseline in IBDQ score and IBDQ remission was defined as a score of ≥170. At week 12 of LUCENT-1, 57.5% of mirikizumab-treated patients achieved IBDQ remission versus 39.8% in placebo 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.

At week 12 in LUCENT-1 and week 40 in LUCENT-2, patients receiving mirikizumab experienced significantly more improvements in work productivity with greater reductions in overall work impairment and activity impairment as assessed by the Work Productivity and Activity Impairment Questionnaire-Ulcerative Colitis (WPAI-UC) questionnaire than patients receiving placebo.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. With 12 months of treatment, up to 23% of mirikizumab treated patients developed anti-drug antibodies, most of which were of low titre and tested positive for neutralising activity. Higher antibody titres in approximately 2% of subjects treated with mirikizumab were associated with lower serum mirikizumab concentrations and reduced clinical response. Clinical data indicate a small risk that neutralising antibodies at titre≥1:160 may reduce mirikizumab efficacy. No association was found between anti-mirikizumab antibodies and hypersensitivity or injection related events.

5.2 PHARMACOKINETIC PROPERTIES

Mirikizumab has pharmacokinetic characteristics typical of an IgG4 monoclonal antibody. It exhibited linear pharmacokinetics with dose-proportional increase in exposure over a dose range of 5 to 2400 mg given as an intravenous injection or over a dose range of 120 to 400 mg given as a subcutaneous injection, in patients with ulcerative colitis or in healthy volunteers. 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 OMVOH, 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.

Metabolism

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

Excretion

In the population PK analysis, mean clearance was 0.0229 L/hr and the mean half-life is 9.3 days in patients with ulcerative colitis. Clearance is independent of dose.

Specific Populations

Age, Sex, Weight, Race, Ethnicity

Population pharmacokinetic analysis showed that age, sex, weight, or race/ethnicity did not have a significant effect on the pharmacokinetics of mirikizumab.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Genotoxicity studies have not been conducted with mirikizumab. As mirikizumab is a monoclonal antibody, it is not expected to interact directly with DNA.

Carcinogenicity

Animal studies have not been conducted to evaluate the carcinogenic potential of mirikizumab.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium Chloride

Sodium citrate dihydrate

Citric acid

Polysorbate 80

Water for Injections

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Unopened Vial

Store refrigerated at 2°C to 8°C in the original carton to protect from light until time of dilution. Do not freeze.

Diluted infusion solution

Mirikizumab is diluted in either 0.9% (9 mg/mL) sodium chloride injection or 5% (50 mg/mL) dextrose (or glucose) injection. If not used immediately, store the dosing solution under refrigerated conditions at 2°C to 8°C.

It is recommended to start the infusion immediately after preparation.

- Do not freeze. Do not use if frozen
- Do not shake
- Do not shake the diluted solution in the prepared infusion bag (gently invert the infusion bag to mix)
- Do not freeze the diluted solution in the prepared infusion bag

Saline solution

If not used immediately, OMVOH 300 mg solution prepared with 0.9% saline may be stored refrigerated (2°C to 8°C) for a maximum of 96 hours or at room temperature (not exceeding 25°C) for a maximum of 10 hours.

Dextrose (or Glucose) solution

If not used immediately, OMVOH 300 mg solution prepared with 5% dextrose (or glucose) may be stored refrigerated (2°C to 8°C) for a maximum of 48 hours or at room temperature (not exceeding 25°C) for a maximum of 5 hours.

Autoinjector (pre-filled pen) and pre-filled syringe

- Store refrigerated at 2°C to 8°C in the original carton to protect from light until use
- May be stored outside of refrigeration in the original carton at not more than 30°C for up to 2 weeks. Once stored out of the refrigerator, do not place back in the refrigerator. If these conditions are exceeded, mirikizumab must be discarded.
- Do not freeze. Do not use if frozen
- Do not shake
- Discard autoinjector (pre-filled pen) or pre-filled syringe in sharps container.

6.5 NATURE AND CONTENTS OF CONTAINER

Vial

OMVOH 300 mg/15 mL is supplied in a single use glass vial with a rubber stopper. The stopper is not made with natural rubber latex.

OMVOH is available in pack size of 1 vial.

Autoinjector (pre-filled pen) and Pre-filled Syringe

OMVOH 100 mg/mL is supplied in a 1 mL autoinjector (pre-filled pen) or pre-filled syringe. The solution is contained in a clear glass syringe barrel with plunger. The plunger is not made with natural rubber latex.

OMVOH is available in pack sizes of 2, 4 or 6 single dose autoinjector (pre-filled pen) or pre-filled syringe*.

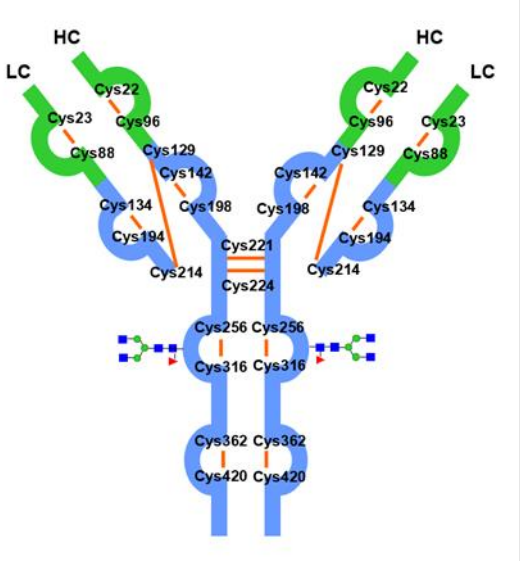
* Not all pack sizes or presentations may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



CAS number

1884201-71-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4

8 SPONSOR

Eli Lilly Australia Pty Ltd

Level 9, 60 Margaret Street, Sydney, NSW 2000

AUSTRALIA

Phone: 1800 454 559

9 DATE OF FIRST APPROVAL

27 September 2023

10 DATE OF REVISION

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	New biological entity