30 March 2023
EMA/197960/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Omvoh

International non-proprietary name: mirikizumab

Procedure No. EMEA/H/C/005122/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADA	Anti-drug antibodies
ADCC	Antibody-Dependent Cell-Mediated Cytotoxicity
AE	Adverse event
AET	Analytical Evaluation Threshold
AEX	Anion Exchange Chromatography
AI	Autoinjector
Asp	Asparagine
ATA	Aurintricarboxylic Acid Ammonium Salt
AUC	Analytical ultracentrifugation
BMI	Body mass index
BSE	Bovine spongiform encephalopathy
CCI	Container closure integrity
CCI(T)	Container Closure Integrity (Testing)
CD	Circular Dichroism
CDC	Complement dependent cytotoxicity
CDR	Complementarity Determining Region
CEP	Certificate of Suitability of the European Pharmacopoeia
CE-SDS non-red	Capillary Electrophoresis Sodium Dodecyl Sulphate non-reduced
CE-SDS red	Capillary Electrophoresis Sodium Dodecyl Sulphate reduced
CEX	Cation Exchange Chromatography
CFU	Colony Forming Unit
CGE	Capillary Electrophoresis
CHMP	Committee for Evaluation of Human Medicinal Products
CHO	Chinese Hamster Ovary
CI	Confidence interval
cIEF	Capillary Isoelectric Focusing
CIP	Clean in Place
CMH	Cochran-Mantel-Haenszel
CoA	Certificate of analysis
COVID-19	coronavirus disease 2019
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
CRP	C-reactive protein
CSR	Clinical study report
Cys	Cysteine
Da	Dalton
DLS	Dynamic Light Scattering
DNA	Deoxyribonucleic Acid
DO	Dissolved oxygen
DoE	Design of Experiment
DP	Drug Product
DS	Drug Substance
DSC	Differential scanning calorimetry
DVI	Detergent Viral Inactivation
EB	Exposure-based
EC50	Half maximal effective concentration
ECB	Extended Cell Bank
ECCO	European Crohn’s and Colitis Organization
eCOA	Electronic clinical outcome assessment
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency
EQ-5D	European QoL Health Questionnaire–5 Dimensions
EQ-5D-5L	European QoL Health Questionnaire–5 Dimensions–5 Levels

ES	endoscopic subscore
EU	European Union
EU	Endotoxin Unit
Fab	Fragment Antigen-binding
FcR	Fc Receptor
FcRn	Neonatal FC receptor
FDS	Formulated drug substance
FMEA	Failure Mode and Effect Analysis
FTIR	Fourier transform infrared
Fuc	Fucose
GMP	Good Manufacturing Practices
GS	Glutamine Synthetase
GSPR	General Safety and Performance Requirements
HC	Heavy Chain
HCP	Host Cell Protein
HDPE	High-Density Polyethylene
HILIC	Hydrophilic interaction liquid chromatography
HPLC	High Performance Liquid Chromatography
HRQoL	health-related quality of life
IBD	Inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICH	International Council For Harmonization Of Technical Requirements For Pharmaceuticals For Human Use
icIEF	Imaged Capillary Isoelectric Focusing
ICP-MS	Intercoupled plasma mass spectrometry
Ig	Immunoglobulin
IgG	Immunoglobulin G
IL	Interleukin
IPC	In-Process Control
IPS	In-Process Specification
ISO	International Organization of Standardization
IsoAsp	Isoaspartic acid
ITT	Intent-to-treat
IV	Intravenous
JAKi	Janus kinase inhibitor
JP	Japanese Pharmacopoeia
KD	Dissociation constant
KPP	Key process parameter
LB	Luria both
LC	Light Chain
LC-MS	Liquid chromatography–mass spectrometry
LoD	Limit of Detection
LoQ	Limit of Quantitation
Lph CI	Low pH Viral Inactivation
LSM	least-squares mean
mAb	Monoclonal Antibody
MALDI	Matrix-Assisted Laser Desorption/Ionisation-
mBOCF	Modified baseline observation carried forward
MCB	Master Cell Bank
MCID	Minimal clinically important difference
MCS	Mental component summary
Met	Methionine
mITT	Modified intent-to-treat
MM	Multimodal
MMRM	Mixed-effects model of repeated measures

MMS	modified Mayo score
MO	Major Objection
MSX	Methionine Sulfoximine
MuLV	Murine Leukemia Virus
MVD	Maximum valid dilution
MVM	Minute Virus of Mice
MWPC	Meaningful within-patient change
NA or N/A	Not Applicable
NAS	New active substance
NBO	Notified Body Opinion
NGHC	Non glycosylated heavy chain
NLT	Not Less Than
NMR	Nuclear magnetic resonance
NMT	Not More Than
NRI	Non-responder imputation
NRS	Numeric Rating Scale
NTU	Nephelometric Turbidity Unit
OC	Other concern
OD	Optical density
OOS	Out of Specification
OPP	Operational Process Parameter
PBA	4-phenyl-3-butenoic-acid
PC	Polycarbonate
PCS	physical component summary
PDE	Permitted Daily Exposure
PDL	Population doubling level
PFS	Pre-Filled Syringe
PGRC	Patient's Global Rating of Change
PGRS	Patient's Global Rating of Severity
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic(s)
PP	Per protocol
PP	Process Parameter
ppb	Parts per billion
ppm	Parts per million
PPQ	Process Performance Qualification
PPV	Porcine Parvovirus
PRO	patient-reported outcome
ProA	Protein A Capture
PRS	Primary Reference Standard
PS80	Polysorbate 80
Q12W	Every 12 weeks
Q4W	Every 4 weeks
QbD	Quality by Design
QoL	Quality of life
QTTP	Quality Target Product Profile
RB	Rectal bleeding
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RH	Relative Humidity
rhIL	Recombinant Human Interleukin
(RP)-UPLC	(Reverse Phase)- Ultra-Performance Liquid Chromatography
RVLP	Retrovirus-Like Particles
S/N	Signal-to-Noise Ratio
SAP	statistical analysis plan
SC	Subcutaneous

SD	Standard deviation
SDS	Sodium Dodecyl Sulfate
SDS-PAGE	Sodium Dodecyl Sulfate Polyacrylamide Gel Electrophoresis
SE	Standard error
SEC	Size Exclusion Chromatography
SF	stool frequency
SF-36	Medical Outcomes Study 36-Item Short-Form Health Survey
SFS	Semi-Finished Syringe
SmPC	Summary of Product Characteristics
SPR	Surface Plasmon Resonance
SST	System suitability test
SUDS	Single-Use Disposable Systems
SV-AUC	Sedimentation velocity- Analytical ultracentrifugation
TAMC	Total Aerobic Microbial Count
TE	treatment-emergent
TEM	Transmission Electron Microscopy
TFF	Tangential Flow Filtration
TMP	Transmembrane pressure
TNF	Tumour necrosis factor
TRIS	Tris(hydroxymethyl)aminomethane
TSE	Transmissible Spongiform Encephalopathy
TYMC	Total Yeast Microbial Count
UC	Ulcerative colitis
USP	United States Pharmacopoeia
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
VF	Virus Filtration
WCB	Working Cell Bank
WPAI:UC	Work Productivity and Activity Impairment:UC
WRS	Working Reference Standard

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Eli Lilly Nederland B.V. submitted on 27 April 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Omvoh, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 26 July 2018.

The applicant applied for the following indication.

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 or a Janus kinase (JAK) inhibitor, or have medical contraindications to such therapies (see section 5.1).

1.2. Legal basis, dossier and content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is

composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0088/2022 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA- 002208-PIP01-17-M02 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.4.2. New active substance status

The applicant requested the active substance mirikizumab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.5. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
22 June 2017	EMEA/H/SAH/079/1/2017/III	Minne Casteels, Rune Kjeken

The scientific advice pertained to the following non-clinical and clinical aspects:

- The non-clinical data package to support a MAA; the need for additional non-clinical studies to assess carcinogenic potential.
- The clinical pharmacology plan with regard to populations with renal and hepatic impairment, drug-drug interactions, and elderly populations; the safety monitoring plan; the proposed Phase 3 clinical programme including a) the primary/secondary endpoints and duration of treatment of pivotal induction studies, b) the primary/secondary endpoints and duration of treatment of the pivotal maintenance study, c) the control group in the induction and maintenance studies; the design of the active comparator study.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jayne Crowe Co-Rapporteur: Agnes Gyurasics

The application was received by the EMA on	27 April 2022
The procedure started on	19 May 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	8 August 2022
The CHMP Co-Rapporteur's critique was circulated to all CHMP and PRAC members on	22 August 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	22 August 2022
The PRAC Rapporteur's updated Assessment Report was circulated to all PRAC and CHMP members on	01 September 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	15 September 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	23 November 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	05 January 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	12 January 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	19 January 2023

The CHMP agreed on a list of outstanding issues to be sent to the applicant on	23 February 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	24 February 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	15 March 2023
The CHMP Rapporteurs circulated the updated CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	23 March 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Omvoh on	30 March 2023
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product	30 March 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

UC is a chronic disease of unknown aetiology that is characterised by inflammation of the colon and rectum. Symptoms include diarrhoea, rectal bleeding, abdominal pain and bowel movement urgency. UC has a relapsing-remitting course, meaning that many patients have intermittent disease flares that are interspersed with periods of remission. It is postulated that UC is caused by unregulated and exaggerated local immune response to environmental triggers in genetically susceptible individuals.

2.1.2. Epidemiology

A systematic review of studies evaluating the worldwide incidence and prevalence of inflammatory bowel disease reported that the prevalence rates for UC were:

- 140 to 286 per 100,000 persons in North America
- 2.4 to 505 per 100,000 persons in Europe
- 4.6 to 57.3 per 100,000 persons in Asia
- 4.7 to 44.3 per 100,000 persons in South America, and
- 10.6 per 100,000 persons in Africa (Ng et al. 2017).

Diagnosis is based on symptoms using supportive evidence from an endoscopy, tissue biopsy and negative stool examination, while ruling out infectious disease.

There are no known preventative medical therapies available.

2.1.3. Aetiology and pathogenesis

The precise aetiology of ulcerative colitis is not well understood. A current hypothesis suggests that primary dysregulation of the mucosal immune system leads to an excessive immunologic response to normal microflora in a genetically susceptible host, finally leading to chronic intestinal inflammation.

The importance of the epithelial barrier in IBD predisposition is supported by reports of abnormal intestinal permeability in patients with IBD and some of their first-degree relatives. Alterations in the balance between proliferation and apoptosis are known to be involved in barrier dysfunction, which leads to IBD.

During the inflammatory phase, resident cells produce cytokines, which recruit immune cells to the site of injury. Infiltrating monocytes differentiate into macrophages, key players in driving an effective immune response through phagocytosis of pathogens and apoptotic neutrophils. Mediators released during the inflammatory phase also recruit fibroblasts to the wound region, thereby initiating the proliferative phase.

Ulcerative colitis is a serious disease that, in some cases, may cause life-threatening complications that can be fatal. The most severe intestinal manifestations of UC are toxic megacolon and perforation. Extra-intestinal complications include arthritis, dermatological conditions, uveitis, and primary sclerosing cholangitis.

The risk of colorectal cancer (CRC) has been suggested to markedly increase with cumulative probabilities of 2% by 10 years, 8% by 20 years, and 18% by 30 years.

The main risk factors for IBD-CRC include certain disease characteristics such as age at onset, extent and duration of disease, as well as non-IBD characteristics such as family history of CRC and concomitant diagnosis of primary sclerosing cholangitis.

2.1.4. Clinical presentation, diagnosis and prognosis

Symptoms include diarrhoea, rectal bleeding, abdominal pain and bowel movement urgency. UC has a relapsing-remitting course, meaning that many patients have intermittent disease flares that are interspersed with periods of remission.

Diagnosis is made endoscopically. Ulcerative colitis is a chronic disease characterised by diffuse mucosal inflammation of the colon. Ulcerative colitis always involves the rectum (i.e., proctitis), and it may extend proximally in a contiguous pattern to involve the sigmoid colon (i.e., proctosigmoiditis), the descending colon (i.e., left-sided colitis), or the entire colon (i.e., pancolitis).

The onset of ulcerative colitis is most common between 15 and 40 years of age, with a second peak in incidence between 50 and 80 years. The disease affects men and women at similar rates.

3% to 8% of patients with UC have primary sclerosing cholangitis, a chronic disease of bile ducts that predisposes affected patients to increased risks of progressive liver disease and colorectal cancer (Tanaka and Mertens 2016). Compared to those without UC, patients with UC are at an increased risk of developing and dying from colorectal cancer (Olén et al. 2020). Fear of cancer and the frequency of endoscopic surveillance procedures to detect UC dysplasia may also impact HRQoL in patients with UC.

2.1.5. Management

Medical therapeutic decisions for UC are categorised into those for (a) induction and (b) maintenance, with a goal of obtaining and maintaining steroid-free remission.

Treatment goals in UC include induction of remission (typically within a 6 to 12 week time frame) and maintenance of remission in the longer term (assessed over 52 weeks of continuous treatment in clinical trials). In both clinical practice and in clinical trials, clinical response and clinical remission are assessed by a combination of endoscopy (improvement in the endoscopic appearance of the mucosa and healing of ulcers) and patient-reported outcomes, including a reduction in stool frequency (SF) and a resolution of RB (Levesque et al. 2015). Control of intestinal inflammation in UC is also associated with a reduction in the risk of hospitalisation, colectomy, and in the longer term, UC associated dysplasia and colorectal cancer.

Medications used for the treatment of UC include 5-aminosalicylic acid (5-ASA)–containing medications (sulfasalazine, mesalazine, balsalazide, olsalazine), corticosteroids, immunomodulators such as AZA and 6-MP and biologic medications.

A significant proportion of patients with moderately to severely active UC may have an inadequate response to medicines such as 5-ASAs or corticosteroids, be unable to maintain a clinical response to 5-ASAs or AZA or be unable to discontinue corticosteroids without a relapse in disease activity (reviewed in Dignass et al. 2012). Many of these patients require additional treatment with the next line of therapy, which could include medical treatment with a biologic medication or surgical treatment with a colectomy.

Biologics, including antitumour necrosis factor (TNF) antibodies (infliximab, adalimumab, golimumab) and vedolizumab, an anti-α4β7 integrin antibody, are indicated for the treatment of UC in patients who fail to respond to, have an inadequate response to, or are intolerant to other medications used in the treatment of UC medications and as a first-line treatment for UC in selected patients.

Approximately 40% to 50% of patients with moderately to severely active UC fail treatment with current biologic or small-molecule therapies in the first year of treatment. Therefore, there is a clear medical need for additional therapeutic options in UC for subjects with inadequate response to or intolerance to conventional therapies and biologic therapies.

2.2. About the product

Mirikizumab is a humanised immunoglobulin G4 (IgG4) isotype monoclonal antibody that binds with high affinity and specificity to the p19 subunit of interleukin (IL-23), a naturally occurring proinflammatory cytokine and inhibits its interaction with the IL-23 receptor.

Interleukin-23 is a member of the IL-12 family of cytokines and has 2 components: the p40 subunit, which is shared by IL-12 and IL-23; and the p19 subunit, which is only found in IL-23. Preclinical studies have shown that IL-12 is a potent inducer of antitumour immunity and plays a key role in the protection against bacterial and viral infections (Hamza et al. 2010; Tugues et al. 2015). Targeting the p19 subunit of IL-23 alone therefore preserves the perceived protective role of IL-12 (Kurtz et al. 2014; Teng et al. 2015).

The applicant is seeking the following indication:

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 or a Janus kinase (JAK) inhibitor, or have medical contraindications to such therapies (see section 5.1).

The proposed dosing regimen for the indication is 300 mg intravenous (IV) infusion every 4 weeks for 3 doses followed by 200 mg subcutaneous (SC) injection every 4 weeks.

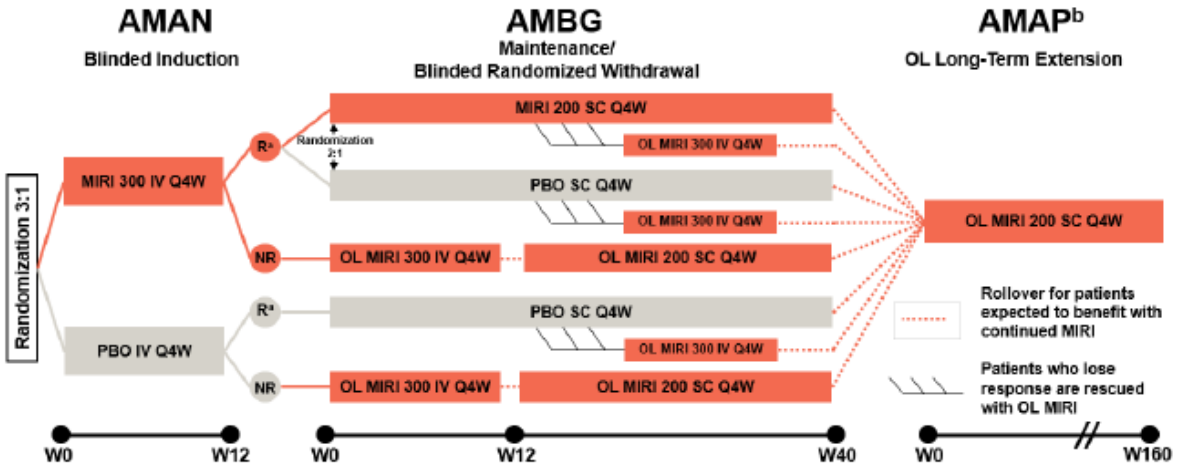
It is proposed that , if patients do not have adequate therapeutic response at week 12 of induction dosing, to consider continuing to dose with 300 mg mirikizumab by intravenous infusion at weeks 12, 16 and 20 (extended induction therapy). If therapeutic benefit is achieved with the additional intravenous therapy, patients may initiate mirikizumab subcutaneous maintenance dosing (200 mg) every 4 weeks, starting at week 24. Discontinue mirikizumab 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. If clinical benefit is achieved from this additional intravenous therapy, patients may resume mirikizumab subcutaneous dosing every 4 weeks.

2.3. Type of application and aspects on development

The mirikizumab UC Phase 3 programme comprised 3 trials:

- 12-week induction Study I6TMC- AMAN (AMAN),
- 40-week maintenance Study 16T-MC-AMBG (AMBG),
- long term extension Study I6T-MC-AMAP.



Abbreviations = IV = intravenous; mg = milligram; MIRI = mirikizumab; NR = nonresponder; MMS = modified Mayo score; OL = open-label; PBO = placebo; Q4W = every 4 weeks; R = responder; SC = subcutaneous; W = week.

[a] Responders at Week 12 of Study AMAN are defined as achieving 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 an RB score of 0 or 1.

[b] Includes patients who completed the Phase 2 Study AMAC, not shown.

The applicant received Scientific Advice from CHMP (EMEA/H/SAH/079/1/2017/III) on 22 June 2017.

The advice was on the preclinical and clinical pharmacology and phase studies in UC and safety monitoring. The development mostly followed the advice however the applicant at that time proposed 2 separate induction studies (AMAN) and (AMAO) both of which planned to enrol 408 patients and test two separate regimens in UC patients who failed or were intolerant to conventional or biological therapies. However only a single induction study was conducted, however, overall, the development

seems to be line with the regulatory requirements: Guideline on the development of new medicinal products for the treatment of Ulcerative colitis (CHMP/EWP/18463/2006 Rev.1)

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as concentrate for solution for infusion or solution for injection containing 300 mg in 15 mL (20 mg/mL) or 100 mg in 1mL (100 mg/mL), respectively, of mirikizumab as active substance.

Other ingredients are: sodium citrate dihydrate, citric acid (anhydrous), sodium chloride, polysorbate 80, water for injection.

For the 300 mg concentrate for solution for infusion, the finished product is available in a type I glass vial (pack size of 1 vial). For the 100 mg solution for injection, the finished product is available in a type I clear glass syringe encased either in a disposable pre-filled syringe (pack sizes of 2 or 6 pre-filled syringes) or in a disposable pre-filled pen (pack sizes of pack sizes of 2, 4 or 6 pre-filled pens). Not all pack sizes may be marketed.

2.4.2. Active Substance

2.4.2.1. General Information

The active substance (INN: mirikizumab, also known as LY3074828) is a humanised IgG4 monoclonal anti-interleukin-23 (anti-IL-23) antibody, produced in CHO cells, 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.

Mirikizumab is composed of two identical immunoglobulin kappa light chains and two identical immunoglobulin gamma heavy chains.

2.4.2.2. Manufacture, process controls and characterisation

Manufacturing of the active substance is performed by Eli Lilly Kinsale Limited, Dunderrow, Kinsale, Co. Cork, Ireland. The active substance is manufactured, packaged, stability tested and quality-control tested in accordance with Good Manufacturing Practice (GMP).

Description of manufacturing process and process controls

The manufacturing process is standard for the production of monoclonal antibodies (mAbs). Generally, the manufacturing process is well-described and an acceptable batch definition has been provided. The ranges of critical process parameters (CPPs) and the routine in-process controls (IPCs) along with acceptance criteria are described for each step.

Manufacturing starts from a Working Cell Bank (WCB), which is expanded through a series of flasks and bioreactors. The culture is harvested, clarified, and then transferred for downstream processing. The downstream manufacture of mirikizumab consists of viral inactivation and clarification, chromatography and filtration unit operations.

Finally, the purified mirikizumab (bulk active substance) is filtered, dispensed into the proposed container closure system and stored.

Two container closure systems are proposed for the active substance: a polycarbonate container (PC) and a high-density polyethylene container (HDPE). The container closure system components comply

with the Ph. Eur. 3.1.6 and Ph. Eur. 3.2.2. Compatibility, specifications and extractables/leachables studies are addressed for both containers.

The registered controls are considered appropriate for routine control of a standard mAb manufacturing process. Overall, the active substance manufacturing process is sufficiently well described in the dossier and is considered acceptable.

Control of materials

Sufficient information on raw materials used in the active substance manufacturing process has been submitted. Compendial raw materials are tested in accordance with the corresponding monograph, while specifications (including test methods) for non-compendial raw materials are presented. No human or animal derived materials are used in the active substance manufacturing process and acceptable documents have been provided for raw materials of biological origin used in the establishment of cell substrate.

Details of developmental genetics and the establishment of the master cell bank (MCB) have been provided in line with ICH Q5B.

The general scheme for the selection, clonal-derivation, identification, and subsequent banking of the Production Cell Line is provided. The approach is sufficiently described and is acceptable. A safety assessment is provided for raw materials of animal origin used during cell line generation.

Establishment of the MCB and WCB is described in accordance with the ICH Q5D. Date of manufacture, labelling, storage conditions, stability testing and storage locations for the MCB and WCB are sufficiently described. Characterisation of the cell banks has been carried out in line with ICH Q5D. The testing of the cell banks is carried out in accordance with the Ph. Eur. 2031 monoclonal antibodies for human use. Genetic stability has been demonstrated for cells at and beyond the limit of cell age. The MCB, WCB and extended cell bank (ECB) were tested for adventitious agents in line with ICH Q5A. The protocol for replacement of the WCB and specifications for qualifying the replacement WCB are described and considered acceptable.

Control of critical steps and intermediates

Overall, the presented control strategy is largely in line with what would be expected for a standard mAb manufacturing process. The upstream cell expansion steps have controls in place to ensure the appropriate number of viable cells with appropriate bioreactor conditions. Appropriate controls are in place throughout the process.

Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process and all process controls have been adequately defined by the applicant, in line with ICH Q8. The limits for all controls have been adequately justified and actions taken if limits are exceeded are specified.

Process validation

A standard approach to process validation has been taken, which is in accordance with the *Guideline on process validation for the manufacture of biotechnologically derived active substance and data to be provided* (EMA/CHMP/BWP/187338/2014). Process development and characterisation studies are outlined in the dossier, together with data on process performance qualification (PPQ) batches manufactured at the commercial site and scale. The results presented for the PPQ batches show that the active substance manufacturing process consistently produces mirikizumab active substance of reproducible quality that complies with the predetermined specification and in-process acceptance criteria.

<u>Process characterisation</u>

Process characterisation followed a relatively standard approach based on risk assessment and DoE process characterisation studies. An initial risk assessment was used to identify potential critical quality attributes (CQAs). Detailed explanations of the scoring system are presented in the dossier. The approach is logical and is therefore considered appropriate. Overall, the list of CQAs is considered typical for a mAb and is fully endorsed. Those process parameters which were considered by the risk assessment to have a potential impact on a CQA were studied. The overall approach for quantifying process parameter impact and determining practical significance is considered acceptable.

In general, the process characterisation studies have resulted in an appropriate level of control of the manufacturing process.

Impurity clearance

The clearance of impurities was addressed, and the results provided show adequate removal capability of the manufacturing process.

Hold times

Data are provided and the results support the hold times proposed.

Resin and filter lifetime studies

The overall approach to establish resin and membrane lifetime uses small-scale data and verification at commercial scale via a protocol, which is in line with the EMA Guideline on process validation for the manufacture of biotechnology-derived active substances (EMA/CHMP/BWP/187338/2014). The proposed reuse cycles are considered acceptable.

Reprocessing

Validation of reprocessing steps was performed. Commercial scale reprocessing protocols have been provided.

Overall, the proposal for reprocessing is in line with current guideline requirements and is considered acceptable.

Transport validation

Transport conditions were adequately justified.

In conclusion, the applicant has provided sufficient data to provide assurance that the manufacturing process is appropriately validated and in a state of control.

Manufacturing process development

The commercial active substance manufacturing process was developed in parallel with the clinical development programme.

Different manufacturing processes have been described and 3 different active substances manufacturers sites had been used throughout the development.

For each change, a comparability study has been carried out demonstrating that the change did not have a significant influence on the quality of the product.

Characterisation

The mirikizumab active substance has been sufficiently characterised using state-of-the-art methods. Brief descriptions of the analytical methods used for characterisation are provided which are acceptable. In general, characterisation is in accordance with the Ph. Eur. 2031 monoclonal antibodies

for human use. The analytical results are consistent with the proposed structure, revealing that the active substance has the expected structure of a human IgG4-type antibody.

The identified product related impurities are aggregates and fragments, which are adequately controlled. Levels of process-related impurities are described and supported by clearance studies. The acceptable exposure limits proposed are supported with adequate references.

2.4.2.3. Specification

In general, the panels of tests are in line with ICH Q6B and are considered appropriate for routine control of a monoclonal antibody both at release and shelf-life.

During the assessment, the applicant updated the active substance specifications/acceptance limits upon request.

Analytical methods

The analytical methods have been sufficiently well described and (non-compendial methods) appropriately validated in accordance with ICH Q2(R1).

Batch analysis

All batches comply with the specifications in place at the time of testing. These data demonstrate that the commercial process is capable of manufacturing a consistent active substance.

Reference materials

A standard approach for two tier reference standards is in place. Two primary reference standards (PRS) have been manufactured and qualified. The primary and working reference standards have been sufficiently characterised.

2.4.2.4. Stability

Stability data are provided in support of a claimed shelf-life of 36 months at ≤-65°C. The studies are conducted in accordance with the ICH Q5C and suitable study protocols are provided.

Studies were carried out in accelerated conditions. Study data are provided in stressed conditions in accordance with ICH Q1A and ICH Q1B. The methods used are considered stability indicating, as supported by the stressed stability study.

At long-term and at accelerated conditions, all results comply with the specifications valid at time of testing. No obvious relevant trends are present at long-term or accelerated conditions.

In conclusion, the presented data support the proposed shelf-life of 36 months at ≤-65°C when stored in the commercial container closure systems.

Commitments to complete the currently ongoing stability studies and to perform post-approval annual stability studies are provided. The proposed protocol (including adequate handling of any confirmed out of specification - OOS) is acceptable.

2.4.3. Finished Medicinal Product

Two presentations are proposed for the mirikizumab finished product: a 100 mg/mL semi-finished syringe (SFS) which is assembled with device components to form either the pre-filled syringe (PFS) or the autoinjector (AI) presentation, and a single use 300 mg/15 mL vial. Each presentation will be addressed separately where necessary.

2.4.3.1. Description of the product and Pharmaceutical Development

Description of the product

The components of the finished product are mirikizumab, sodium citrate dihydrate, citric acid (anhydrous), sodium chloride, polysorbate 80, water for injection.

100 mg/mL SFS

Mirikizumab SFS 100 mg/mL is supplied as a non-pyrogenic parenteral solution for subcutaneous administration contained in a 1 mL long, Type I borosilicate glass syringe barrel with laminated bromobutyl elastomeric plunger.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients in the formulation. There are no materials of animal or human origin listed in the finished product composition. The formulation data presented show the commercial composition is suitable to maintain the quality of the finished product. The compatibility of the active substance with excipients is supported by stability data. There is no overage proposed, although excess volume is filled into each syringe to enable delivery of 1.0 mL.

300 mg/15 mL vial

Mirikizumab vial 300 mg/15 mL is supplied as a sterile, non-pyrogenic, preservative-free solution in a 20-mL glass vial closed with an elastomeric stopper, intended for single use.

The mirikizumab vial 300 mg/15 mL finished product is diluted with 0.9% Sodium Chloride Injection or 5% Dextrose Injection prior to administration by intravenous infusion. The finished product composition of the vial presentation is identical to the mirikizumab SFS presentation, except for the active substance concentration (20 mg/mL vs 100 mg/mL) and polysorbate 80 concentration.

The same formulation development approach has been taken for the vial as the SFS and the majority of the data has been replicated. The results of the formulation studies demonstrate the commercial composition is suitable to maintain the quality of the finished product, which is supported by stability data. There is no overage proposed, although excess volume is filled into each vial to enable delivery of 15.0 mL.

Pharmaceutical development

The pharmaceutical development programme, including the formulation, the manufacturing process, the quality target product profile (QTPP) and the container closure systems for the finished product, was developed using a science and risk-based approach consistent with quality by design (QbD) elements. The QTPP was defined by taking into consideration the pharmaceutical product quality attributes required to meet the needs of the patient and is considered acceptable.

The QTPP and preliminary CQAs were used to design pre-formulation and formulation development studies with the goal of developing a stable commercial mirikizumab finished product formulation.

100 mg/mL SFS

The chosen process characterisation studies are considered acceptable, and the acceptance ranges determined from these studies are considered appropriate.

During the development of the final commercial mirikizumab SFS 100 mg/mL finished product, changes were made that led to the optimisation of the formulation composition and the manufacturing process to support the new solution in a PFS presentation. Other change was the addition of a 2 mL PFS presentation. Comparability studies were performed between presentations and data suggest that the presentations are comparable. Comparability studies were performed to compare finished product-batches manufactured from active substance manufactured at three Lilly sites. The results suggest that the finished product batches manufactured from active substance batches from any of these sites are comparable.

The semi-finished syringe primary container closure system is assembled with delivery device components to form the final combination product. Adequate detailed descriptions have been provided for the container closure system components of the SFS. The container closure system used for mirikizumab SFS 100 mg/mL has been shown to be suitable to protect the product from physico-chemical and microbiological factors.

Technical information and specifications are provided for both the PFS and AI devices. A Major Objection was raised during the procedure regarding the lack of a Notified Body Opinion for the medical devices, which the applicant provided, supporting the conformity of each device with the relevant GSPRs set out in Annex I of Regulation (EU) 2017/745.

300 mg/15 mL vial

The mirikizumab vial 300 mg/15 mL manufacturing process is largely aligned with the manufacturing process for the mirikizumab SFS 100 mg/mL presentation.

During the development of the final commercial mirikizumab finished product, changes were made. To demonstrate comparability between the presentations, a comparability assessment was conducted and the results demonstrate that presentations are comparable. Comparability studies were performed to compare finished product batches manufactured from active substance manufactured at three Lilly sites. The results suggest that the finished product batches manufactured from active substance batches from any of these sites are comparable.

The container closure consists of clear, type I glass vial with a chlorobutyl stopper that is sealed with a two-piece flip-top aluminium seal. The materials of construction and the function of each component of the container closure system has been provided. The container closure integrity (CCI) has been demonstrated through physico-chemical and microbiological container-closure integrity tests (CCIT).

The vial container closure system used for mirikizumab vial 300 mg/15 mL has been shown to be suitable to protect the product from physico-chemical and microbiological factors.

An in-use study was conducted to assess the physico-chemical compatibility and stability of diluted intravenous solutions of mirikizumab with representative components and was considered acceptable.

2.4.3.2. Manufacture of the product and process controls

Manufacture

100 mg/mL SFS

All sites registered for the finished product are fully GMP compliant. The SFS finished product manufacturing process is standard for a monoclonal antibody and consists of buffer excipient solution compounding, finished product formulation compounding, sterile filtration, aseptic syringe filling and plungering and visual inspection. A manufacturing process flow diagram and an adequate description of each manufacturing process unit operation has been provided. The information provided is considered acceptable.

300 mg/15 mL vial

The vial finished product manufacturing process is standard for a monoclonal antibody and consists of buffer excipient solution compounding, finished product formulation compounding, sterile filtration, filling, stoppering and sealing, visual inspection and packaging and labelling. A manufacturing process flow diagram and an adequate description of each manufacturing process unit operation has been provided. The information provided is considered acceptable.

Process controls

The process control strategy for both mirikizumab SFS and vial finished products manufacture is outlined and includes CPPs, OPPs, CIPCs, IPSs and IPCs. The proposed control strategy is aligned to the established controls developed throughout the pharmaceutical development process and is similar between the two presentations. However, the ranges proposed for the vial presentation processing parameters and in-process controls are slightly different, which is acceptable. Hold times have been proposed and are considered adequate.

Process validation

To validate the SFS and vial finished product manufacturing processes, 3 PPQ batches for each presentation were manufactured at commercial scale.

A summary of the process validation for the PPQ batches is provided and all batches met the acceptance criteria. The data provided demonstrate that both the SFS and the vial finished product manufacturing processes are under control and reproducible within the established process ranges and set points, resulting in the finished product meeting its specifications.

A shipping study was performed, and all results met the acceptance criteria. Validation data have been provided regarding the device assembly, which is considered acceptable.

In conclusion, the validation studies demonstrated consistency and robustness of both manufacturing processes corresponding to each product presentation.

2.4.3.3. Product specification

100 mg/mL SFS

For the SFS presentation, the panel of release tests covers relevant aspects of purity, potency and safety, and consists of the following tests performed: appearance, colour, clarity, bacterial endotoxins, sterility, pH, osmolality, particulate matter, extractable volume (in compliance with Ph. Eur.), identity testing (sub-unit RP-UPLC, cell-based bioassay), quantity (UV), potency (cell-based bioassay), purity testing (SEC, non-reduced CE-SDS), charge heterogeneity (icIEF), polysorbate 80 (HPLC-UV) and syringe break-loose force and glide force (for which in-house methods are used). Additional, testing will be performed on the pre-filled syringe (PFS) and the autoinjector (AI).

The proposed release tests are in line with the expectations of ICH Q6B and the Ph. Eur. monograph on monoclonal antibodies. The acceptance criteria set for the specifications were discussed and updated during assessment and considered acceptable.

No new impurities have been introduced during manufacture of mirikizumab finished product. A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "*Questions and answers for marketing authorisation holders/Applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products*" (EMA/409815/2020) and the "*Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004 - Nitrosamine impurities in human medicinal products*" (EMA/369136/2020). Based on the

information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities.

300 mg/15 mL vial

For the vial presentation, the panel of release tests is identical to the SFS presentation, with the exception that the syringe functionality tests are removed. The release specification limits are also identical, except for the polysorbate 80 range. The conclusions regarding the nitrosamine and elemental impurities risk assessments mentioned for the SFS presentation are also applicable for the vial presentation.

Analytical methods

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines. The validation of the majority of in-house methods are provided in the active substance section, these are considered acceptable and fully validated. Method transfer reports have been provided for the analytical procedures, confirming the successful transfer of the methods between sites.

Batch analysis

100 mg/mL SFS

Batch analysis data are provided for primary stability/process validation batches representative of the commercial process, commercial formulation batches, early development batches (lyophilised finished product vials), PFS batches and autoinjector batches. All batches met the acceptance criteria in use at time of development. Batch analysis data for the 100 mg/mL mirikizumab finished product in the PFS and AI demonstrate that there is no impact on devices following assembly and all the batches met specification.

300 mg/15 mL vial

Batch analysis data are provided for process validation batches representative of the commercial process, primary stability and clinical batches. Batches were tested according to the specification in use at time of development. All batches met the commercial release acceptance criteria and confirmed consistency of the manufacturing process.

Reference materials

The reference standard used for both 100 mg/mL SFS and 300 mg/15 mL vial finished product is the same as that for the active substance.

2.4.3.4. Stability of the product

100 mg/mL SFS

For the SFS presentation, the shelf-life claimed by the applicant is 24 months protected from light at 2-8°C.

Stability data up to 36 months at 2-8°C are provided to support the proposed shelf-life. The stability studies were in general performed in accordance with ICH Q5C.

24 months of stability data are currently available for the finished product. Long-term storage data for the 24 months show the finished product is stable, with no trends or OOS observed.

Accelerated storage data at 30°C/65% relative humidity (RH) for 6 months show the batches are very stable.

Supporting data are provided.

Photostability studies were performed in accordance with ICH Q1B. Based on the photostability results, the finished product was recommended to be stored in its outer carton to protect it from light. This is considered satisfactory.

Based on the data provided, the shelf-life and storage conditions as stated in the SmPC (shelf-life of 24 months protected from light at 2-8°C with a patient in-use period of two weeks at NMT 30°C) are acceptable.

As part of the post-approval stability commitment, one finished product batch per year will be subjected to stability testing and evaluation for continuous stability monitoring.

300 mg/15 mL vial

For the vial presentation, the shelf-life claimed by the applicant is 24 months protected from light at 2-8°C with a patient use period of two weeks at NMT 30°C.

Stability data up to 36 months at 2-8°C and 30°C/65% or 30°C/75% are provided to support the proposed shelf-life. 24 months of stability data are currently available on finished product batches and the long-term storage data for the 24 months show the finished product is stable, with no trends or OOS observed.

Supporting data are provided.

Photostability studies were performed on vial finished product batch, in accordance with ICH Q1B. The results observed for the SFS presentation were also seen for the vial presentation.

Based on available stability data, the shelf-life and storage conditions as stated in the SmPC (shelf-life of 24 months protected from light at 2-8°C) are acceptable.

Prior to use, the finished product will be diluted in 0.9% sodium chloride injection or 5% dextrose injection. For dilution in sodium chloride, the samples may be stored under refrigerated conditions (2-8°C) for up to 96 total hours, of which not more than 10 hours are permitted at non-refrigerated temperatures (not to exceed 25°C). For dilution in dextrose, the samples may be stored under refrigerated conditions (2-8°C) for up to 48 total hours, of which not more than 5 hours are permitted at non-refrigerated temperatures (not to exceed 25°C). The proposed storage of the diluted finished product is supported by the data provided during the in-use study.

As part of the post-approval stability commitment, one finished product batch per year will be subjected to stability testing and evaluation for continuous stability monitoring.

2.4.3.5. Adventitious agents

The strategy to control adventitious agents consists of controlling potential sources of virus contamination both to the cell bank system and the production process, and viral clearance processes and is well described. No animal-derived raw materials are used during the routine manufacturing process, however a number of reagents of animal origin have been identified as being used during development of the cell line. Risk materials are described for the cell line generation. Purification steps are described and considered acceptable. The risk of adventitious agents from animal derived raw materials is considered to be low.

Testing of the MCB, WCB and cells at the limit of *in vitro* cell age for freedom from adventitious agents is described. The panel of tests proposed is adequate and complies with ICH Q5A.

The viral clearance studies comply with ICH Q5A and performed using appropriate scaled-down models. Overall, the results of viral clearance studies demonstrate the production process has sufficient capacity to inactivate or remove viruses.

2.4.3.6. GMO

N/A

2.4.3.7. Post-approval change management protocol(s)

N/A

2.4.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

During the procedure, a Major Objection was raised concerning the lack of a Notified Body Opinion for the PFS and autoinjector devices for demonstrating conformity with the relevant GSPRs set out in Annex I of Regulation (EU) 2017/745. The Major Objection, as well as all the other concerns, have been satisfactorily resolved.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physico-chemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data have been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendation(s) for future quality development

N/A

2.5. Non-clinical aspects

2.5.1. Introduction

Mirikizumab is a humanised IgG4 variant monoclonal antibody that was designed to specifically bind to the p19 subunit of interleukin (IL) 23. By binding to the p19 subunit, but not the p40 subunit, mirkizumab affects IL-23 signalling alone and does not modulate IL-12 signalling which shares the p40 subunit. Evidence from the literature suggests that inhibition of IL-23p19 can prevent intestinal inflammation. IL-23 is involved in the maintenance and amplification of T helper (Th)17 cells, which play an important role in the pathogenesis of disorders including ulcerative colitis.

All pivotal nonclinical toxicology studies were conducted in Organisation of Economic Co-operation and Development (OECD) member countries, in accordance with OECD Test Guidelines and Principles of Good Laboratory Practice (GLP), and according to relevant International Conference on Harmonisation (ICH) guidelines that were in effect at the time.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

The specificity and functional activity of mirikizumab has been characterised both *in vitro* and *in vivo*.

In vitro binding studies established that mirikizumab binds with high affinity to human IL-23 with a calculated KD value of 21 pM using surface plasmon resonance analysis. Similar binding kinetics were demonstrated for cynomolgus monkey IL-23 with a calculated value of 55 pM, however, the binding affinity for rabbit IL-23 was > 1000 fold lower and no binding to mouse or rat IL-23 was detectable. In functional activity assays IC50's of 82 pM for human IL-23 and 120 pM for cynomolgus monkey IL-23 were determined. Considering the absence of binding to rodent IL-23, a mouse surrogate antibody, LSN2479016, was also developed to enable its use in proof of concept studies. It demonstrated binding affinity (KD=103 pM) and activity (IC50= 400 pM) in a similar range, albeit slight lower, to that of the clinical candidate, mirikizumab. Further characterisation of the binding of mirikizumab to human IL-23 suggested that it functioned to inhibit the interaction of IL-23 with the IL-23R without affecting IL-12 mediated signalling.

The *in vivo* proof of concept studies are limited, owing in part to the absence of activity of mirikizumab in rodents. In mice mirikizumab significantly inhibited the ability of human IL-23 to prime the murine splenocytes for production of IL-17 upon restimulation with anti-CD3 and anti-CD28 antibodies ex vivo. Similarly, in a model of psoriasis-like disease in mice induced by intradermal injection of human IL-23, systemic administration of mirikizumab decreased the expression of disease markers including IL-17A, IL-17F and keratin-16.

Of closest relevant to the proposed indication was the IBD model in which a mouse surrogate anti-IL-23 antibody was tested. The model utilises the transfer of a subset of CD4+ T-cells to syngeneic SCID mice which results in a chronic, progressive colitis and wasting disease. Both prophylactic and therapeutic treatment paradigms were tested in this setting. Macro- and microscopic analysis of the colon suggested that use of the anti-IL-23 antibody was associated with decreases in weight/length and histological scores of the colon. No clear dose response was seen in either setting and in the most relevant treatment paradigm the statistically significant effects on the measured parameters were only seen in the 1 and 3 mg/kg group and not at the higher dose of 10 mg/kg. In particular, the histology score for this 10 mg/kg group was very similar to that of the control IgG group. The applicant was asked to discuss these findings and they considered that the study was sufficiently powered to demonstrate efficacy but did not provide any possible cause for the absence of effects at the mid and high doses. As this was a mouse model of IBD the issue is not considered significant and superseded by more relevant clinical data.

2.5.2.2. Secondary pharmacodynamic studies

As an IgG4 antibody, Fc effector functions would be expected to be low. This is supported by the negative screen with mirikizumab for binding to human Fcy receptors and in addition to C1q complement. The positive controls functioned as expected suggesting a low potential for unintended Fc receptor activity.

Furthermore, a tissue cross-reactivity study performed with human and cynomolgus monkey tissues (see toxicology section) did not identify any specific mirikizumab staining suggesting a low potential for off-target binding and pharmacological effects.

2.5.2.3. Safety pharmacology programme

No standalone safety pharmacology studies were performed, and safety pharmacology endpoints were incorporated within the 4 week repeat-dose toxicity study in line with the ICH S6 (R1) guideline. No mirikizumab-related changes in cardiovascular, respiratory, or central nervous system parameters were noted at the doses up to 100 mg/kg/week.

2.5.2.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies have been performed. As a monoclonal antibody the absence of pharmacodynamic drug-interaction studies for mirikizumab is acceptable.

2.5.3. Pharmacokinetics

The pharmacokinetics of mirikizumab were evaluated in single dose studies in male cynomolgus monkeys using IV and SC administration. The PK reports of the single dose studies (Studies 8340712 and 8256194) do not contain important information such as individual serum concentrations and/or in-study validation data. The applicant provided said bioanalytical reports for assessment and the data was considered acceptable in support of the aforementioned PK studies. In addition, the pharmacokinetics were measured after repeat dose administration as part of repeat dose toxicity studies in line with ICH S6 (R1). Bioanalytical methods included an ELISA method for mirikizumab detection, and an ACE assay was developed for ADA measurement. Both assays were appropriately validated, and the bioanalytical analysis of the toxicity studies performed in compliance with GLP.

Dose proportional increases in mirikizumab exposure were observed across the battery of studies and no obvious sex differences were evident. The mean half-life ranged between 50.5 and 72 hours in monkeys after single dose subcutaneous administration. Absolute bioavailability via this route ranged from 24% to 61%. There was no evidence of accumulation following repeated administration. Reduced mirikizumab exposure was observed in female animals (1 mg/kg/week) at Day 29 versus Day 1 in the 4-week study. In the first 6 month repeat dose toxicity study where the animals were dosed via weekly subcutaneous injection, 6 of 16 monkeys exhibited reduced exposure at Day 176 versus Day 1. This was observed in 3/4 males in the 10 mg/kg/week group (mirikizumab below LLOQ in these animals) and 3/4 females in the 100 mg/kg group (as per Study 20043324 report). ADAs were not measured in either of these studies.

In the second 6-month study mirikizumab was dosed twice weekly via intravenous injection. Dose-proportional increases in exposure were observed, with no sex differences. ADAs were measured in this study with 7 animals (4 at 100 mg/kg, 3 at 300 mg/kg) testing positive for ADAs. Exposure at Day 176 was lower in one ADA-positive female, however, other ADA-positive animals did not exhibit any significant reduction in serum mirikizumab levels. Exposure and ADA levels were also measured in the ePPND study where the animals were dosed twice weekly via intravenous injection from GD 21 to parturition. The majority of pregnant females (12/15) were ADA-positive (5/10 infants also ADA-positive); this was not associated with reduced exposure in either mothers or infants. Thus, the impact of ADA generation does not appear to alter exposure (see Toxicology section for more discussion).

No distribution, metabolism or excretion studies were performed for mirikizumab and none would be expected for a monoclonal antibody. Placental transfer studies were not conducted, however, the presence of mirikizumab in the serum of infants was noted for 10 of 10 infants measured on Day 28 post birth (BD 28) and for 1 of 10 at BD 84. The applicant considers this attributable to placental transfer. No studies on milk excretion were conducted, however, the applicant maintains that IgG antibodies are known to be excreted in human milk. The exposure in infants is most likely due to

placental transfer and, as any exposure via primate milk, is anticipated to be low and subject to degradation in the gastrointestinal tract of infants. This is an acceptable conclusion, and this information has been considered in 4.6. of the SmPC.

Overall, the pharmacokinetic evaluation of mirikizumab is acceptable.

2.5.4. Toxicology

The toxicology package submitted by the applicant comprised studies in a single species (cynomolgus monkey) using the intended clinical routes of administration (intravenous and subcutaneous). The choice of a single species is in line with relevant guidance for biopharmaceuticals and the applicant has demonstrated that cynomolgus monkeys are the appropriate species of choice.

2.5.4.1. Single dose toxicity

Single-dose toxicity studies with mirikizumab have not been conducted which is acceptable and in line with the guidance.

2.5.4.2. Repeat dose toxicity

The pivotal studies included a 4-week repeat dose toxicity study which used both subcutaneous and intravenous routes of administration, and two 6-month repeat dose toxicity studies, one using weekly subcutaneous injections and the second using twice weekly intravenous injections. All studies were performed in compliance with GLP.

Toxicities in the general repeat dose studies were considered non-adverse and transient and no target organ of toxicity was identified. Mild cell infiltration at injection sites was noted in the 4-week study; this was not associated with any clinical observations or macroscopic findings. There was a total absence of toxicity in the first 6-month study at doses up to 100 mg/kg/week (subcutaneous administration). The second 6-month study administered twice weekly doses of 100 or 300 mg/kg mirikizumab intravenously. This resulted in greater systemic exposure and some mild toxicities were observed. These included minimal increases in blood glucose in males and increased cholesterol levels (both sexes) at the highest dose which returned to pre-treatment levels by the end of dosing. Haemosiderin deposition in liver cells was noted post-mortem, possibly indicative of a degree of iron overload which may have impacted cholesterol levels. The applicant provided additional detail on the haemosiderin finding, which was observed in a single female animal. The aetiology of this observation was attributed to a secondary effect of idiosyncratic immune-mediated haemolytic anaemia and is not indicative of a generalised iron disorder or drug-related effects on hepatic cells. The applicant did not provide a possible mechanism for the elevation in cholesterol levels, however as levels were not elevated at Day 180 and no evidence of hepatic injury or dysfunction was observed it is possible that the cholesterol changes may not be physiologically relevant. In relation to blood glucose, the increases were in males only and up to 68% higher in individual animals, albeit returning to approximately pre-treatment levels at the end of dosing. Although significantly elevated blood glucose has not observed clinically with mirikizumab, there is clinical evidence in other IL-23 inhibitors for a potential effect on blood glucose homeostasis. Further discussion was provided on this point by the applicant. The increases in glucose were transient and also considered within the normal range for male cynomolgus monkeys. Furthermore, the limited clinical evidence surrounding IL-23 inhibitors and blood glucose homeostasis suggests a blood glucose-lowering effect (if any), in contrast with the observations in male cynomolgus monkeys. Overall, it can be agreed that the clinical relevance of these findings is limited. Some haematologic changes were observed in one female at 300 mg/kg/dose, correlating with

immune-mediated haemolysis as a result of mirikizumab exposure. Minimal microscopic changes in cells in the bone marrow, lymph node, liver and spleen correlated with this, however the low incidence, lack of dose response and absence of clinical observations suggest that the clinical relevance of these observation is also minimal. In both six-month studies immunophenotyping, T-dependent antibody responses and NK cell cytotoxicity was assessed without any significant effect of mirikizumab on the parameters measured.

2.5.4.3. Genotoxicity

Because mirikizumab is a monoclonal antibody, no genetic toxicity studies were conducted. This acceptable and in line with the requirements of ICH S6 (R1)

2.5.4.4. Carcinogenicity

A weight-of-evidence approach was used to assess carcinogenicity in lieu of dedicated carcinogenicity studies. The on-target activity of mirikizumab to reduce circulating IL-23 is not likely to be tumorigenic, as elevated Il-23 is associated with higher tumour incidence and progression. The absence of proliferative signals in repeat dose toxicity studies also supports the lack of carcinogenic potential of mirkizumab as does the absence of any significant immunotoxicity or immunomodulatory activity in these studies. Thus, the applicant's approach and conclusions are acceptable.

2.5.4.5. Reproductive and developmental toxicity

Reproductive and developmental toxicity was evaluated in a single enhanced pre- and postnatal development (ePPND) study in cynomolgus monkeys. The study was conducted largely in line with ICH S5 (R3). It was also carried out as part of an agreed Paediatric Investigation Plan (PIP). Mirikizumab was administered intravenously twice weekly at a single dose level of 300 mg/kg from GD 21 until parturition with infants followed up for 6 months after birth.

No evidence of maternal toxicity was noted with clinical observations in adult females limited to non-adverse minimally increased levels of cholesterol compared to controls on GD 140. The incidence of embryo/fetal loss was higher in the mirikizumab treated group at 26.7% (4/15) compared to the control group at 6.7% (1/15). The incidence rate of the mirikizumab treated group is within the range of the historical control values for the facility and the applicant has concluded that the increased incidence in the mirikizumab group is not treatment related as the vehicle control group survival rate was unexpectedly low, confounding a direct comparison. The applicant was requested to provide a table with each of the control values from the 22 ePPND studies which are referenced as the historical control range to further support this assertion of a lack of treatment effect. The data subsequently provided demonstrates that the historical control data was suitably robust and the increased incidence relative to concurrent control is unlikely to be related to mirikizumab. High prenatal loss rates from 0 to 40% have been reported for the cynomolgus monkey according to the literature cited by the applicant. The applicant was asked to comment on the adequacy of group size in order to evaluate adverse effects on development given the high and variable fetal/infant loss rate in this species. A group size of 15 pregnant cynomolgus monkeys were used in this study, in line with relevant guidance (ICH S6, ICH S5 (R3)) and several literature studies. The number of evaluable infants a PND7 in this study were 13 and 10 for control and mirikizumab groups, respectively, which is considered adequate for the assessment of postnatal development. The sex ratio and mean gestation lengths were comparable between groups. The loss of two infants occurred within seven days of birth (1 in control; 1 in mirikizumab group). In surviving infants there were no mirikizumab related changes in changes in clinical signs, body weight, neurobehavioral or neurologic evaluations, external evaluations,

morphometric measurements, ophthalmology, and respiration or heart rates. In addition, an assessment of immunophenotype, TDAR, and NK cell activity was performed in the infants with no mirikizumab related effects seen.

Adequate exposure was achieved in maternal species and exposure was also confirmed in offspring up to 84 days post-birth. Concentration ratios of mirikizumab in infant serum to mother serum ranged from 1.09 to 19.2 on postpartum day (PPD)14 and from 0.696 to 18.0 on PPD28. ADAs were detected in 12 of 15 pregnant females and five of 10 infants with no apparent neutralizing impact. There is no indication that mirikizumab was measured in maternal milk and this is reflected in labelling. In SmPC section 4.6 the applicant states contraception should be used for 10 weeks post treatment, however the basis of this is unclear. The applicant confirmed that the time period represents an approximate 7 half-lives of exposure based on the half-life of 9.3 days. This is acceptable. A revision of the wording in relation to 'Breastfeeding' in section 4.6 of the SmPC was updated in line with other monoclonal antibodies.

2.5.4.6. Toxicokinetic data

Toxicokinetic data confirmed adequate exposure was achieved across the studies. The applicant derived exposure-based safety margins based on 'normalised' AUC to account for differences in dosing regimen between animal and clinical regimens. The exposure-based safety margin for both induction and maintenance phases of clinical treatment are sufficient. As discussed in the Pharmacokinetics section, ADA generation did not impact exposure.

2.5.4.7. Local tolerance

Local tolerance was investigated as part of repeat dose toxicology studies using subcutaneous administration. Mirikizumab appears to be well tolerated with minimal irritancy at the site of administration which consisted of non-adverse perivascular eosinophil and mononuclear cell infiltration at the injection site. This evaluation is considered acceptable.

2.5.4.8. Other toxicity studies

Tissue cross-reactivity study

The cross-reactivity of mirikizumab was assessed in a full panel of normal tissues from human and cynomolgus monkey donors. This GLP-compliant tissue reactivity study confirmed the specificity or mirikizumab for soluble IL-23 by the absence of staining in human and monkey tissue

Immunotoxicity

Immunotoxicity was concomitantly investigated in repeat dose studies and no changes in parameters of T-cell or B-cell function indicate that mirikizumab is not potently immunosuppressive.

2.5.5. Ecotoxicity/environmental risk assessment

Mirikizumab is a sequence of amino acids and a protein and in accordance with the CHMP guideline on the environmental risk assessment (EMEA/CHMP/SWP/4447/00) is exempted from testing because of the chemical structure.

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, mirikizumab is not expected to pose a risk to the environment.

2.5.6. Discussion on non-clinical aspects

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.

The *in vitro* primary pharmacodynamic studies have sufficiently characterised the binding of mirikizumab to human IL-23 and identified cynomolgus monkeys as the only species with relevant pharmacological activity. Whilst the proof-of-concept studies are limited, it is acknowledged the limitations on available nonclinical models of ulcerative colitis. The provided study in an IBS model is considered of some relevance, and while adequately powered to demonstrate efficacy it remains unclear why there is an absence of efficacy of the top dose. Despite this, clinical efficacy data supersedes this study and thus the clinical relevance in the proposed indication is limited.

The provided PK package is in line with the expectations for a monoclonal antibody.

The nonclinical toxicology package is broadly in line with the requirements of ICH S6 (R1) with cynomolgus monkeys identified as the only species with relevant pharmacological activity. In general, mirikizumab was well tolerated.

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). The effect of mirikizumab on human fertility has not been evaluated which was considered acceptable by the CHMP.

In the intravenous 6-month study there were several observations that could be potentially of clinical relevance and required further explanation and discussion by the applicant. Two findings of concern were raised, related to possible effects on glucose homeostasis and liver function. The position presented by the applicant suggests that blood glucose homeostasis is unlikely to be altered by mirikizumab in clinical settings as effects in monkeys were transient and the elevation was still within the normal range for this species. Similarly, the observation of haemosiderin deposits in a single female monkey, in the absence of any pathological correlate related to liver dysfunction suggests this has limited clinical relevance. These considerations were accepted by the CHMP.

In the ePPND study an increased incidence of embryo/fetal loss was seen in the mirikizumab treated group. The applicant has argued that the study is confounded by the atypically low level of embryo/fetal loss in the control group and that the levels seen in the mirikizumab treated group are within the bounds of historical control data and hence are not mirikizumab related. The applicant subsequently provided such data in support of their position. As there is also a limited amount of data from the use of mirikizumab in pregnant women the SmPC advises in 4.6 to avoid Omvoh during pregnancy which is acceptable. The applicant also provided data on group sizing in the ePPND study that demonstrated a suitable group size for dams and infants was included in the study.

Placental transfer studies were not conducted, however, the presence of mirikizumab in the serum of infants was noted for 10 of 10 infants measured on Day 28 post birth (BD 28) and for 1 of 10 at BD 84. The applicant considers this attributable to placental transfer. No studies on milk excretion were conducted, however, IgG antibodies are known to be excreted in human milk. The exposure in infants is most likely due to placental transfer and, as any exposure via primate milk, is anticipated to be low and subject to degradation in the gastrointestinal tract of infants. As a precaution this information has

been considered in 4.6. of the SmPC outlining that it is preferable to avoid treatment with Omvoh during pregnancy and that Omvoh could be used during breast feeding if clinically needed.

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, Mirikizumab is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

The MAA for Omvoh is considered approvable from a non-clinical perspective.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Tabular overview of clinical studies

The Phase 3 clinical trial programme of mirikizumab in patients with moderate-to-severe UC consists of the following studies:

- Study AMAN: This 12-week induction study, including both conventional-failed and biologic-failed patients.
- Study I6T-MC-AMBG (AMBG): A maintenance study with a 40-week treatment duration.
- Study I6T-MC-AMAP (AMAP): A long-term extension study.

Study Identifier; Location of Study Report; Study Status; Type of Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
			For Part B, Period 1, the injection sites were in diagonally opposite quadrants. For Period 2, the injection site was either of the unused quadrants from Period 1.			
16T-MC-AMAA; 5.3.3.2; Completed; Full	The primary objective was to characterize the tolerability and safety of mirikizumab	A multicenter, ascending-dose, parallel-group, first in human Phase 1 single-dose study	Reconstituted 50 mL mirikizumab was given as IV infusion at 7 dose levels including 5, 20, 60, 120, 200, 350, and 600 mg, over at least 30 minutes or 120 mg mirikizumab SC into the skinfold of the left or right abdominal wall and was divided across two 1-mL injections as a single dose. Approximately 50 mL placebo was given IV over at least 30 minutes as a single dose	Healthy subjects: 45 of which 40 were patients with psoriasis and 5 were healthy subjects. • IV dose: Of the 40 subjects with psoriasis, 33 subjects received IV doses of mirikizumab; 3 subjects received 5 mg; and 5 subjects per cohort for 20, 60, 120, 200, 350, and 600 mg; 7 subjects received IV doses of placebo. • SC dose: The 5 healthy subjects received 120-mg mirikizumab SC doses.	Healthy subjects and patients with chronic plaque psoriasis based on an investigator-confirmed diagnosis of chronic psoriasis vulgaris for at least 6 months prior to baseline	Single-dose administration on Day 1, followed for 12 weeks posttreatment

Study Identifier; Location of Study Report; Study Status; Type of Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
16T-JE-AMAD; 5.3.3.1; Completed; Full	The primary objective was to explore the safety and tolerability of mirikizumab in healthy Japanese and Caucasian subjects to define an appropriate dose for further clinical research in Japan	Phase 1, single-site, subject- and investigator-blind, randomized, placebo-controlled, single-dose study	Reconstituted mirikizumab or placebo was administered as a slow IV infusion of at least 30 minutes. 1.4 mL mirikizumab was given as 2 SC injections into the skinfold of the left or right abdominal wall. Cohort 1: 600 mg IV (24 ml of 25 mg/mL) Cohort 2: 200 mg IV (10 ml of 20 mg/mL) Cohort 3: 200 mg SC (2.8 mL [1.4 mL × 2 injections] of 72 mg/mL) Cohort 4: 60 mg IV (10 ml of 6 mg/mL) Cohort 5: 1200 mg IV (48 ml of 25 mg/mL) Cohort 6: 2400 mg IV (96 ml of 25 mg/mL)	Healthy subjects: 51 (26 Japanese and 25 Caucasian). • Mirikizumab single dose: 39 of which 33 received IV administration and 6 received SC administration) • Placebo single dose: 12 of which 10 received IV administration and 2 received SC administration	Healthy subjects	Single-dose administration on Day 1. The follow-up period was 12 weeks after dosing for all cohorts.
16T-MC-AMAQ; 5.3.1.2; Completed; Full	Part A • To evaluate the PK of mirikizumab solution formulation after administration of 250-mg doses using 2 × 1-mL and 1 × 2-mL PFS injections in healthy subjects. • To assess the safety and tolerability of,	Phase 1, single-center, open-label, randomized, 2-part, parallel-treatment crossover study	Part A: • Reference: 250-mg mirikizumab solution formulation, 2 × 1-mL 125-mg/mL PFS injections using an investigational PFS targeting a 5- to 10-second injection time for each injection • Test 1: 250-mg mirikizumab solution formulation, 1 × 2-mL 125-mg/mL PFS injection using an investigational PFS targeting a 5- to 15-second injection time	Healthy subjects: 72 (36 subjects per study Parts A and B): • Part A: Reference: 18 Test 1: 18 • Part B: Test 2 and 3: 18 Test 4 and 5: 18	Healthy subjects	Part A, study drug was administered on Day 1. Part B, on Days 1 and 2, subjects received study drug. The follow-up period included outpatient visits for a total of 12 weeks (Days 4, 8, 11, 15, 22, 29, 43, 57, 71,

	and pain associated with, mirikizumab PFS administrations in healthy subjects. Part B • To compare the safety and tolerability of, and pain associated with, mirikizumab solution formulation after administration of 125- and 250-mg doses using 1-mL AI and 2-mL AI SC injections with different injection speeds (slow and fast) in healthy subjects.		Part B: • Tests 2 and 3: 250-mg mirikizumab solution formulation, 1 × 2-mL 125-mg/mL AI slow injection (Test 2; targeting an approximately 13-second injection time) and fast injection (Test 3; targeting an approximately 5-second injection time) using an investigational 2 mL AI • Tests 4 and 5: 125-mg mirikizumab solution formulation, 1 × 1-mL 125 mg/mL AI slow injection (Test 4; targeting an approximately 7-second injection time) and fast injection (Test 5; targeting an approximately 4.5-second injection time) using an investigational 1 mL AI			and 85 for Part A; Days 15, 43, and 86 for Part B) following dose administration on Day 1.
16T-MC-AMAR; 5.3.1.2; Completed; Full	• To evaluate the PK after administration of 250-mg doses of mirikizumab solution formulation using 2 × 1-mL PFS and 1 × 2-mL AI injections in healthy subjects. • To assess the safety and tolerability of mirikizumab in healthy subjects. • To assess pain associated with mirikizumab PFS and AI SC administrations in healthy subjects at 3 different injection sites (arm, thigh, and abdomen).	Phase 1, single-center, randomized, parallel-arm, open-label, single-dose study	Test Formulation: 250-mg mirikizumab solution formulation, 1 × 2-mL 125-mg/mL AI injection, • Test 1: administered in the arm • Test 2: administered in the thigh • Test 3: administered in the abdomen Reference formulation: 250-mg mirikizumab solution formulation, 2 × 1-mL 125-mg/mL PFS injections targeting a 5- to 10-second injection time for each injection, • Reference 1: administered in the arm • Reference 2: administered in the thigh • Reference 3: administered in the abdomen.	Healthy subjects: 66 with 11 subjects randomized to each treatment: • Test 1: 11 • Test 2: 11 • Test 3: 11 • Reference 1: 11 • Reference 2: 11 • Reference 3: 11	Healthy subjects	Study drug was administered on Day 1. The follow-up period included outpatient visits for a total of 12 weeks (Days 4, 8, 11, 15, 22, 29, 43, 57, 71, and 85) following dose administration on Day 1.
16T-MC-AMBD; 5.3.4.1; Completed; Full	To assess the safety and tolerability of single 300-, 600-, and 1200-mg doses of mirikizumab IV; 200- and 400-mg mirikizumab single SC doses in healthy Chinese subjects.	Phase 1, subject- and investigator-blinded, randomized, placebo-controlled, parallel-group, single-dose study in healthy Chinese subjects	Subjects were randomized to receive a single dose of mirikizumab (10 subjects) or placebo (2 subjects) within each cohort: • Cohort 1: 300 mg IV infused over at least 30 minutes • Cohort 2: 600 mg IV infused over at least 60 minutes • Cohort 3: 1200 mg IV infused over at least 2 hours • Cohort 4: 200 mg SC • Cohort 5: 400 mg SC IV Cohorts Mirikizumab or placebo was administered IV using a forearm vein at an infusion rate no greater than 10 mg/minute. SC Cohorts	Healthy subjects: 60 • Placebo IV: 6 • 300 mg mirikizumab IV: 10 • 600 mg mirikizumab IV: 10 • 1200 mg mirikizumab IV: 10 • Placebo SC: 4 • 200 mg mirikizumab SC: 10 • 400 mg mirikizumab SC: 10	Healthy subjects	Single-dose administration on Day 1 Outpatient follow-up visits at predefined times through Day 85 for PK and immunogenicity sampling and safety assessments.

			Mirikizumab or placebo was administered SC using pre-filled syringes designed to deliver 1 mL each. • Subjects in the 200-mg SC cohort received 2 injections, 1 into the skinfold of each lower abdominal wall quadrant (left and right). • Subjects in the 400-mg SC cohort received 4 injections, 1 into the skinfold of each upper and lower abdominal wall quadrant (left and right).			
16T-MC-AMBE; 5.3.1.2; Completed; Full	• To evaluate the PK after SC administration of 125-mg doses of mirikizumab solution formulation using a 1-mL PFS and a 1-mL AI injector in healthy subjects. • To assess pain associated with mirikizumab PFS and AI SC administrations in healthy subjects at 3 different injection sites (arm, thigh, and abdomen).	Phase 1, single-center, randomized, parallel-arm, open-label, single-dose study	Test formulation: 1 mL AI injector containing 125 mg mirikizumab solution • Test 1: administered in the arm • Test 2: administered in the thigh • Test 3: administered in the abdomen Reference formulation: 1-mL PFS containing 125-mg mirikizumab solution • Reference 1: administered in the arm • Reference 2: administered in the thigh • Reference 3: administered in the abdomen	Healthy subjects: 66 with 11 subjects randomized to each treatment: • Test 1: 11 • Test 2: 11 • Test 3: 11 • Reference 1: 11 • Reference 2: 11 • Reference 3: 11	Healthy subjects	Study drug was administered on Day 1. Outpatient Follow-up Period (12 weeks): The follow-up period included outpatient visits for a total of 12 weeks (Days 4, 8, 11, 15, 22, 29, 43, 57, 71, and 85) following dose administration on Day 1

Study Identifier; Location of Study Report; Study Status; Type of Report	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s); Dosage Regimen; Route of Administration**	**Number of Subjects**	**Healthy Subjects or Diagnosis of Patients**	**Duration of Treatment**
Pharmacokinetic and Initial Tolerability Studies In Patients with Moderate-to-Severe Plaque Psoriasis						
16T-MC-AMBP; 5.3.2.2; Completed; Full	To assess the effects of multiple doses of mirikizumab on the PK of a drug cocktail of CYP substrates in patients with moderate-to-severe psoriasis	Phase 1, multicenter, 2-period, fixed-sequence, open-label study	250-mg, 2 × 1-mL PFS (125-mg per 1-mL PFS) mirikizumab single-use PFS SC injection, Drug cocktail: midazolam [0.5-mL (1-mg) syrup, oral], warfarin + Vitamin K [2 × 5-mg (10-mg) warfarin tablets + 2 × 5-mg (10-mg) vitamin K tablets], dextromethorphan [2 × 15-mg (30-mg) liquid gel capsules], omeprazole (1 × 20-mg tablet), and caffeine [10-mL (20-mg/ml) solution], co-administered with approximately 240 mL of room temperature water, in a sitting position	29 patients received at least 1 dose of study treatment	Patients with moderate-to-severe plaque psoriasis based on the investigator-confirmed diagnosis of chronic psoriasis vulgaris for at least 6 months prior to screening	Mirikizumab: Once every 4 weeks from Period 2 Day 1 through Period 2 Day 113 Drug cocktail: single dose on Period 1 Day 1 and Period 2 Day 116
Controlled Clinical Studies in Patients with Ulcerative colitis						
16T-MC-AMAC; 5.3.5.1; Completed; Full	The primary objective of this study was to test the hypothesis that treatment with mirikizumab is superior to placebo in inducing clinical remission at Week 12 in patients with moderately to severely active ulcerative colitis. Clinical	Phase 2, multicenter, randomized, double-blind, parallel-group, placebo-controlled study in patients with moderately to severely active ulcerative colitis.	Induction period (12-week induction period) Patients were randomized in a 1:1:1:1 ratio to • 600-mg mirikizumab IV (fixed dosing) • 200-mg mirikizumab IV (exposure-based dosing): • 50-mg mirikizumab IV (exposure-based dosing): • 50 mg mirikizumab administered as an IV infusion at Weeks 0, 4,	Patients: 249 • 600 mg mirikizumab IV: 61 • 200 mg mirikizumab IV: 62 • 50 mg mirikizumab IV: 63 • Placebo IV: 63	Patients with moderately to severely active ulcerative colitis	During the 12-week induction period: 12 weeks, patients received IV mirikizumab or IV placebo. During the 92-week Maintenance period, patients received SC mirikizumab or SC placebo.

	remission was defined as having achieved the following: • Mayo rectal bleeding sub score of 0, • Mayo stool frequency sub score of 0 or 1 (with 1-point decrease from baseline), and • Mayo endoscopy sub score of 0 or 1.		and 8 • Placebo IV: Placebo administered as an IV infusion at Weeks 0, 4, and 8 Maintenance Period Patients who achieved clinical response at Week 12 entered the blinded maintenance period. The maintenance period • occurred from Week 12 (Visit 8) to Week 104 (Visit 31), and • evaluated the long-term safety and durability of clinical response and remission in patients who achieved clinical response at Week 12. Patients who received mirikizumab in the induction period were re-randomized to • 200 mg mirikizumab SC Q4W, or 200 mg mirikizumab SC Q12W.			
16T-MC-AMAN; 5.3.5.1; Global cohort[a] Completed; Full	To test the hypothesis that mirikizumab is superior to placebo in inducing clinical remission at Week 12 in patients with moderately to severely active ulcerative colitis	Phase 3, multicenter, randomized, double-blind, parallel, placebo-controlled induction study	• 300 mg mirikizumab IV Q4W • Placebo IV infusion Q4W	Patients: 1281 • Mirikizumab: 959 • Placebo: 322	Patients with moderately to severely active ulcerative colitis	12 weeks
16T-MC-AMBG; 5.3.5.1; Interim; Ongoing[b]	To test the hypothesis that mirikizumab is superior to placebo in achieving clinical remission at Week 40 (Week 52 of continuous therapy) among patients induced into clinical response with mirikizumab in Study AMAN	Phase 3, multicenter, randomized, double-blind, parallel, placebo-controlled maintenance study	Mirikizumab Induction Responders: • 200 mg mirikizumab SC Q4W • Placebo SC Q4W Placebo Induction Responders: • Placebo SC Q4W Non-Responders: • 300 mg mirikizumab IV Q4W followed by 200 mg mirikizumab SC Q4W Rescue Therapy: • 300 mg mirikizumab IV Q4W	Patients: 1177 • Mirikizumab Induction Responders: 581 • Placebo Induction Responders: 135 • Non-responders: 461	Patients with moderately to severely active ulcerative colitis	40 weeks
Controlled Clinical Studies in Patients with Crohn's disease						
16T-MC-AMAG; 5.3.5.4; Completed; Full	To test the hypothesis that treatment with mirikizumab is superior to placebo in the proportion of subjects with endoscopic response at Week 12, defined as 50% reduction from baseline in SES-CD Score	Phase 2, multicenter, randomized, parallel-arm, placebo-controlled study	**Period 1 (Double Blind):** • Mirikizumab Dose Arm 1: 1000 mg IV Q4W • Mirikizumab Dose Arm 2: 600 mg IV Q4W • Mirikizumab Dose Arm 3: 200 mg IV Q4W • Placebo: IV Q4W **Period 2 (Double Blind and Double Dummy)** • Mirikizumab Dose Arm 1: 1000 mg IV Q4W[c] or 300 mg SC Q4W[c] • Mirikizumab Dose Arm 2: 600 mg IV Q4W[c] or 300 mg SC Q4W[c] • Mirikizumab Dose Arm 3: 200 mg IV Q4W[c] or 300 mg SC Q4W[c] • Mirikizumab Subjects with no	Patients: 191 • 200 mg mirikizumab: 31 • 600 mg mirikizumab: 32 • 1000 mg mirikizumab: 64 • Placebo: 64	Patients with moderately to severely active Crohn's disease	Period 1: Weeks 0 to 12 Period 2: Weeks 12 to 52 Period 3: Weeks 52 to 104

			Week 12 SES-CD improvement 1000 mg mirikizumab IV Q4W + SC Placebo Q4W • Placebo: 1000 mg mirikizumab IV Q4W+ SC Placebo Q4W **Period 3 (Open Label)** • Mirikizumab Dose Arm 1: 300 mg SC Q4W • Mirikizumab Dose Arm 2: 300 mg SC Q4W • Mirikizumab Dose Arm 3: 300 mg SC Q4W • Mirikizumab Subjects with no Week 12 SES-CD improvement: 300 mg SC Q4W • Placebo: 300 mg SC Q4W			
16T-MC-AMAM; Not Applicable; Ongoing	To evaluate whether treatment with mirikizumab is superior to placebo as assessed by endoscopic response at Week 52 and clinical remission by patient reported outcomes at Week 52	Phase 3, multicenter, randomized, double-blind, double-dummy, parallel-group, active- and placebo-controlled	• 900 mg mirikizumab IV Q4W for 3 doses, then 300 mg SC Q4W • ~6 mg/kg ustekinumab IV for one dose, then 90 mg SC Q8W • Placebo ○ When Period 1 concludes (Week 12), responders continue receiving placebo, and NR at Week 12 will receive mirikizumab as described above.	1100 patients are planned to be randomized and 600 will be exposed to mirikizumab.	Patients with moderately to severely active Crohn's disease	52 Weeks
Controlled Clinical Studies in Patients with Moderate-to-Severe Plaque Psoriasis						
16T-MC-AMAF; 5.3.5.4; Completed; Full	The primary objective of this study was to test the hypothesis that	Phase 2, multicenter, randomized,	During the 16-week induction period, patients received mirikizumab SC or placebo SC.	Patients: 205 • 30 mg mirikizumab SC	Patients with moderate-to severe plaque	Induction Period: 16-week (mirikizumab SC or

Study Identifier; Location of Study Report; Study Status; Type of Report	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s); Dosage Regimen; Route of Administration**	**Number of Subjects**	**Healthy Subjects or Diagnosis of Patients**	**Duration of Treatment**
	treatment with mirikizumab is superior to placebo in inducing PASI 90 response at Week 16 in patients with moderate-to- severe plaque psoriasis.	parallel-arm, placebo-controlled trial in patients with moderate-to-severe plaque psoriasis	• Arm 1: 30 mg mirikizumab SC at Weeks 0 and 8 • Arm 2: 100 mg mirikizumab SC at Weeks 0 and 8 • Arm 3: 300 mg mirikizumab SC at Weeks 0 and 8 • Comparator: Placebo SC at Weeks 0 and 8 During the 88-week maintenance period, patients received mirikizumab PRN based upon disease activity at the end of the Induction Period. • At Week 16, if response was less than PASI 90 then the patient received 300 mg mirikizumab SC Q8W. • At Week 16, if response was at or greater than PASI 90 then the patient received 30 mg mirikizumab SC, as needed	QW8: 51 • 100 mg mirikizumab SC QW8: 51 • 300 mg mirikizumab SC QW8: 51 • Placebo SC QW8: 52	psoriasis	placebo SC) Maintenance Period: 88-week (mirikizumab PRN based upon disease activity)
16T-MC-AMAJ; 5.3.5.4; Completed; Full	To assess whether mirikizumab induction dosing is superior to placebo with respect to high levels of clinical response in patients with moderate-to-severe plaque psoriasis	Phase 3, multicenter, randomized, double-blind, placebo and controlled study	• 250 mg mirikizumab SC Q4W/250 mg Q8W • 250 mg mirikizumab SC Q4W/125 mg Q8W • Placebo SC Q4W • 300 mg secukinumab SC	Patients: 1465 • 250 mg mirikizumab SC Q4W/250 mg Q8W: 454 • 250 mg mirikizumab SC Q4W/125 mg Q8W: 451 • Placebo SC Q4W:	Patients with moderate-to-severe plaque psoriasis	Induction Period: Week 0 to Week 16 Maintenance Period: Week 16 to Week 52

Study Identifier; Location of Study Report; Study Status; Type of Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
				112 • 300 mg secukinumab SC: 448		
16T-MC-AMAK; 5.3.5.4; Completed; Full	To assess whether mirikizumab induction dosing is superior to placebo in the treatment of patients with respect to high levels of clinical response in patients with moderate-to-severe plaque psoriasis	Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, multi-period study	• 250 mg mirikizumab SC Q4W/250 mg Q8W • 250 mg mirikizumab SC Q4W/125 mg Q8W • 250 mg mirikizumab SC Q4W/placebo Q8W • Placebo SC Q4W/Q8W • Placebo SC Q4W/ 250 mg mirikizumab Q4W/250 mg mirikizumab Q8W	Patients: 530 • 250 mg mirikizumab Q4W: 423 • Placebo Q4W: 107	Patients with moderate-to-severe plaque psoriasis	Induction Period: Week 0 to Week 16 Maintenance Period: Week 16 through Week 52
Uncontrolled Studies						
16T-MC-AMAH; Not Applicable; Ongoing	To evaluate the long-term maintenance of efficacy of mirikizumab in patients with moderate-to-severe plaque psoriasis	Phase 3, multicenter, long-term extension	250 mg or 125 mg mirikizumab administered SC Q8W	Patients: 1951	Adult patients with moderate-to-severe plaque psoriasis	208 Weeks
16T-MC-AMAP; Not Applicable; Ongoing	To evaluate the long-term efficacy of mirikizumab in patients from Study AMBG who completed Week 40 visit on blinded SC mirikizumab	Phase 3, multicenter, open-label long term extension study	200 mg mirikizumab SC	Patients: 904	Patients with moderately to severely active ulcerative colitis	3 years maximum for each patient

Study Identifier; Location of Study Report; Study Status; Type of Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
16T-MC-AMAX; Not Applicable; Ongoing	To assess the effect of mirikizumab in the maintenance of endoscopic response in participants from Study AMAM who completed treatment on blinded SC mirikizumab and achieved endoscopic response at Week 52 of Study AMAM.	Phase 3, multicenter, open-label, long-term extension study	Induction Period: Study AMAM non-responders receive 900 mg mirikizumab 3 doses IV induction Q4W, all others receive 300 mg mirikizumab 3 doses SC Q4W. Long-term Extension Period: All participants receive 300 mg mirikizumab SC Q4W	Patients: 108	Patients with moderately to severely active Crohn's Disease	Induction Period: Week 0 to Week 12 Long-term Extension Period: Week 12 to Week 156

Abbreviations: AI = auto injector; CRU = clinical research unit; CYP = cytochrome P450; IV = intravenous; LY900021 = mirikizumab co-administered with LY9999QS; LY9999QS = recombinant human hyaluronidase; NR = Non-responders; PASI = psoriasis area and severity index; PFS = pre-filled syringe; PK = pharmacokinetic; PRN = as needed; Q4W = once every 4 weeks; Q8W = once every 8 weeks; Q12W = once every 12 weeks; SC = subcutaneous SES-CD = Simple Endoscopic Score for Crohn's Disease.

a The global cohort testing the primary outcome is completed. A maximized extended enrolment in China is ongoing and remains blinded.

b Data cutoff is for primary outcome data and the lock for efficacy of global cohort is completed.

c Also administer the placebo by the appropriate route; for example, if active LY is administered intravenously, then administer placebo via SC route, and vice versa. Administer IV preparation first, followed by SC preparation.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Characterisation of the pharmacokinetics (PK) of mirikizumab for the treatment of UC was conducted with data from four clinical pharmacology Phase 1 studies (AMAA, AMAD, AMBD and AMBP), one Phase 2 study (AMAC) and two Phase 3 studies (AMAN and AMBG). Population PK (PopPK) analyses were conducted to establish the final PK and E-R relationships of mirikizumab to support the proposed

dosing regimen. The proposed dose regimen is 300 mg IV Q4W for 12 weeks (induction) and then 200 mg SC Q4W thereafter (maintenance).

Bioanalytical methods

PK Assay

The PK assay uses a standard ELISA format based on binding to IL-23. The method is sufficiently described in the dossier and was initially validated at ICON and then revalidated at WuXi. The assay was validated over a range of 100 to 10000 ng/ml using a characterised reference standard. The validation criteria examined included specificity, precision, accuracy, matrix effects, dilution linearity, and sample stability. The results were all within the recommended acceptance criteria outlined in the EMA Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2) and show that the assays are sufficiently precise and accurate for correct determination of mirikizumab serum concentration. Cross validation data showed equivalent performance between the ICON and WuXi assays. Bioanalytical reports were provided for each relevant clinical trial. Each report included the in-study validation data and the raw data from the sample analysis. The reports show that the assays performed as expected. The incurred sample reanalysis passing rate was ≥93%.

Immumogenicity assays

For the Phase 3 trials, the ADA assay used an affinity capture elution bridge format. ADAs are unbound from mirikizumab by acid dissociation, followed by capture by plate bound mirikizumab. The captured ADA is then eluted and mixed with ruthenium- and biotinylated mirikizumab. The ADAs form a bridge between the ruthenium- and biotinylated mirikizumab, which can be detected using the standard MSD approach. The approach employs four Tiers. The first Tier is the screening assay, Tier 2 is the confirmatory assay, Tier 3 is the titre assay and Tier 4 is the Nab assay (which uses excess unlabelled rhIL-23 to determine neutralisation capacity).

The assay was developed at Lilly Research Laboratories and validated at BioAgilytix Laboratories, then transferred from LRL to WuXi AppTec Co., Ltd. Separate validation reports have been provided for both sites. The assay is described in sufficient detail in the dossier and sufficient data on the validation of the assay have been provided. Details of the cut-point determinations have been provided and are considered acceptable. The assay sensitivity was determined to be 3 ng/ml, which is considered appropriately sensitive for an ADA assay. The drug tolerance of the assay was above the maximum trough exposures for Phase 3 clinical trials. Therefore, interference and a risk of false negative conclusions is excluded. Interference from serum factors such as haemoglobin, lipids, and bilirubin were studied, and the assay shows sufficient tolerance. The assay should acceptable precision. Sample stability was adequately addressed.

Overall the immunogenicity assays for the Phase 3 trials have been appropriately validated and meet the requirements of the EMA Guideline on Immunogenicity assessment of therapeutic proteins (EMEA/CHMP/BMWP/14327/2006 Rev 1) and the EMA Guideline on immunogenicity assessment of monoclonal antibodies intended for *in vivo* clinical use (EMA/CHMP/BMWP/86289/2010).

Two previous version of the immunogenicity assay was also used. A version validated at PPD was used in the Phase 1 Study I6T-MCAMAA, and a version validated at to Pacific Biomarkers Inc. (PBI;Seattle, Washington, USA) was used for Phase 1 studies (I6T-JE-AMAD, I6T-MC-AMAE, I6T-MC-AMAL, I9O-MC-AABA) and Phase 2 studies (I6T-MC-AMAC, I6T-MC-AMAF). This previous assay format had reduced sensitivity, drug tolerance, and dynamic range, as compared to the improved assay used for the Phase 3 trials. Validation results are provided in the dossier. For the PPD assay, the sensitivity was 67 ng/ml which was considered too high. The sensitivity was improved in the PBI assay to 8.6 ng/ml, slightly higher than the Phase 3 assay sensitivity of 3 ng/mL, but still considered acceptable. Drug tolerance

was above the estimated maximum trough concentration. There was no interference form lipaemic or haemolytic samples. Overall, the assay is considered acceptable.

Bioanalytical reports were provided for each relevant clinical trial. Each report included the in-study validation data and the raw data from the sample analysis. The reports show that the assays performed as expected.

Validation reports have been provided for the following additional assays:
Midazolam and 1'-Hydroxymidazolam in Human Plasma by Turbo Ion Spray LC/MS/MS

- Omeprazole, 5-Hydroxy Omeprazole, and Omeprazole Sulfone in Human Plasma by Turbo Ion Spray LC/MS/MS
- Dextromethorphan and Dextrorphan in Human Plasma by HPLC with MS/MS Detection
- (R)- and (S)-Warfarin in Human Plasma by HPLC with MS/MS Detection
- Caffeine and Paraxanthine in Human Plasma by HPLC with MS/MS Detection

Based on the validation data provided, it is concluded that these assays have been appropriately validated in accordance with the requirements of the EMA Guideline on bioanalytical method validation. Therefore, their use is supported.

Absorption

Following SC doses of mirikizumab in patients with UC, peak concentrations were achieved within 2 to 3 days. The geometric mean SC bioavailability across injection sties in patients with UC was estimated to be 44% (CV 34%) in the Phase 3 PopPK analysis.

Study AMBW demonstrated bioequivalence following administration of 200 mg mirikizumab SC between the to-be-marketed autoinjector (AI) and pre-filled syringe (PFS) as the 90% CI for the ratios of geometric LS means (AI:PFS) for AUC(0-tlast), AUC(0-∞), and Cmax were entirely contained within the prespecified confidence limits of 0.8 and 1.25. There was no statistically significant difference in tmax between AI and PFS (Table 2.7.1.8).

Table 2.7.1.8. Statistical Analysis of the Pharmacokinetic Parameters of Mirikizumab for Study AMBW

Statistical Analysis of the Pharmacokinetic Parameters of Mirikizumab Overall for Study I6T-MC-AMBW

Parameter	Device	n	Geometric least squares mean	Ratio of geometric least squares mean (AI:PFS)	90% CI for the ratio (Lower, Upper)
AUC(0-tlast) (ug.day/mL)	PFS (Reference)	116	245		
	AI (Test)	119	257	1.05	(0.970, 1.14)
AUC(0-∞) (ug.day/mL)	PFS (Reference)	120	247		
	AI (Test)	120	262	1.06	(0.981, 1.15)
Cmax (ug/mL)	PFS (Reference)	120	14.4		
	AI (Test)	120	15.2	1.06	(0.975, 1.14)

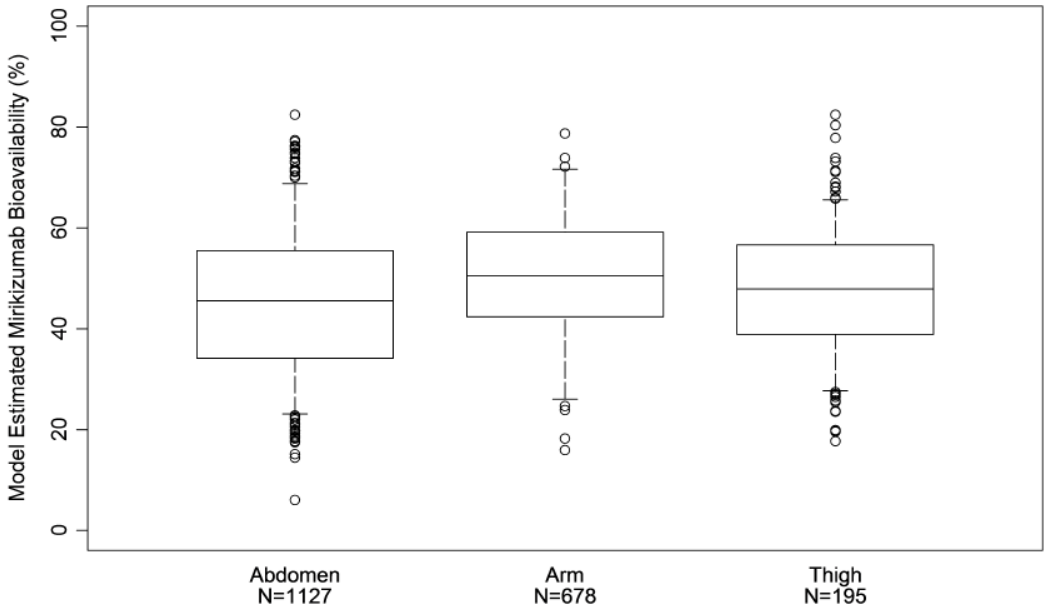
Abbreviations: AI = 200 mg Mirikizumab 2 x 1-mL (100 mg/mL) autoinjector (Test); AUC(0-∞) = area under the concentration versus time curve from time zero to infinity; AUC(0-tlast) = area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration; CI = confidence interval; Cmax = maximum observed drug concentration; n = number of observations; PFS = 200 mg Mirikizumab 2 x 1-mL (100 mg/mL) prefilled syringe (Reference)
Model: Log(PK) = Delivery Device + Injection Location + Weight Stratification + Random Error

Statistical Analysis of the Pharmacokinetic Parameters of Mirikizumab Overall for Study I6T-MC-AMBW

Parameter	Device	n	Median	Median of differences (AI - PFS)	Approximate 90% CI for the difference (Lower, Upper)	P-value
tmax (day)	PFS (Reference)	120	4.00			
	AI (Test)	120	4.00	0.00	(-0.02, 0.01)	0.7553

Abbreviations: AI = 200 mg Mirikizumab 2 x 1-mL (100 mg/mL) autoinjector (Test); CI = confidence interval; n = number of observations; PFS = 200 mg Mirikizumab 2 x 1-mL (100 mg/mL) prefilled syringe (Reference); tmax = time of maximum observed drug concentration
tmax is analyzed using a Wilcoxon rank-sum test

Although Study AMBW was not powered for the comparisons, when statistical analyses were conducted on data for each injection site separately, the 90% CIs for all comparisons were completely contained within the confidence limits of 0.8 to 1.25 following administration into the abdomen and thigh. The geometric mean ratio of AUC and Cmax was up to 12% higher for AI compared to PFS with the upper bound of the 90% CI for the various PK parameters falling slightly above 1.25 following administration into the arm. There was no difference in tmax between AI and PFS at any of the injection sites. In the popPK analysis, no significant difference in the bioavailability was identified among the 3 injection sites based on the covariate analysis (Figure 2.7.1.2).



Abbreviation: N = number of samples.

Note: The horizontal line in each box represents the median; the top and bottom sides of the box represent the 75th and 25th percentiles; the whiskers extend to the 95th and 5th percentiles; and circles represent data points outside of 5th or 95th percentile.

Figure 2.7.1.2. Boxplots of model estimated bioavailability following subcutaneous injection for the injection site of abdomen, arm, and thigh.

Distribution

Based on the Phase 3 popPK analysis, the estimated geometric mean (CV%) central and peripheral volumes of distribution were 3.10 L (18%) and 1.65 L (40%) in patients with UC, resulting in a total volume of distribution at steady state of 4.83 L (21%).

Elimination

Mirikizumab is a monoclonal antibody and is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgGs. The estimated geometric mean (geometric CV) systemic clearance was 0.0229 L/h (34%) in patients with UC. Clearance was independent of the dose. The geometric mean (geometric CV%) elimination half-life (t1/2) for mirikizumab was estimated as 9.3 days (40%).

Dose proportionality and time dependencies

Mirikizumab exposure increased proportionally over a dose range of 5 to 2400 mg given as an IV infusion or over a dose range of 120 to 400 mg given as a SC injection. A PK model with linear clearance best described the data in all popPK analyses, which supports that the PK of mirikizumab are linear with respect to dose.

The observed trough concentrations for mirikizumab were similar at Weeks 4, 8, and 12 in Study AMAN (Table 2.7.2.5) and at Weeks 4, 12, 24, and 40 for the 2 groups of patients in Study AMBG (Table 2.7.2.6). The lack of apparent accumulation is consistent with expectations, based on the t1/2 of mirikizumab of approximately 10 days and the 4-week dosing interval.

Table 2.7.2.5. Summary of Mirikizumab Trough Concentrations during Induction Period Following Mirikizumab 300 mg IV Q4W

Mirikizumab Trough Concentration (µg/mL)		
Time point (n)	**Median (5th – 95th percentile)**	**Geometric Mean (%CV)**
Week 4 (n = 930)	2.65 (0.308, 8.77)	2.30 (148)
Week 8 (n = 891)	3.14 (0.407, 10.2)	2.69 (132)
Week 12 (n = 836)	3.52 (0.466, 11.2)	3.08 (128)

Abbreviations: BLQ = below limit of quantitation; CV = coefficient of variation; IV = intravenous; LLOQ = lower limit of quantitation; n = number of samples; Q4W = every 4 weeks.
Note: Trough is defined as being collected between 21 and 35 days from the last dose for Q4W dosing regimen. BLQ concentrations were represented as 0.05 µg/mL, which is half of the assay LLOQ.

Table 2.7.2.6. Summary of Mirikizumab Trough Concentrations Following Mirikizumab 200 mg SC Q4W or 300 mg IV Q4W

Mirikizumab Trough Concentration (µg/mL)						
Treatment	**200 mg SC Q4W**			**300 mg IV Q4W**		
Time point	**N**	**Median (5th – 95th percentile)**	**Geometric mean (%CV)**	**N**	**Median (5th – 95th percentile)**	**Geometric mean (%CV)**
Week 0	354	4.19 (0.816-11.8)	3.72 (110)	284	2.44 (0.320-8.76)	2.12 (141)
Week 4	352	1.99 (0.450-6.38)	1.93 (101)	432	2.48 (0.320-8.32)	2.17 (136)
Week 12	333	2.22 (0.492-6.17)	2.03 (99.7)	327	2.87 (0.472-9.53)	2.60 (127)
Week 24	530	2.10 (0.444-6.69)	1.97 (102)		NC	NC
Week 40	464	2.28 (0.489-6.75)	2.09 (103)		NC	NC

Abbreviations: BLQ = below limit of quantitation; CV = coefficient of variation; IV = intravenous; LLOQ = lower limit of quantitation; N = number of samples; NC = not calculated; Q4W = every 4 weeks; SC = subcutaneous.
Note: Results from Visit 5 (Week 12) of Study AMAN were included as Week 0 for patients who started on either 300 mg IV Q4W or 200 mg SC Q4W in this study. Responders in Study AMAN who received rescue therapy of 300 mg IV Q4W were not included in this summary. Trough is defined as being collected between 21 and 35 days from last dose for Q4W dosing regimen. BLQ concentrations were represented as 0.05 µg/mL, which is half of the assay LLOQ.

Pharmacokinetics in the target population

Population PK analyses

Two separate Phase 3 population PK analyses were conducted, one using only data from Study AMAN (detailed in the Clinical AR) and one using combined data from Studies AMAN and AMBG. The popPK model developed using the combined data from Studies AMAN and AMBG was the model used to inform the overall conclusions about mirikizumab PK in patients with UC (detailed below).

In total, the final PK model dataset contained 7578 observations from 1129 patients. 147 BQL concentrations, representing 1.94% of the total concentration samples, were excluded from the analysis. A 2-compartment model best described the combined data. Body weight was a significant covariate on clearance and volume parameters, with estimated allometric exponents. Time-varying albumin was a significant covariate on clearance. BMI was found to have a significant impact on bioavailability, where patients with a lower BMI tended to have higher bioavailability. The final estimated PK parameters from the combined analysis were similar to the AMAN-only analysis and are shown in Table 9.2. Bootstrap (data not shown) and VPC (Figure 9.7) supported the validity of the model and demonstrated that all parameters were well estimated.

Table 9.2. Summary of Population Pharmacokinetic Model Estimated Parameters for Mirikizumab Based on the Studies AMAN and AMBG

Parameter Description	Population Estimate (95% CI, %SEE)[a]	Inter-Individual Variability (95% CI, %SEE)[a,b,f]
Clearance		
Parameter for CL[c] (L/hr)	0.022 (0.0192 – 0.0250, 6.96)	30.1% (28.2% – 32.1%, 6.16)
Albumin effect on CL	-0.981 (-1.09 – -0.832, 6.70)	---
Parameter for Q[c] (L/hr)	0.00870 (0.00352 – 0.0188 , 42.2)	---
Baseline weight effect on CL and Q	0.534 (0.438 – 0.623, 12.6)	---
Volume of Distribution		
Parameter for V_2[d] (L)	3.11 (3.07 – 3.15, 0.695)	18.1% (14.0% – 21.8%, 21.8)
Parameter for V_3[d] (L)	1.69 (1.03 – 2.57, 25.9)	59.3% (35.1% – 84.6%, 19.6)
Baseline weight effect on V_2 and V_3	0.525 (0.459 – 0.585, 7.56)	---
Covariance between CL and V_2	0.0241 (0.0176 – 0.0316, 14.4)	
Bioavailability		
Parameter for F1 (%)[e]	47.6 (34.5 – 59.5, 15.9)	64.3% (53.8% – 77.6%, 21.2)
Baseline BMI effect on F1	-0.0474 (-0.0628 - -0.0344, 16.1)	---
First Order Absorption Rate Constant		
Parameter for Ka (h^{-1})	0.00706 (0.00537 – 0.00998, 17.3)	---
Residual Error		
Proportional (%)	19.6% (17.6% - 21.4%, 4.55)	
Additive (ng/mL)	171 (127 - 210, 11.3)	

Abbreviations: BMI = body mass index; CI = confidence interval; CL = clearance; F1 = bioavailability; IIV = interindividual variability; Ka = first order absorption rate constant; Q = inter-compartmental clearance; SEE = standard error of the estimate; V_2 = volume of distribution of the central compartment; V_3 = volume of distribution of the peripheral compartment.

[a] The CI was estimated using bootstrap.

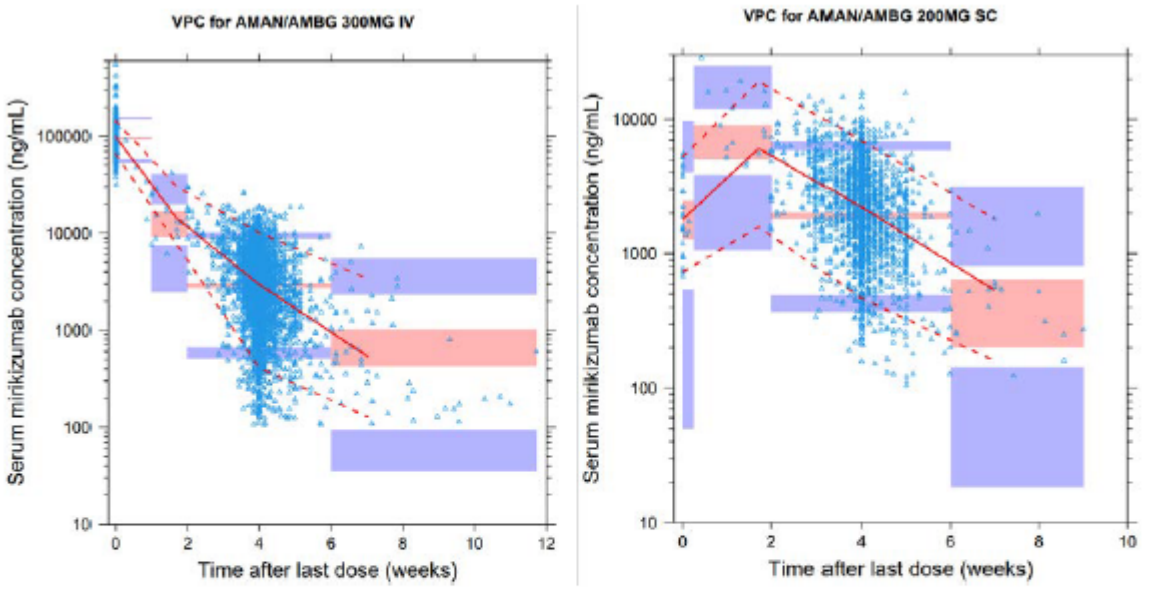
[b] IIV for CL, V_2 and V_3 were calculated using the following equation for log-normal distributions of the random effects for $\%IIV = 100 \times \sqrt{(e^{OMEGA_N} - 1)}$, where $OMEGA_N$ is the variance of the parameter. Inter-individual variability for bioavailability (F1) was incorporated in an additive manner in the logit domain, hence the following equation was used to calculate the IIV for F1: $\%IIV_F = 100 \times \sqrt{OMEGA_{F1}}$

[c] The table provides the population estimate. To obtain individual clearance estimates, use the following equation: CL,individual = CL*(Baseline weight/70.7)$^{0.534}$*(Albumin/45.0)$^{-0.981}$; Q,individual = Q*(Baseline weight/70.7)$^{0.534}$

[d] The table provides the population estimate. To obtain individual volume estimates, use the following equations: V_2,individual = V_2*(Baseline weight/70.7)$^{0.525}$; V_3,individual = V_3*(Baseline weight/70.7)$^{0.525}$

[e] Estimate is on the logit parameter for bioavailability. This translates to bioavailability of 55% and 40% for patients with baseline BMI of 20 kg/m^2 (10th percentile of analysis population) and 32 kg/m^2 (90th percentile of the analysis population).

[f] Eta shrinkage for CL, V_2, V_3, and F1 are 8.82%, 27.7%, 33.4%, and 36.1%, respectively.



Abbreviations: IV = intravenous; PK = pharmacokinetics; SC = subcutaneous; VPC = visual predictive check.
Blue triangle: individual observed concentration data; solid red line: median of observed concentrations; dashed red lines: 5th and 95th percentiles of observed concentrations; pink shaded area: confidence interval for the median of simulated data; blue shaded areas: confidence intervals for the 5th and 95th percentiles of simulated data.

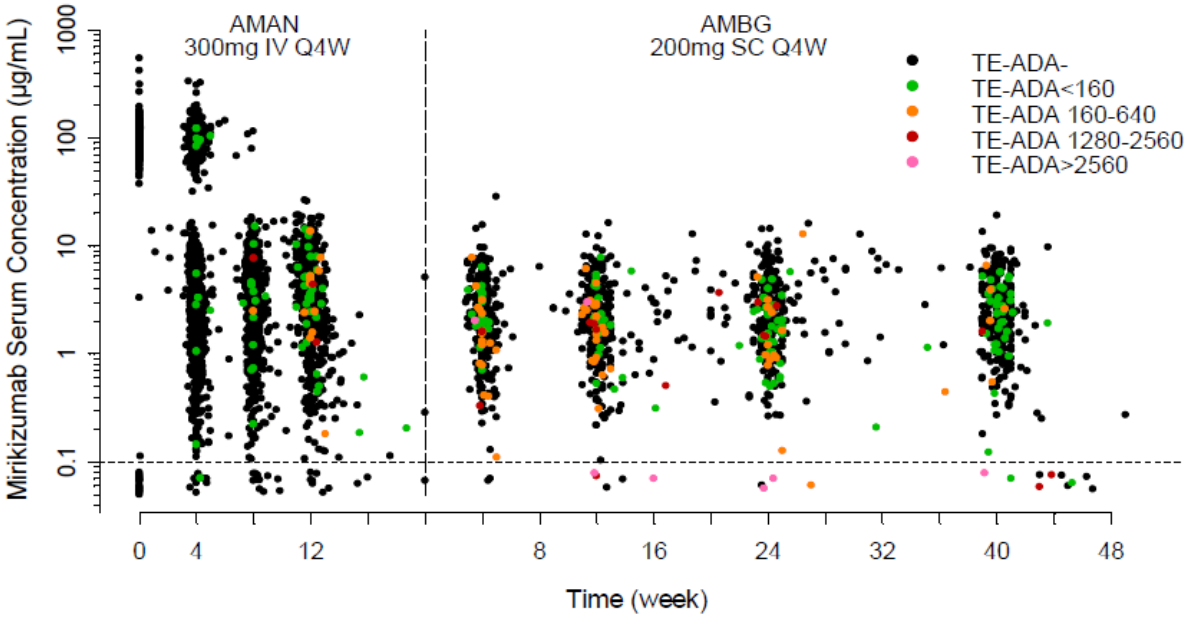
Figure 9.7. Visual predictive check for mirikizumab final PK model for Studies AMAN and AMBG stratify by route of administration.

The final AMAN/AMBG popPK model was used to perform simulations of mirikizumab exposure following 300 mg IV Q4W and 200 mg SC Q4W dose regimens. These simulations were used to illustrate the impact of body weight, BMI and albumin on mirikizumab exposures (see Special populations).

Immunogenicity

By Week 40 of Study AMBG (that is, 52 weeks of mirikizumab treatment), approximately 23% (88/385) of subjects treated with mirikizumab at the recommended dose developed antibodies to mirikizumab. Overall titres in mirikizumab-treated patients were low. For the majority of treatment-emergent (TE) anti-drug antibody (ADA)-positive patients, the magnitude of their ADA titres decreased over time.

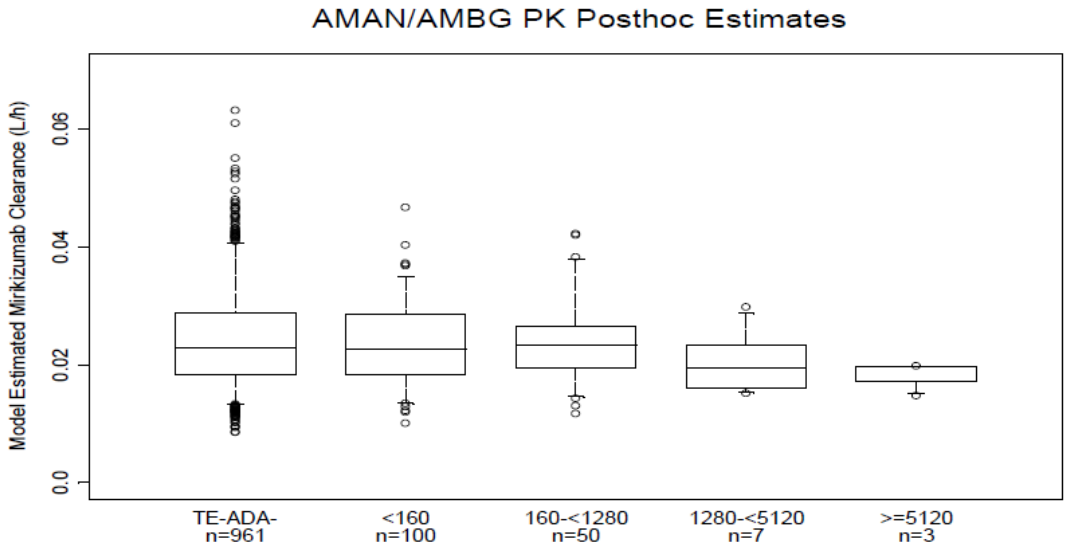
Figure ISI.8.1 shows scatterplots of the observed mirikizumab concentrations over time during IV and SC dosing in Studies AMAN and AMBG, with ADA positive samples grouped and identified based on the maximum titre developed during the IV or SC treatment periods. The majority of patients who were TE ADA positive had mirikizumab exposure that was consistent with patients who were TE ADA negative. For patients with titres of 1:160 or higher, mirikizumab concentrations trended lower in a small number of patients. Upon further investigation, it was found that of the 32 patients who had a maximum TE ADA titre of 1:160 or higher, 10 patients were identified as having reduced mirikizumab exposures after first development of TE ADA.



Abbreviations: IV = intravenous; LLOQ = lower limit of quantitation of the LY3074828 (mirikizumab) bioanalytical assay; Q4W = every 4 weeks; SC = subcutaneous; TE ADA = treatment-emergent anti-drug antibody.
Note: Individual dots represent individual PK samples. The week 4 visit in study AMAN included samples taken both before and after the mirikizumab infusion. The horizontal dashed line represents the LLOQ value (0.1 µg/mL) reported from bioanalytical results.

Figure ISI.8.1. Observed mirikizumab concentrations following mirikizumab 300 mg IV Q4W in Study AMAN and 200 mg SC Q4W in Study AMBG by TE ADA maximum titer categories.

PK modelling found that immunogenicity was not a statistically significant factor that impacted mirikizumab PK. When the individual model-estimated CL values were compared among TE ADA titre groups, no difference in the CL estimates was found between TE ADA positive and TE ADA negative patients, or among the various TE ADA titre groups (Figure ISI.8.2). The lack of statistical significance is likely related to only a small proportion of patients recording titres high enough to show a decrease in exposure to mirikizumab.



Abbreviations: n = number of patients; TE ADA = treatment-emergent anti-drug antibody.
Note: Patients were categorized by the maximum observed TE ADA (1:X) in the population PK analysis dataset. The horizontal line in each box represents the median; the top and bottom sides of the box represent the 25th and 75th percentiles; the whiskers extend to the 5th and 95th percentiles; and circles represent data points outside of the 5th or 95th percentile.

Figure ISI.8.2. Boxplots of model-estimated post hoc clearance values versus treatment-emergent anti-drug antibody titer categories in Studies AMAN and AMBG.

Overall, similar proportions of TE ADA-positive and TE ADA-negative patients achieved successful clinical outcomes after treatment with mirikizumab. However, there was an association between TE ADA-positive patients who had higher TE ADA titres and lower efficacy responses to mirikizumab as measured by the endpoints of clinical remission and clinical response at Week 40 in Study AMBG, when compared to low titre TE ADA-positive and TE ADA-negative patients. This trend was also seen when assessing additional symptomatic, clinical, and endoscopic UC outcomes. Overall, in 2.0% of patients treated with 300 mg mirikizumab IV Q4W in induction followed by 200 mg SC Q4W through study AMBG, higher titre TE ADA was associated with reduced PK and loss of efficacy.

No clinically meaningful differences in the frequency of hypersensitivity events, injection site reactions, and infusion site reactions were observed in TE ADA-positive patients compared with TE ADA-negative patients.

Overall, in a minimal proportion of patients, an association between TE ADA titre and decreased PK and efficacy was identified; however, TE ADA did not appear to mediate the occurrence of hypersensitivity events or other AEs related to injection and infusion sites.

Special populations

Renal and hepatic impairment

Specific clinical pharmacology studies to evaluate the effects of renal impairment and hepatic impairment on the PK of mirikizumab were not conducted. This is acceptable. Mirikizumab is a monoclonal antibody and expected to be eliminated via proteolytic degradation to amino acids.

In the Phase 2 Study AMAC, CrCL ranged from 11.1 to 281 mL/min and baseline bilirubin ranged from 1.5 to 25 µmol/L. The Phase 2 PopPK analysis did not find any relationship between these laboratory

parameters and mirikizumab PK. The Phase 3 PopPK analysis also confirmed no relationship between CrCL (range of 36.2 and 291 mL/min) and baseline bilirubin (range of 1.5 and 29 µmol/L) to mirikizumab PK.

Gender

The Phase 3 PopPK analyses revealed that sex (60.9% male; 39.1% female) did not affect mirikizumab PK.

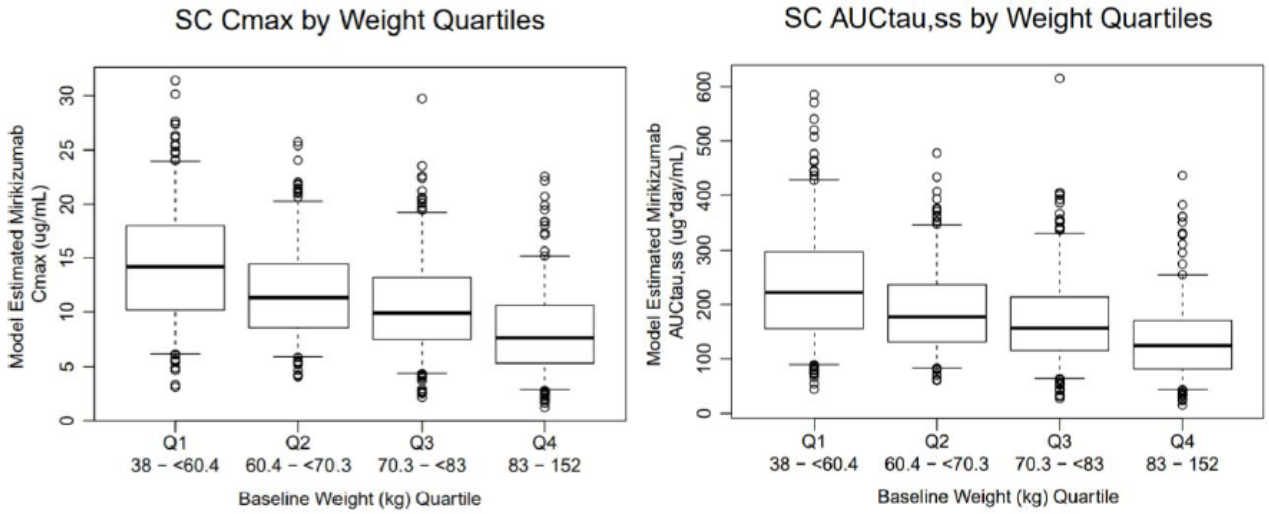
Race

Ethnicity and race were not identified as clinically significant covariates as tested in the Phase 3 PopPK analysis (N = 1129). The races tested were Caucasian (74.7%), Asian (22.2%), African descent (1.06%), Native American (0.974%), and other (1.06%), and ethnicity was Hispanic (3.81%).

Weight

Body weight was a statistically significant covariate on clearance and volume in the popPK analyses. As a result, there was an overall trend for serum concentrations to decrease as body weight increased. Overall, the range of body weights in Studies AMAN and AMBG was 34 to 152 kg.

When stratified into body weight quartiles, a large degree of overlap in exposures was noted between body weight quartile groups for the 300-mg IV Q4W dosing regimen (Figure 2.7.2.10). The median AUC following 300 mg IV dosing in patients in the highest body weight quartile (83 to 152 kg) was 451 µg·day/mL versus an overall population median AUC of 539 µg·day/mL. This difference in AUC between typical and higher body weights, with the AUC in patients with high body weight being approximately 16% lower, is small relative to the between-patient variability for AUC observed for the IV dosing regimen (CV=34.4%). Similarly, the median Cmax in the highest body weight quartile was 84.4 µg/mL versus an overall population median of 99.4 µg/mL, which is also a small difference (15% lower) relative to the between-patient variability for Cmax for the IV dosing regimen (CV =22.7%). These results indicate that body weight does not have a clinically relevant impact on the exposure of mirikizumab, and no dose adjustment on the basis of body weight is needed.

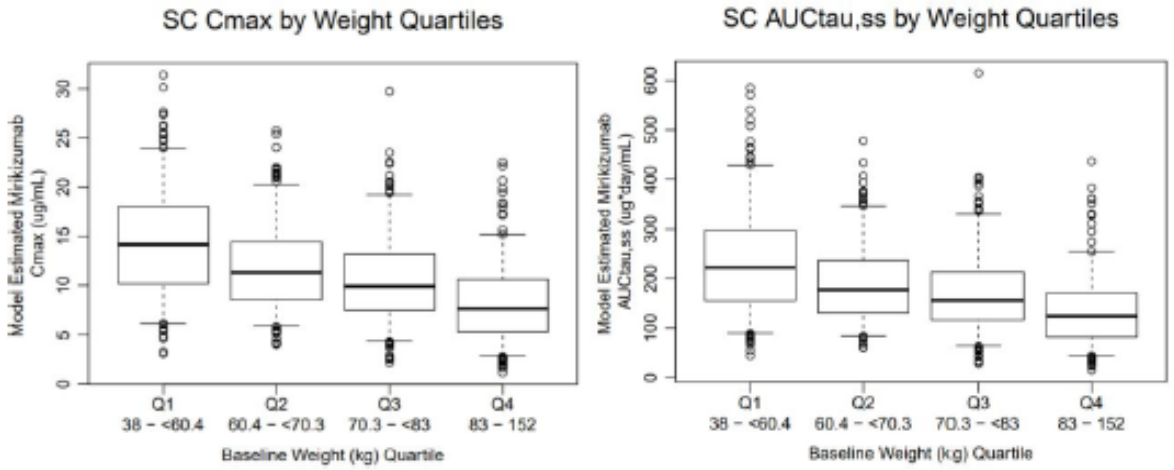


Abbreviations: $AUC_{\tau,ss}$ = area under the concentration versus time curve during one dosing interval at steady state; C_{max} = maximum concentration during one dosing interval at steady state; PK = pharmacokinetics; PopPK = population pharmacokinetics; Q = quartile; SC = subcutaneous.

Note: The horizontal line in each box represents the median; the top and bottom sides of the box represent the 75th and 25th percentiles; the whiskers extend to the 95th and 5th percentiles; and circles represent data points outside of 5th or 95th percentile.

Figure 11.3. Boxplots of covariate effects on the PK of mirikizumab post-subcutaneous administration from the PopPK Analysis.

Body mass index (BMI) was a statistically significant covariate on SC bioavailability. The overall range of BMI in Studies AMAN and AMBG was 13.8 to 53.5 kg/m2. As BMI affects SC bioavailability and body weight affects clearance, the exposure with the SC dosing regimen would be impacted by both patient factors in combination. As body weight is a more typical measure of body size, Figure 11.3 shows boxplots of the AUC and Cmax relative to the quartiles of body weight, which would also account for the impact of correlated BMI differences in patients with UC. With SC dosing, the median AUC in patients in the highest body weight quartile was 124 µg*day/mL versus an overall population median AUC of 165 µg*day/mL. This difference in AUC between typical and high body weights is small relative to the overall range in AUC values. Similarly, the median Cmax in the highest body weight quartile was 7.65 µg/mL versus an overall population median of 10.6 µg/mL, respectively, which is also a small difference relative to the overall range in Cmax values.



Abbreviations: $AUC_{\tau,ss}$ = area under the concentration versus time curve during one dosing interval at steady state; C_{max} = maximum concentration during one dosing interval at steady state; PK = pharmacokinetics; PopPK = population pharmacokinetics; Q = quartile; SC = subcutaneous.

Note: The horizontal line in each box represents the median; the top and bottom sides of the box represent the 75th and 25th percentiles; the whiskers extend to the 95th and 5th percentiles; and circles represent data points outside of 5th or 95th percentile.

Figure 11.3. Boxplots of covariate effects on the PK of mirikizumab post-subcutaneous administration from the PopPK Analysis.

Overall, a significant overlap in mirikizumab exposure was observed across patient body weight/BMI groups, and the difference in exposure between the highest body weight patients and a typical patient is small relative to the overall range of exposures. In addition, the E-R analysis found, in general, a lack of relationship between efficacy and mirikizumab exposure in the exposure range at the recommended doses. Therefore, the difference in the exposure of mirikizumab due to the body size effect is not expected to result in detectable differences in the efficacy endpoints. The body size effect on mirikizumab exposure is not considered clinically relevant and no dose adjustment on the basis of body weight is needed.

Elderly

The effect of age on mirikizumab PK was investigated in the popPK analyses and was found not to be a clinically significant covariate. Of the 1362 subjects with UC exposed to mirikizumab in Phase 2 and Phase 3 studies, 99 (7.27%) patients were 65 years or older and 11 (0.808%) patients were 75 years or older.

Children

No data available.

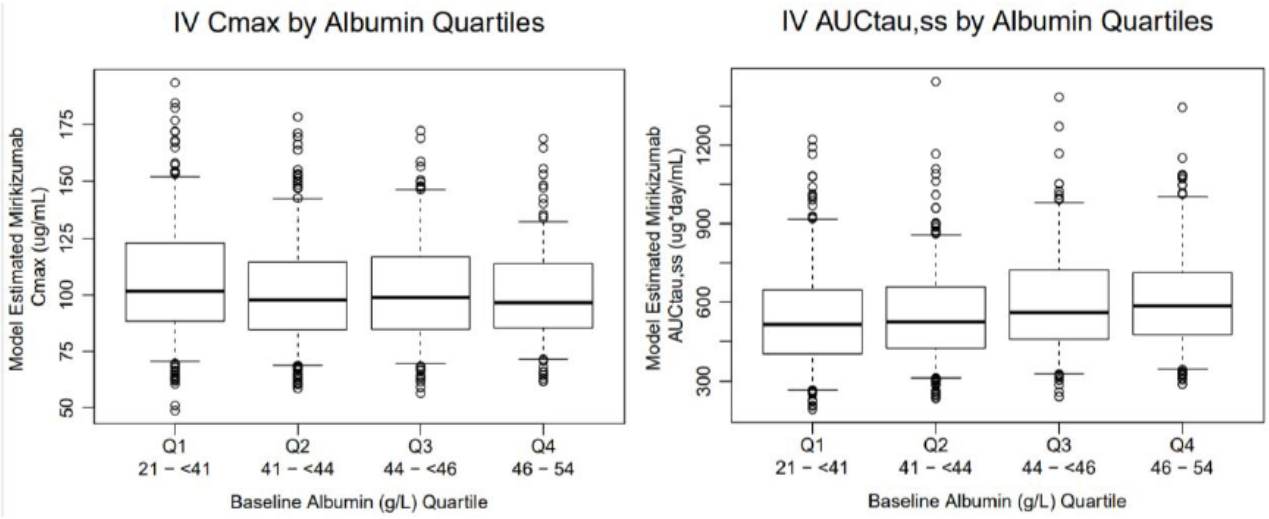
Severity of disease state

Baseline faecal calprotectin, baseline MMS and MMS subscores, duration of disease, prior biologic treatment experience, and baseline CRP, as measures of baseline disease severity, were tested as covariates on clearance in the popPK analyses. None of them were identified as a significant covariate.

Albumin concentration was a statistically significant covariate on clearance. Patients with more severe disease tend to have lower albumin concentrations, and patients with lower albumin concentrations tend to have a lower AUC (area under the curve). However, a large degree of overlap in exposures was noted when patients were stratified by quartiles of the albumin concentration (Figure 2.7.2.9). With

the 300-mg Q4W IV dosing regimen, the median estimated AUC in patients in the lowest quartile of albumin concentrations (21 to 41 g/L) was 515 µg·day/mL versus an overall population median AUC of 539 µg·day/mL based on data in Study AMAN. This difference in AUC for patients with low albumin concentrations is small relative to the overall range in AUC values. Similarly, the median Cmax in the lowest albumin concentration quartile was 102 µg/mL versus a population median of 99.4 µg/mL, which is also a small difference relative to the overall range in Cmax values.

These results indicate that disease state did not have a clinically relevant impact on the exposure of mirikizumab and no dose adjustment on the basis of disease state is needed.



Abbreviations: $AUC_{tau,ss}$ = area under the concentration versus time curve during 1 dosing interval at steady state; C_{max} = maximum concentration during a dosing interval at steady state; IV = intravenous; PK = pharmacokinetics; PopPK = population pharmacokinetics; Q = quartile; Q4W = every 4 weeks.
Note: The horizontal line in each box represents the median; the top and bottom sides of the box represent the 75th and 25th percentiles; the whiskers extend to the 95th and 5th percentiles; and circles represent data points outside of 5th or 95th percentile.

Figure 2.7.2.9. Box plot of relationship between mirikizumab exposure and albumin concentrations with 300-mg IV Q4W dosing regimen from the Phase 3 PopPK analysis.

Pharmacokinetic interaction studies

Effect of mirikizumab on the PK of other drugs

Mirikizumab is a monoclonal antibody that is unlikely to have any direct effect on drug-metabolizing enzymes. However, chronic inflammation can lead to disease-drug interactions by reducing the expression and activity of some CYP enzymes. This may alter the systemic exposure of CYP substrates (Wang et al. 2014).

Study AMBP was a clinical DDI study conducted in patients with moderate-to-severe psoriasis (PsO) using a "probe cocktail" approach. A drug cocktail of CYP substrates was administered as single oral dose during Period 1. The drug cocktail included midazolam 1 mg (CYP3A), warfarin 10 mg (CYP2C9), dextromethorphan 30 mg (CYP2D6), omeprazole 20 mg (CYP2C19) and caffeine 100 mg (CYP1A2). Mirikizumab 250 mg SC Q4W was administered for 5 doses before the drug cocktail oral doses were administered again in period 2.

The results showed that multiple SC doses of mirikizumab are unlikely to change CYP activity to a degree that would be expected to contribute clinically meaningful changes in the exposure of CYP3A, CYP2C9, CYP2D6, CYP2C19, or CYP1A2 substrates. The 90% CIs for the ratios of geometric LS mean Cmax, AUC(0-∞), and AUC(0-tlast) were contained within the 0.8 to 1.25 boundaries for each of the cocktail drugs (and their metabolites) apart from omeprazole. For omeprazole, the upper limits of the 90% CIs for Cmax and AUC(0-tlast) were 1.26, but the 90% CI for AUC(0-∞) was contained within the 0.8 to 1.25 boundaries. For all cocktail drugs (and their metabolites), multiple mirikizumab doses did not have an effect on median tmax.

2.6.2.2. Pharmacodynamics

Characterisation of the pharmacodynamics (PD) of mirikizumab for the treatment of UC was conducted with data from one Phase 2 study (AMAC) and two Phase 3 studies (AMAN and AMBG). PK/PD analyses were conducted to assess the E-R relationships for efficacy and safety to support the proposed dosing regimen.

Mechanism of action

Mirikizumab (LY3074828) is a humanised immunoglobulin G4 (IgG4) isotype monoclonal antibody that binds with high affinity and specificity to the p19 subunit of interleukin-23 (IL-23), a naturally occurring proinflammatory cytokine, and inhibits its interaction with the IL-23 receptor (IL-23R).

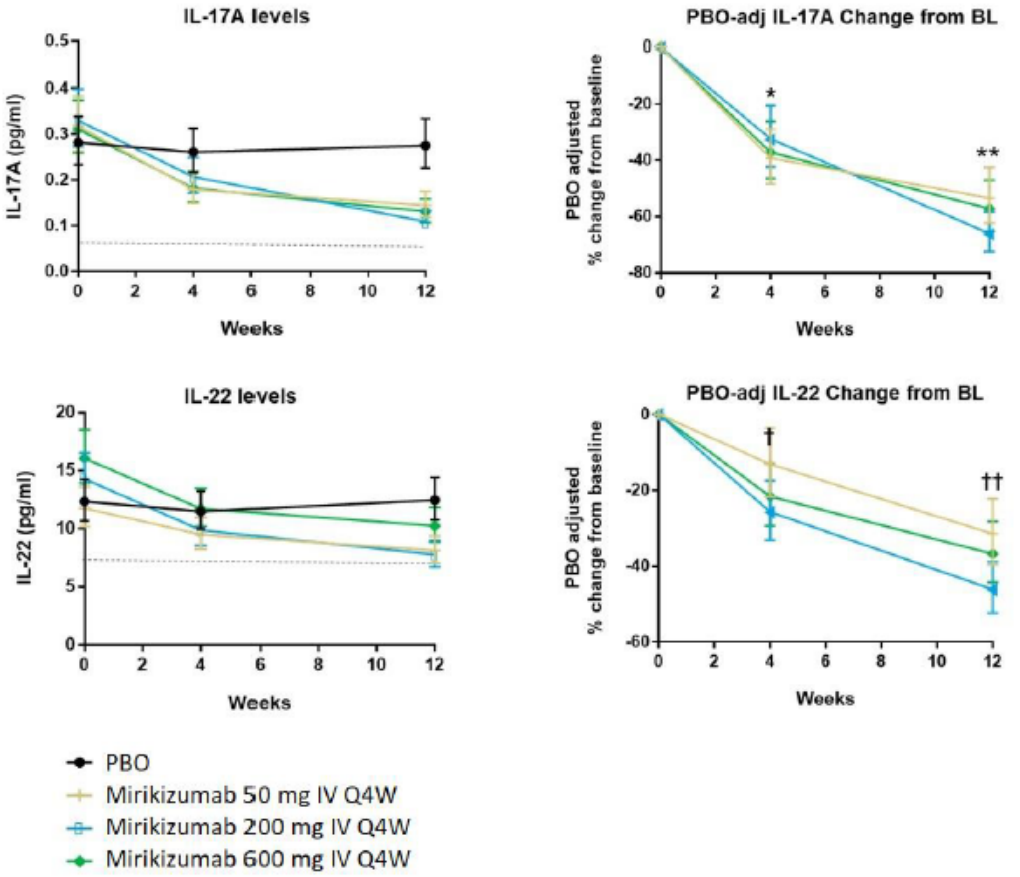
Mirikizumab is being developed for the treatment of immune-mediated diseases in which the IL-23 pathway is thought to have a pathogenic role.

Primary and Secondary pharmacology

Cytokines (Phase 1 and Phase 2 studies)

In the Phase 1 Study AMAA (patients with PsO), no apparent change in IL-23 concentration was observed in any of the mirikizumab dose groups. This is consistent with mirikizumab's proposed mechanism of action in blocking IL-23 signalling rather than production.

In the Phase 2 Study AMAC, statistically significant reductions were observed for both IL-17A and IL-22 at 4 and 12 weeks post-baseline after mirikizumab treatment in patients with UC (Figure 2.7.2.12). IL-17A and IL-22 are downstream components of the IL-23 cytokine signaling pathway, which is known to be involved in the pathology of UC (Mizoguchi et al. 2018). Reductions in plasma IL-17A and IL-22 concentrations confirm the biologic activity of mirikizumab as a p19-directed anti-IL-23 antibody in patients with moderately to severely active UC.



Abbreviations: adj = adjusted; BL = baseline; IL = interleukin; PBO = placebo; Q4W = every 4 weeks; UC = ulcerative colitis.

Note: * 50 mg mirikizumab p=0.002; 200 mg mirikizumab p=0.015; 600 mg mirikizumab p=0.004; ** All miri groups p<0.001; † 50 mg mirikizumab p=0.178; 200 mg mirikizumab p=0.005; 600 mg mirikizumab p=0.020; †† 50 mg mirikizumab p=0.003; 200 mg mirikizumab p<0.001; 600 mg mirikizumab p<0.001.

Horizontal dashed line indicates IL-17A and IL-22 concentrations in healthy subjects.

Figure 2.7.2.12. Changes in the IL-17A and IL-22 concentrations following mirikizumab 50, 200, and 600 mg IV Q4W induction doses in patients with UC (Phase 2 Study AMAC).

C-reactive protein (Phase 3 studies)

Patients in the mirikizumab treatment group showed a nominally significantly greater LS mean reduction in CRP from baseline at Week 12 in Study AMAN [-4.6 mg/L in the mirikizumab group compared to -0.9 mg/L in the placebo group (LS mean difference = -3.7, p<.001)] and Week 40 in Study AMBG compared to the placebo group [-4.7 mg/L in the mirikizumab group compared to -1.4 mg/L in the placebo group (LS mean difference = -3.3, p<.001)].

Table 2.7.2.11 summarises absolute CRP values in Study AMAN. Table 2.7.2.12 summarises absolute CRP values in patients who responded to mirikizumab at Week 12 of Study AMAN. These results show that the induction and maintenance dosing regimens led to a clinically meaningful difference in LS mean CRP at Week 40 of Study AMBG (52 weeks of treatment).

Table 2.7.2.11. Absolute Values of CRP (ANCOVA with mBOCF) Modified Intent-to-Treat Population Study I6T-MC-AMAN - Induction Period

	Placebo IV Q4W (N = 294)	Mirikizumab 300 mg IV Q4W (N = 868)
Baseline		
n	279	837
LS mean (SE), mg/L	9.44 (0.91)	9.25 (0.53)
Median, mg/L	4.25	4.04
Week 12		
n	279	837
LS mean (SE), mg/L	8.42 (0.57)	4.68 (0.35)
Median, mg/L	3.13	1.70

Abbreviations: ANCOVA = analysis of covariance; CRP = C-reactive protein; IV = intravenous; LS = least squares; mBOCF = modified baseline observation carried forward; mITT = modified intent to treat; n = number of subjects in the population with baseline and postbaseline value at the specified time point; N = number of patients in the mITT population; Q4W = every 4 weeks; SE = standard error.

Table 2.7.2.12. Absolute Values of CRP (ANCOVA with mBOCF) Modified Intent-to-Treat Population – Mirikizumab Induction Responders Study I6T-MC-AMBG – Randomized Withdrawal Maintenance Period

	Placebo SC Q4W (N = 179)	Mirikizumab 200 mg SC Q4W (N = 365)
Week 0 of Study AMAN (Baseline)		
n	178	359
LS Mean (SE), mg/L	7.28 (1.10)	8.88 (0.78)
Median, mg/L	3.04	3.79
Week 40 of Study AMBG		
n	178	359
LS Mean (SE), mg/L	6.95 (0.73)	3.63 (0.55)
Median, mg/L	1.64	1.35

Abbreviations: ANCOVA = analysis of covariance; CRP = C-reactive protein; LS = least squares; mBOCF = modified baseline observation carried forward; mITT = modified intent to treat; n = number of subjects in the population with baseline and postbaseline value at the specified time point; N = number of patients in the mITT population; n = number of subjects in the population with baseline and post-baseline value at the specified time point; Q4W = every 4 weeks; SC = subcutaneous; SE = standard error.

Faecal calprotectin (Phase 3 studies)

Patients in the mirikizumab treatment group showed a nominally significantly greater LS mean reduction in faecal calprotectin from baseline at Week 12 in Study AMAN [1875 mg/kg in the mirikizumab group compared to -940 mg/kg in the placebo group (LS mean difference = -936, p<.001)], and Week 40 in Study AMBG compared to the placebo group [-1995 mg/kg in the mirikizumab group compared to -1156 mg/kg in the placebo group (LS mean difference = -840, p<.001)].

Table 2.7.2.13 summarises absolute faecal calprotectin values in Study AMAN. Table 2.7.2.14 summarises absolute faecal calprotectin values in patients who responded to mirikizumab at Week 12 of Study AMAN.

Table 2.7.2.13. Absolute Values of Fecal Calprotectin (ANCOVA with mBOCF) Modified Intent-to-Treat Population Study I6T-MC-AMAN - Induction Period

	Placebo IV Q4W (N = 294)	Mirikizumab 300 mg IV Q4W (N = 868)
Baseline		
n	243	722
LS mean (SE), mg/kg	2970 (303.5)	3121 (176.1)
Median, mg/kg	1465	1556
Week 12		
n	243	722
LS mean (SE), mg/kg	2386 (206.9)	1222 (129.9)
Median, mg/kg	1040	398

Abbreviations: ANCOVA = analysis of covariance; IV = intravenous; LS = least squares; mBOCF = modified baseline observation carried forward; mITT = modified intent to treat; n = number of subjects in the population with baseline and postbaseline values at the specified time point; N = number of patients in the mITT population; Q4W = every 4 weeks; SE = standard error.

Table 2.7.2.14. Absolute Values of Fecal Calprotectin (ANCOVA with mBOCF) Modified Intent-to-Treat Population – Mirikizumab Induction Responders Study I6T-MC-AMBG – Randomized Withdrawal Maintenance Period

	Placebo SC Q4W (N = 179)	Mirikizumab 200 mg SC Q4W (N = 365)
Week 0 of Study AMAN (Baseline)		
n	156	302
LS Mean (SE), mg/kg	3279 (367.0)	2884 (263.8)
Median, mg/kg	1750	1472
Week 40 of Study AMBG		
n	156	302
LS Mean (SE), mg/kg	1863 (221.4)	1023 (172.4)
Median, mg/kg	496	155

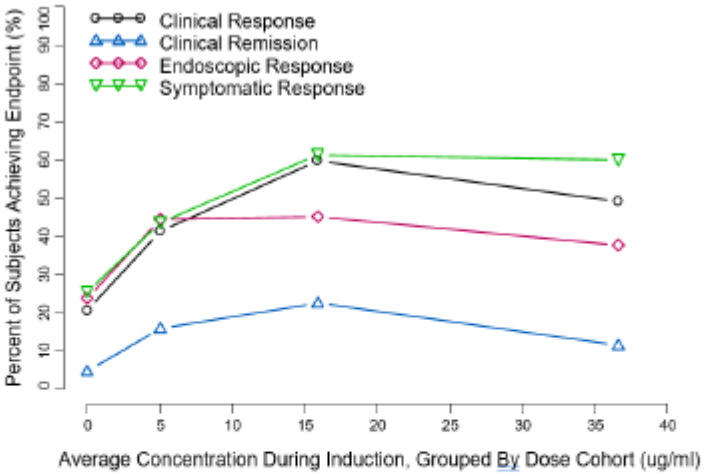
Abbreviations: ANCOVA = analysis of covariance; IV = intravenous; LS = least squares; mBOCF = modified baseline observation carried forward; mITT = modified intent to treat; n = number of subjects in the population with baseline and postbaseline value at the specified time point; N = number of patients in the mITT population; Q4W = every 4 weeks; SE = standard error.

Exposure-response relationships for efficacy

Clinical endpoints were defined using the modified Mayo score (MMS) and included clinical response, clinical remission and endoscopic response. The mirikizumab exposure metric was Cavg.

Induction dosing

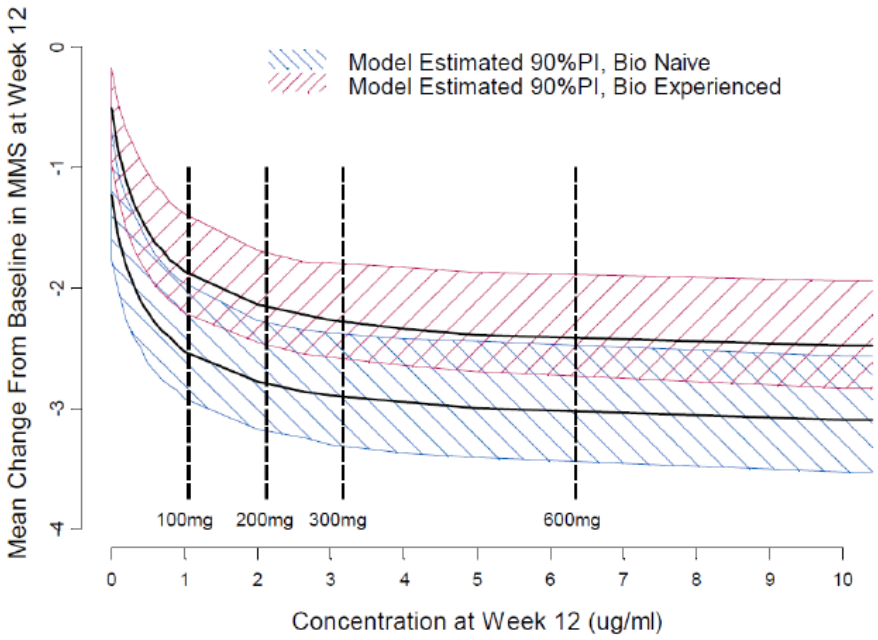
The Phase 2 dose-ranging Study AMAC evaluated IV doses of mirikizumab in a range of 50 mg to 600 mg Q4W. Dose levels in the 50-mg and 200-mg dose groups were adjusted based on drug exposures during the induction period, which resulted in overall average dose levels during the induction period of 100 and 250 mg, respectively. The observed clinical response, clinical remission, and change in the MMS at induction Week 12 tended to increase with mirikizumab exposure up to the 200-mg exposure-based cohort, and then either levelled off or decreased at higher mirikizumab doses or exposures (Figure 2.7.2.13).



Abbreviation: PK = pharmacokinetics.
Note: Concentration points are at the median of the PK model-estimated average concentration in the placebo, 50-, 200-, and 600-mg cohorts from left to right.

Figure 2.7.2.13. Rates at Week 12 for select induction endpoints of interest relative to average concentration of mirikizumab in each dose cohort in Study I6T-MC-AMAC.

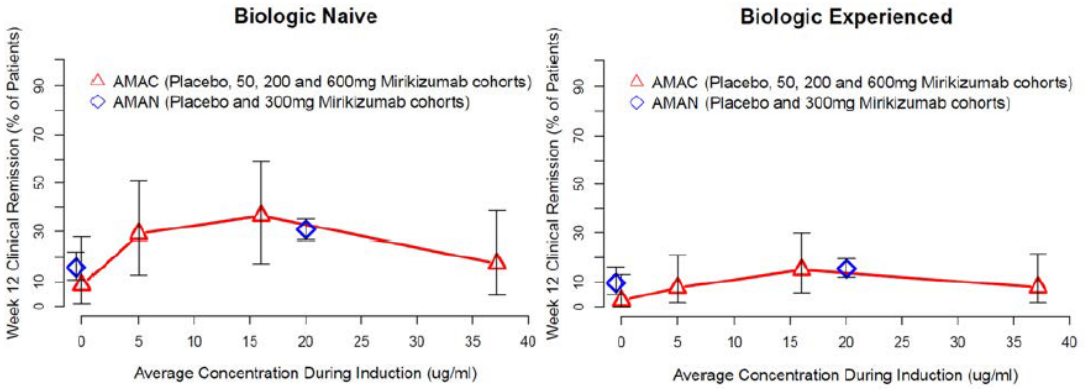
The model-based analyses of data from Study AMAC showed that the E-R relationship was statistically significant for clinical response and change in the MMS. In general, patient factors had a stronger impact on Week 12 efficacy than mirikizumab exposure. Based on the E-R model for Week 12 MMS change established with Study AMAC, induction doses of greater than 200 mg IV Q4W are expected to be on the plateau of the E-R curve and a dose of 300 mg IV Q4W is projected to produce 87% of maximal efficacy (Figure 2.5.3.1).



Abbreviations: MMS = modified Mayo score; PI = projection interval; Bio Naïve = biologic-naïve; Bio Experienced = biologic-experienced; IV = intravenous.
Note: Projection intervals are based on simulation of 500 replicated trials with an N = 500 each for biologic-naïve and biologic-experienced patients. Vertical dashed lines represent the median expected Week 12 concentrations for fixed IV doses administered Q4W.

Figure 2.5.3.1 **Simulated change in modified Mayo score at Week 12 versus Week 12 concentration of mirikizumab based on I6T-MC-AMAC exposure-response model.**

The efficacy observed at Week 12 in the Phase 3 induction study AMAN is generally consistent with expectations for a 300 mg IV Q4W dose based on the observed and modelled E-R relationships in the Phase 2 Study AMAC (Figure 2.5.3.2).



Abbreviations: AMAC = I6T-MC-AMAC; AMAN = I6T-MC-AMAN.

Note: AMAC data points represent the percentage of patients that achieved clinical remission in each of the study cohorts, from left to right: Placebo, 50 mg, 200 mg, and 600 mg mirikizumab. The points for both AMAC and AMAN are plotted along the x-axis at the median time-averaged concentration for each cohort. Due to the application of exposure-based dose adjustments, the overall average induction dose received by patients in AMAC in the 50-mg and 200-mg cohorts were 100 mg and 250 mg, respectively.

Figure 2.5.3.2 **Exposure-response relationship for clinical remission at the end of induction treatment in bio-naïve and bio-experienced patients with UC in Phase 2 and Phase 3 studies.**

Model-based analyses of the relationships between mirikizumab exposure and Week 12 clinical remission, clinical response, endoscopic improvement, and change in the MMS in Study AMAN were conducted. None of the covariates tested, including weight and BMI, were found to have an impact on the mirikizumab effect parameters in any of the efficacy models, suggesting no dose adjustment is needed for the covariates tested. A significant confounding effect was observed while examining relationships between individual subject exposures and individual subject efficacy in an exposure quartile analysis, which limited the conclusions that could be made about cause-effect of exposure response relationships using data alone from Study AMAN where one dose level was studied.

Maintenance dosing

Two maintenance dose regimens of 200 mg SC Q4W and 200 mg SC Q12W were evaluated in the Phase 2 Study AMAC. As expected, the Q12W regimen produced a concentration profile with greater difference between peak and trough concentrations over a dosing interval as compared to the Q4W regimen. Although the Q12W regimen produced moderate efficacy at Week 52 based on the binary efficacy measures, the mirikizumab concentration profile with the Q12W regimen did not maintain consistent symptomatic efficacy. On the other hand, the Q4W treatment group generally had a numerically greater treatment effect across the assessed clinical and histologic endpoints, and the effect in the Q4W group was more consistent than in the Q12W group. The Q4W regimen also produced trough concentrations that were similar to the Week 12 trough concentration produced in the 200-mg IV induction cohort that achieved the best efficacy.

Model-based and graphical examination of the relationship between mirikizumab exposure and clinical response, clinical remission, and MMS change at Week 52 during the maintenance period in the Phase 2 Study AMAC did not reveal any significant relationships. Similar analyses were conducted at the end of the maintenance period of the Phase 3 maintenance Study AMBG, focused on patients that had achieved clinical response in the induction Phase 3 Study AMAN. The analysis found no significant relationship between mirikizumab exposure and Week 40 efficacy in the exposure range at the single dose level of 200 mg SC evaluated in Study AMBG.

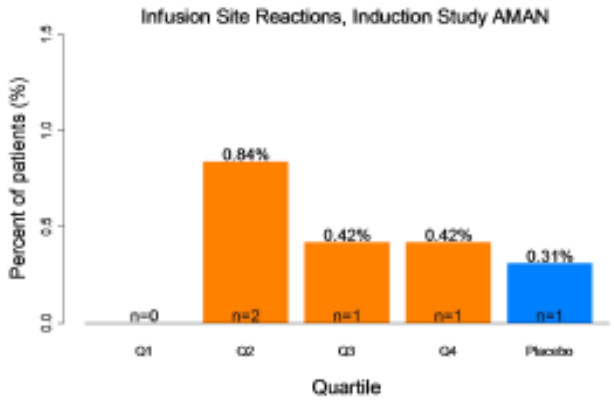
Overall, the robust efficacy observed in the Phase 3 maintenance study AMBG and the E-R data for maintenance treatment indicate that maintenance efficacy was not sensitive to differences in exposure across patients with the 200 mg SC Q4W dosing regimen, demonstrating that this dose regimen provided maximal efficacy in UC patients.

Exposure-Response Relationships for Safety

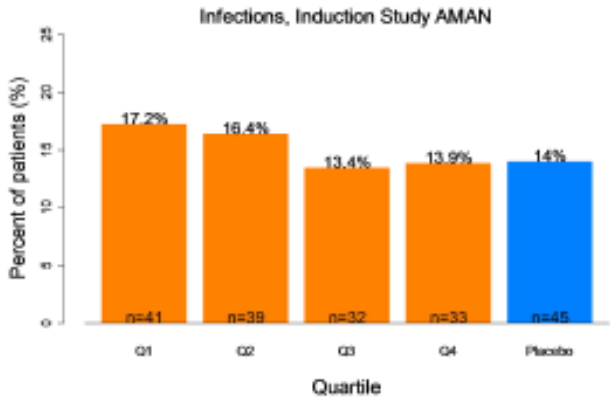
Model-predicted average concentrations were determined for each patient in Studies AMAN and AMBG. Patients were stratified by quartile ranges of predicted average concentration. The number of patients reporting the following AEs of special interest was summarised for each exposure quartile:

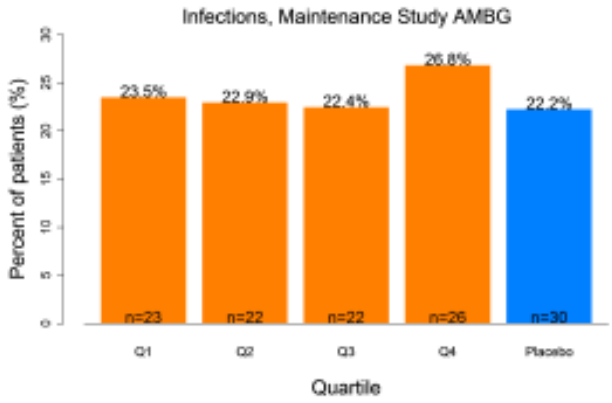
- injection site reactions (Study AMBG) and infusion site reactions (Study AMAN)
- infections, serious infections, and opportunistic infections, and
- hypersensitivity reactions (Figure 2.7.2.21).

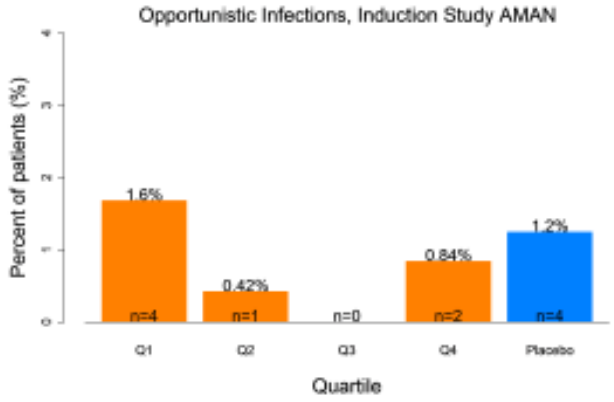
There was no apparent mirikizumab concentration relationship with any AEs of special interest evaluated in the exposure quartile analysis for either the induction Study AMAN or the maintenance Study AMBG.


Infusion Site Reactions, Induction Study AMAN
Percent of patients (%)
0.0
0.5
1.0
1.5
0.84%
0.42%
0.42%
0.31%
n=0
n=2
n=1
n=1
n=1
Q1
Q2
Q3
Q4
Placebo
Quartile

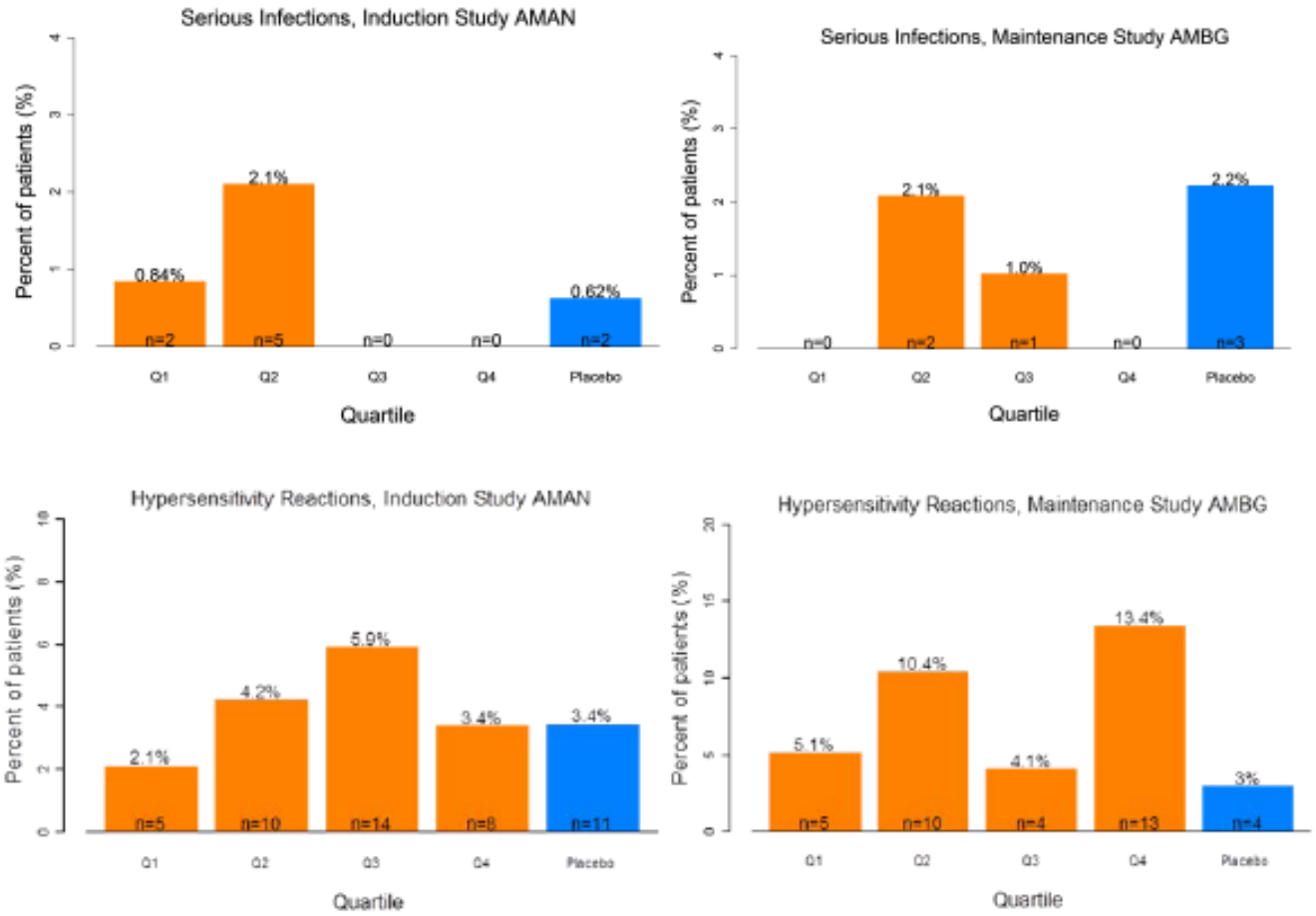

Injection Site Reactions, Maintenance Study AMBG
Percent of patients (%)
0
5
10
15
7.1%
11.5%
5.1%
11.3%
2.2%
n=7
n=11
n=5
n=11
n=3
Q1
Q2
Q3
Q4
Placebo
Quartile


Infections, Induction Study AMAN
Percent of patients (%)
0
5
10
15
20
25
17.2%
16.4%
13.4%
13.9%
14%
n=41
n=39
n=32
n=33
n=45
Q1
Q2
Q3
Q4
Placebo
Quartile


Infections, Maintenance Study AMBG
Percent of patients (%)
0
5
10
15
20
25
30
23.5%
22.9%
22.4%
26.8%
22.2%
n=23
n=22
n=22
n=26
n=30
Q1
Q2
Q3
Q4
Placebo
Quartile


Opportunistic Infections, Induction Study AMAN
Percent of patients (%)
0
1
2
3
4
1.6%
0.42%
0.84%
1.2%
n=4
n=1
n=0
n=2
n=4
Q1
Q2
Q3
Q4
Placebo
Quartile


Opportunistic Infections, Maintenance Study AMBG
Percent of patients (%)
0
1
2
3
4
3.1%
2.1%
2.0%
2.2%
n=3
n=2
n=2
n=0
n=3
Q1
Q2
Q3
Q4
Placebo
Quartile



Abbreviations: n = number of patients who experienced the adverse event; Q = quartile. Study AMAN average concentration quartiles: Q1: <15.2 µg/mL. Q2: 15.2 to 19.7 µg/mL. Q3: 19.7 to 24.9 µg/mL. Q4: ≥24.9 µg/mL
Study AMBG average concentration quartiles: Q1: <4.50 µg/mL. Q2: 4.50 to 6.80 µg/mL. Q3: 6.80 to 9.13 µg/mL. Q4: ≥9.13 µg/mL.
Note: Placebo group in AMBG plots (right panel) represent patients who were AMAN placebo responder and received placebo in AMBG. Opportunistic infection plots include opportunistic infections defined by narrow search terms and potential opportunistic infections defined by broad search terms. Hypersensitivity reaction plots include immediate events defined by both broad and narrow search terms and nonimmediate events defined by narrow search terms.

Figure 2.7.2.21. Exposure-response analyses: summary of adverse events by average concentration quartile up to Week 12 for induction dosing in Study AMAN (left panels) and up to Week 40 for maintenance dosing in Study AMBG (right panels).

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

Bioanalytical methods

The bioanalytical methods have been appropriately validated and no issues are raised.

Population PK Analyses

Population PK analyses of Phase 3 data from Study AMAN alone and Studies AMAN plus AMBG were presented. In both analyses, typical monoclonal 2-compartment linear models (both absorption and clearance) best described mirikizumab concentration-time profiles. The AMAN plus AMBG model estimated systemic clearance to be 0.022 L/hr and SC bioavailability to be 47.6% (geomean: 44%; geoCV%: 34%). These estimates are consistent with results from the clinical trials in patients with UC, healthy subjects, and patients with psoriasis.

There are no issues of concern for either popPK model. The final model parameters were estimated with good precision. Shrinkage was low for clearance and moderate for volume and bioavailability parameters. As such, individual post-hoc estimates can be considered reasonably reliable. The VPCs suggested that the final models fit the observed data well. However, variability appeared to be slightly overestimated for the AMAN/AMBG final model.

Body weight and serum albumin concentrations were found to be significant patient covariates related to mirikizumab clearance, with higher body weights associated with higher clearance, and lower albumin concentrations associated with higher clearance. Baseline BMI was found to be related to SC bioavailability, with higher BMI values associated with lower SC bioavailability. No other covariates were identified to significantly affect the PK of mirikizumab. Simulations of mirikizumab exposure using the final model showed that changes in mirikizumab exposure related to changes in patient covariates were small relative to overall variability in exposure (see Special Populations for further discussion).

Absorption

Bioavailability

The PK results were generally consistent across the 3 Phase 1 studies (AMAA, AMAD and AMBD), which were conducted in healthy subjects and patients with PsO. SC bioavailability was around 40%. The PK of mirikizumab appeared to be dose proportional. Mirikizumab serum concentrations followed a bi-exponential decline following IV administration. The PK of mirikizumab following IV and SC doses were comparable between Japanese and Caucasian subjects.

Overall, TE ADA were present in low-to-moderate frequencies across the Phase 1 trials and the presence of TE ADA had minimal apparent impact on PK. However, the small number of participants and the designs of these trials, do not allow definitive conclusions to be drawn on the impact of ADA.

Bioequivalence

In Phase 3 studies, the solution formulation used for IV induction dosing (Mirikizumab Injection, 300 mg/15 mL) and the solution formulation used for SC maintenance dosing (Mirikizumab Injection, 100 mg/mL) is the same as the to-be-marketed formulation. Therefore, no bioequivalence study was needed. However, SC administration in the Phase 3 trials was only conducted with a PFS. Therefore, Study AMBD was necessary to show bioequivalence between the to-be-marketed autoinjector (AI) and PFS.

The design and methodology of Study AMBD were acceptable. Bioequivalence following SC administration of mirikizumab between the AI and PFS was demonstrated as the 90% CI for the ratios of geometric LS means (AI:PFS) for AUC(0-tlast), AUC(0-∞), and Cmax were entirely contained within the confidence limits of 0.8 and 1.25. There was no statistically significant difference in tmax.

The results of an additional analysis in Study AMBD suggested that mirikizumab can be administered in the abdomen, upper arm, or thigh and achieve similar serum exposure regardless of anatomical injection location.

Distribution

The relatively small volume of distribution of mirikizumab (4.83 L) is typical of monoclonal antibodies, which are largely confined to the vascular and interstitial spaces due to their large molecular size and poor lipophilicity.

Elimination

No specific excretion or metabolism studies were conducted. This is acceptable because mirikizumab is a protein which is primarily cleared by proteolytic catabolism and broken down into small peptides and individual amino acids.

Dose proportionality and time dependency

It is agreed that mirikizumab exhibits dose proportional PK within the dose ranges studied. There is minimal accumulation of mirikizumab over time, which is expected given its half-life of ~10 days and the dosing interval of 4 weeks.

Pharmacokinetics in the target population

The PK of mirikizumab in patients with UC were determined in the PopPK analyses. The data from the Phase 2 and Phase 3 studies suggest that the PK of mirikizumab in patients with UC is similar to the PK in healthy subjects.

Immunogenicity

In the Phase 2 trial (AMAC), the incidence of treatment emergent ADA was 47.8% in patients with UC. Almost half of the mirikizumab-treated patients were NAb positive (45.6%).

Across three Phase 3 studies of mirikizumab, immunogenicity incidence was relatively low (around 20%) and the majority of TE ADAs were characterised as having neutralizing activity. According to the applicant, this is not unexpected as most ADAs target the complementarity-determining regions of any monoclonal antibody therapeutic. More important was the observed impact of high ADA titres leading to reduced mirikizumab exposure and reduced efficacy. However, most patients had no TE ADA or low titre TE ADA and the magnitude of their ADA titres decreased over time. Therefore, this is not considered to be a major concern.

No clinically meaningful differences in the frequency of hypersensitivity events, injection site reactions and infusion site reactions were observed in TE ADA positive patients compared with TE ADA negative patients.

Overall, it is agreed that mirikizumab has an acceptable immunogenicity profile.

Special populations

Overall, the changes in mirikizumab PK and exposures relative to patient factors are consistent with expectations for a mAb. There was no apparent impact of renal or hepatic function, gender, age and race on mirikizumab PK in the popPK analyses.

Significant covariates included body weight (CL/V), albumin (CL) and BMI (bioavailability). However, the applicant showed that the magnitude of the changes in exposure related to these patient factors were small relative to the overall range of exposures caused by random unexplained variability. Further, the E-R analyses indicated that efficacy and safety of mirikizumab were generally not sensitive to the variations in exposure observed across individuals at the dose levels that were studied in Studies AMAN and AMBG.

Therefore, it is agreed that dose adjustments of mirikizumab due to patient factors are not warranted.

Interactions

Mirikizumab is a monoclonal antibody that is unlikely to have any direct effect on drug-metabolizing enzymes. However, chronic inflammation may lead to disease-drug interactions by reducing the expression and activity of some CYP enzymes.

Study AMBP evaluated the effects of multiple 250-mg subcutaneous doses of mirikizumab on the PK of a drug cocktail of CYP substrates in patients with moderate-to-severe psoriasis. The study design and methodology is considered acceptable. The results showed that multiple SC doses or mirikizumab are unlikely to change CYP activity in patients with moderate-to-severe psoriasis to a degree that would be expected to contribute to clinically meaningful changes in the exposure of CYP3A, CYP2C9, CYP2D6, CYP2C19, or CYP1A2 substrates. An adequate justification for the extrapolation of the results of Study AMBP to patients with UC was provided.

As anticipated, concomitant drugs did not have a significant impact on mirikizumab PK since mirikizumab is not eliminated intact in the urine or metabolised by CYP450 enzymes.

Pharmacodynamics

Mechanism of action

Mirikizumab binds to the p19 subunit of interleukin-23 (IL-23), a naturally occurring pro-inflammatory cytokine, and inhibits its interaction with the IL-23 receptor (IL-23R). The proposed mechanism of action supports the selection of PD biomarkers investigated in the clinical studies.

Primary pharmacology

The results from PD evaluations in the clinical studies provide support for the proposed mechanism of action of mirikizumab in the treatment of patients with UC.

Secondary pharmacology

The lack of formal secondary PD studies is acceptable. Monoclonal antibodies such as mirikizumab have a very low likelihood for ion channel interactions and therefore thorough QT/QTc studies are not generally needed.

Pharmacodynamic interactions

No PD interaction studies were conducted. This is not unusual in clinical developments of monoclonal antibodies and is based on the argument that they are specific for their ligand(s) and unbound molecules are rapidly degraded into pharmacologically inactive peptides and amino acids.

Exposure-response analyses

Efficacy

Induction dosing:

Based on Phase 2 data, response tended to increase with exposure up to the 200 mg cohort and then either plateau or decrease at higher exposures. Model-based exposure-efficacy analyses of Study AMAN found prior biologic experience to reduce the placebo effect, thus, decreasing the predicted efficacy rates for both the placebo and mirikizumab patients. No covariates were found to have an impact on the mirikizumab effect parameters in any of the efficacy models.

The developed E-R model predicted 300 mg Q4W IV to produce 87% of the maximal effect possible with mirikizumab. It is agreed that it seems unlikely that efficacy would further increase above the 300 mg and then sharply decrease before getting to 600 mg since the overall E-R profile is relatively flat

over a wide exposure range. The efficacy of the 300 mg Q4W IV induction dose was confirmed in Phase 3 study AMAN.

Maintenance dosing:

2 SC doses evaluated – 200 mg Q4W or Q12W; Q12W dose produced moderate efficacy at week 52 it did not maintain consistent symptomatic efficacy due to greater difference between peaks and troughs. Q4W dosing achieved best efficacy and produced trough similar to week 12 after induction dosing. Analyses support 200 mg Q4W SC for maintenance dosing in UC.

Model-based exposure-efficacy analyses of Study AMBG found clinical remission at the end of induction to be a significant predictor of the placebo effect parameters at the end of maintenance treatment at Week 40, where patients that had achieved clinical remission after induction treatment having higher efficacy at the end of maintenance treatment. No covariates were found to have an impact on the mirikizumab effect parameters in any of the efficacy models for Study AMBG, and mirikizumab exposure was not a significant predictor of efficacy in these models with the dose regimens that were evaluated.

Two, not mutually exclusive hypotheses were offered to explain the apparent lack of concentration–effect relationships:

1. Most of the concentrations were on the plateau of the concentration-effect curve.

2. Disease-related patient factors at baseline control the clinical outcome. Compared to these factors, mirikizumab concentration differences among patients have a small effect. None of the patient-related factors have a strong predictive effect alone and the Phase III studies were not powered to show numerous weak effects.

In fact, strong evidence for confounded exposure-efficacy relationships was found when analysing and comparing data from Studies AMAC, AMAN, and AMBG, showing that there are patient factors that exaggerate the steepness of the observed exposure-efficacy relationships. This suggests that data from a single dose level study and using any form of grouping based on exposure or model based analyses of individual patient data cannot be used to understand the true cause-effect relationships or predict the efficacy that would have been achieved at different dose levels.

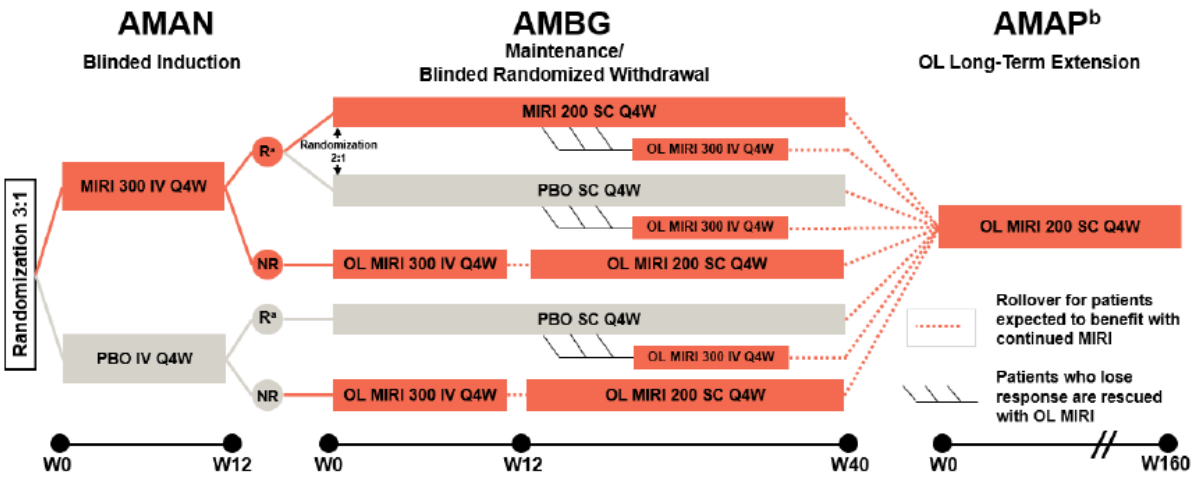
Safety

E-R for safety was explored for AEs of special interest up to Week 12 and Week 40 – injection site reactions; infections; hypersensitivity reactions. No apparent relationship. There was no apparent mirikizumab concentration relationship with any AEs of special interest evaluated for either the induction Study AMAN or the maintenance Study AMBG.

2.6.4. Conclusions on clinical pharmacology

Relevant studies of clinical pharmacology have been provided in support of this submission. The application is approvable from a clinical pharmacology perspective.

2.6.5. Clinical efficacy



Abbreviations = IV = intravenous; mg = milligram; MIRI = mirikizumab; NR = nonresponder; MMS = modified Mayo score; OL = open-label; PBO = placebo; Q4W = every 4 weeks; R = responder; SC = subcutaneous; W = week.

[a] Responders at Week 12 of Study AMAN are defined as achieving 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 an RB score of 0 or 1.

[b] Includes patients who completed the Phase 2 Study AMAC, not shown.

2.6.5.1. Dose response study(ies)

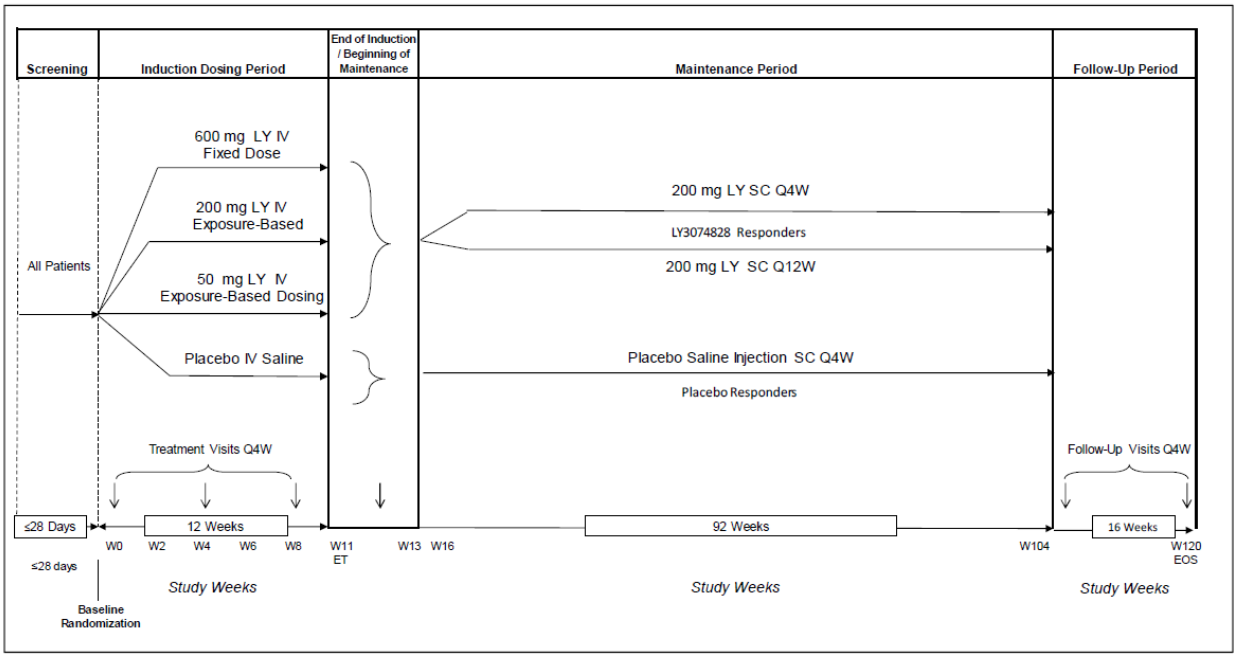
Title

A Phase 2, Multicentre, Randomised, Double-Blind, Parallel, Placebo-Controlled Study of LY3074828 in Subjects with Moderate to Severe Ulcerative Colitis (I6T-MC-AMAC).

Design

The purpose of Study I6T-MC-AMAC (AMAC) was to test the hypothesis that mirikizumab, compared to placebo, can induce significantly higher rates of clinical remission in patients with moderate-to-severe UC. Study AMAC includes 12 weeks of double-blind treatment with mirikizumab or placebo (i.e., Induction period), followed by two 92-week periods:

- Maintenance period to evaluate long-term safety and durability of clinical response and remission in patients who achieved clinical response at Week 12, or
- Extension period to explore the effect of additional dosing on clinical response in patients who did not achieve clinical response at Week 12.



Abbreviations: EOS = end of study; ET = early termination; IV = intravenous; LY = mirikizumab (LY3074828); Q4W = every 4 weeks; Q12W = once every 12 weeks; SC = subcutaneous; W = study week.
Notes: Based on the plasma concentration of mirikizumab, individual patients in the mirikizumab 50 mg and 200 mg treatment groups had their dose of mirikizumab increase; patients in the mirikizumab 600 mg treatment group remained at a fixed dose throughout the Induction Period. Patients who did not achieve clinical response at Week 12 had the option to discontinue the study or enter the Extension Period. The Maintenance Follow-Up Period occurred from Week 104 (Visit 31) or early termination visit (ETV), if the patient discontinued the study for any reason, to a minimum of 16 weeks following that visit. The Maintenance Follow-Up Period assessed patient safety.

Figure AMAC.9.1. Study design for the Screening, Induction, Maintenance, and Maintenance Follow-up Periods.

The design of the study is acceptable. The applicant has clarified how blinding was maintained in the induction period for patients receiving dose adjustments in the 50mg and 100mg arms of the trial.

The applicant has also clarified the rationale for the choice of the doses used in the maintenance phase, (mirikizumab SC 200 mg Q4W and mirikizumab SC 200 mg Q12W.

Study participants

The study population included male or female patients between 18 and 75 years of age who

- had a diagnosis of UC for ≥3 months before baseline
- had moderately-to-severely active UC, as defined by a MMS score of 6 to 12 with an endoscopic subscore ≥2 within 14 days before the first dose of study drug, and
- had evidence of UC extending proximal to the rectum.

The study population either

- had received treatment with 1 or more biologic agents with or without documented history of failure to respond or tolerate such treatment, or were naïve to biologic therapy and had at least 1 of the following:
    - an inadequate response or failure to tolerate current treatment with oral or IV corticosteroids or immunomodulators, or
    - a history of corticosteroid dependence.

Treatments:

In the induction phase, patients were randomised in a 1:1:1:1 ratio to;

- mirikizumab intravenous (IV) 600 mg (fixed dosing)
- mirikizumab IV 200 mg (exposure-based [EB] dosing)
- mirikizumab IV 50 mg (EB dosing), or
- placebo IV.

Patients received study drug at Weeks 0, 4, and 8.

Patients who received mirikizumab in the induction period and achieved remission were re-randomised to

- mirikizumab SC 200 mg every 4 weeks (Q4W), or
- mirikizumab SC 200 mg every 12 weeks (Q12W).

Patients who received placebo in the induction period received SC placebo Q4W.

Objectives and endpoints

The primary objective of this study was to test the hypothesis that treatment with mirikizumab is superior to placebo in inducing clinical remission at Week 12 in patients with moderate-to-severe UC. Clinical remission is defined as having achieved the following:

- Mayo rectal bleeding subscore of 0,
- Mayo stool frequency subscore of 0 or 1 (with 1-point decrease from baseline), and

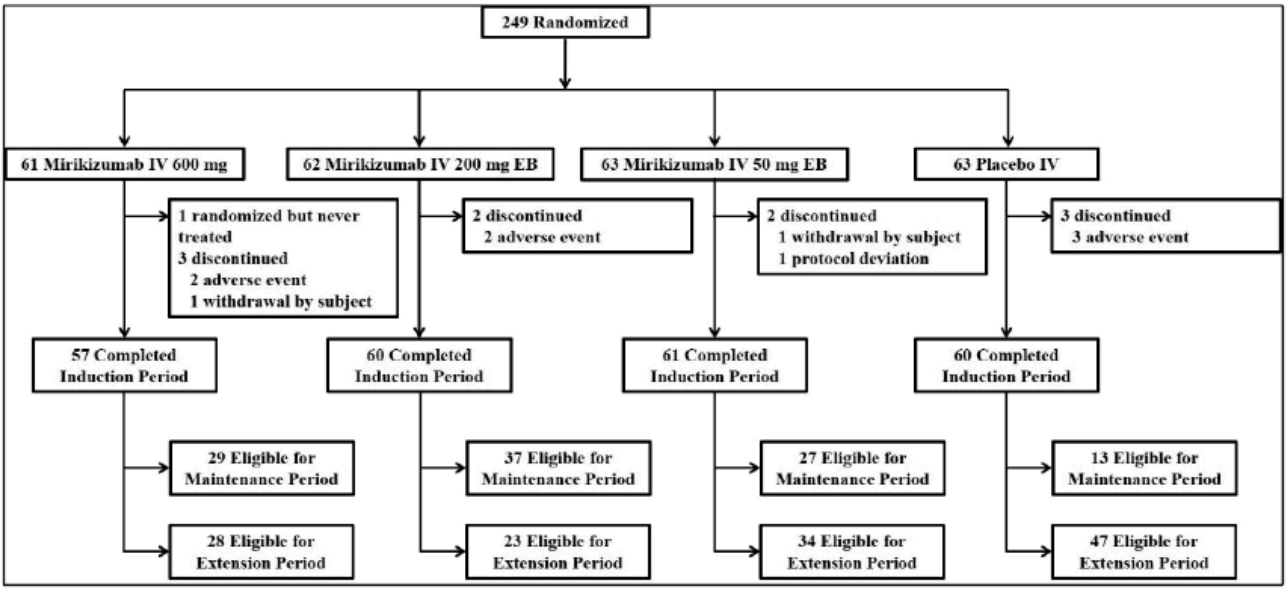
Mayo endoscopy subscore of 0 or 1

Supportive secondary efficacy safety and PK endpoints were also assessed.

Participant flow

A total of 249 patients were randomised to 1 of 4 treatment groups as the ITT Population. One patient in the mirikizumab IV 600 mg treatment group was randomised but never treated with study drug.

A total of 238 patients (95.6%) completed the Induction Period. Ten patients (4%) discontinued during the Induction period.



Recruitment

The baseline characteristics of the patients for the induction period are summarised below.

Summary of Baseline Demographic and Disease Characteristics - Categorical Variables

		Placebo IV Q4W (N = 63)	Miri 50 mg IV Q4W EB (N = 63)	Miri 200 mg IV Q4W EB (N = 62)	Miri 600 mg IV Q4W (N = 61)	Total
Age category	<65 years	59 (93.7%)	59 (93.7%)	56 (90.3%)	58 (95.1%)	232 (93.2%)
Sex	Female	27 (42.9%)	25 (39.7%)	25 (40.3%)	23 (37.7%)	100 (40.2%)
Race	Asian	10 (15.9%)	5 (7.9%)	13 (21.0%)	5 (8.2%)	33 (13.3%)
	Black or African American	1 (1.6%)	1 (1.6%)	5 (8.1%)	0	7 (2.8%)
Smoking status	Yes	18 (28.6%)	18 (28.6%)	25 (40.3%)	23 (37.7%)	84 (33.7%)
	No	45 (71.4%)	45 (71.4%)	37 (59.7%)	38 (62.3%)	165 (66.3%)
MMS	6 to 8	27 (42.9%)	24 (38.7%)	27 (44.3%)	26 (42.6%)	104 (42.1%)
	9 to 12	36 (57.1%)	38 (61.3%)	34 (55.7%)	35 (57.4%)	143 (57.9%)
CRP concentration						
Prior biologic use	Yes	40 (63.5%)	39 (61.9%)	40 (64.5%)	38 (62.3%)	157 (63.1%)
	No	23 (36.5%)	24 (38.1%)	22 (35.5%)	23 (37.7%)	92 (36.9%)

Summary of Baseline Demographic and Disease Characteristics - Continuous Variables

	Placebo IV Q4W (N = 63)	Miri 50 mg IV Q4W EB (N = 63)	Miri 200 mg IV Q4W EB (N = 62)	Miri 600 mg IV Q4W (N = 61)	Total
Age (years)	42.6 (13.47)	41.8 (14.06)	43.4 (14.75)	42.4 (13.37)	42.6 (13.85)
Weight (kg)	74.1 (16.87)	77.0 (17.21)	75.6 (17.34)	73.0 (15.09)	74.9 (16.63)
BMI (kg/m2)	25.0 (4.82)	25.9 (5.08)	25.5 (5.54)	24.8 (4.87)	25.3 (5.07)

Summary of Concomitant Use of Corticosteroids, 5-ASA, or Thiopurines ITT

	Placebo IV Q4W (N = 63)	Miri 50 mg IV Q4W EB (N = 63)	Miri 200 mg IV Q4W EB (N = 62)	Miri 600 mg IV Q4W (N = 61)	Total
Corticosteroids	33 (52.4%)	29 (46.0%)	25 (40.3%)	35 (57.4%)	122 (49.0%)
5-ASA	47 (74.6%)	42 (66.7%)	56 (90.3%)	39 (63.9%)	184 (73.9%)
Thiopurines	25 (39.7%)	15 (23.8%)	18 (29.0%)	11 (18.0%)	69 (27.7%)

Overall, there were no significant differences between the treatment groups, although there was a considerable amount of variability in the incidence of medication use across the 4 groups. This has however not produced any obvious confounding effects on the outcome of the trial.

Results

The primary outcome of this trial was clinical remission at Week 12.

There was no significant difference in the proportion of patients who achieved clinical remission at Week 12 between either the mirikizumab IV 600 mg or 50 mg EB treatment groups and the placebo group.

As the primary outcome was not met, no control for multiplicity was carried out for any of the other outcomes. Consequently, these results should be treated as indicative only.

Results for the Primary Endpoint: Clinical Remission at Week 12

	Placebo IV Q4W (N = 63)	Miri 50 mg IV Q4W EB (N = 63)	Miri 200 mg IV Q4W EB (N = 62)	Miri 600 mg IV Q4W (N = 61)
Response, n (%)	3 (4.8%)	10 (15.9%)	14 (22.6%)	7 (11.5%)
Difference vs. Placebo,		11.1% (0.7%, 21.6%)	17.8% (6.2%, 29.5%)	6.7% (-2.9%, 16.3%)
p-value vs. Placebo	---	0.066	0.004	0.142

Abbreviations: CI = confidence interval; EB = exposure-based dosing; ITT = intent-to-treat; IV = intravenous; Miri = mirikizumab; N = number of patients in the ITT Population; n = number of patients within each specific category; NRI = non-responder imputation; Q4W = every 4 weeks; vs. = versus.

Secondary endpoints

For the secondary endpoint, only those results with significant differences are presented.

The major secondary endpoint for this study was clinical response at Week 12. As the study was not powered to formally assess this endpoint, the results can be taken as indicative only.

A significantly greater proportion of patients achieved a clinical response in all the treatment groups at week 12 compared to placebo.

Results for the Secondary Endpoint: Clinical Response at Week 12

	Placebo IV Q4W (N = 63)	Miri 50 mg IV Q4W (N = 63)	Miri 200 mg IV Q4W (N = 62)	Miri 600 mg IV Q4W (N = 61)
Response, n (%)	13 (20.6%)	26 (41.3%)	37 (59.7%)	30 (49.2%)
Difference vs. Placebo,		20.6% (4.9%, 36.4%)	39.0% (23.3%, 54.8%)	28.5% (12.5%, 44.6%)
p-value vs. Placebo	---	0.014	<.001	0.001

Secondary Endpoints: PGI-S Score at Week 12, and PGI-I Score at Weeks 4, 8, and 12

At Week 12, each mirikizumab treatment group, compared with the placebo group, achieved a significantly greater improvement from baseline in PGI S Score. This trend was also seen in the PGI-I Scores at weeks 4, 8 and 12.

Results for the Secondary Endpoint: PGI-S Score at Week 12

	Placebo IV Q4W (N = 63)	Miri 50 mg IV Q4W EB (N = 63)	Miri 200 mg IV Q4W EB (N = 62)	Miri 600 mg IV Q4W (N = 61)
CFB, LS Mean (SE)	-0.84 (0.187)	-1.43 (0.195)	-1.90 (0.182)	-1.74 (0.193)
Difference vs. Placebo,		-0.59 (-1.07, -0.11)	-1.06 (-1.54, -0.59)	-0.90 (-1.39, -0.41)
p-value vs. Placebo	---	0.016	<.001	<.001

Results for the Secondary Endpoint: PGI-I Score at Weeks 4, 8, and 12

	Placebo IV Q4W (N = 63)	Miri 50 mg IV Q4W EB (N = 63)	Miri 200 mg IV Q4W EB (N = 62)	Miri 600 mg IV Q4W (N = 61)
Mean (SD) at Week 4	3.71 (1.054)	3.15 (1.291)	2.92 (0.936)	2.98 (0.948)
Mean (SD) at Week 8	3.33 (1.380)	2.79 (1.320)	2.41 (0.990)	2.80 (1.176)
Mean (SD) at Week 12	3.37 (1.462)	2.69 (1.313)	2.39 (0.988)	2.53 (1.157)

IBDQ Total Score at Week 12

Change from baseline

At Week 12, the mirikizumab IV 200 mg EB and 600 mg treatment groups, compared with the placebo group, achieved a significantly greater improvement from baseline in IBDQ Score.

Results for the Secondary Endpoint: IBDQ Total Score at Week 12

	Placebo IV Q4W (N = 63)	Miri 50 mg IV Q4W EB (N = 63)	Miri 200 mg IV Q4W EB (N = 62)	Miri 600 mg IV Q4W (N = 61)
CFB, LS Mean (SE)	22.3 (4.41)	33.0 (4.52)	42.8 (4.40)	45.2 (4.54)
Difference vs. Placebo,		10.7 (-1.0, 22.5)	20.5 (8.7, 32.3)	22.9 (11.0, 34.9)
p-value vs. Placebo	---	0.073	<.001	<.001

SF-36 at Week 12

Change from baseline

At Week 12, each mirikizumab treatment group, compared with the placebo group, achieved a significantly greater improvement from baseline in SF-36 PCS score.

At Week 12, the mirikizumab IV 200 mg EB and 600 mg treatment groups, compared with the placebo group, achieved a significantly greater improvement from baseline in SF-36 MCS Score. There was no difference in the improvement from baseline in SF-36 MCS score between the mirikizumab IV 50 mg EB treatment group and the placebo group.

Results for the Secondary Endpoint: SF-36 PCS and MCS Scores at Week 12

	Placebo IV Q4W (N = 63)	Miri 50 mg IV Q4W EB (N = 63)	Miri 200 mg IV Q4W EB (N = 62)	Miri 600 mg IV Q4W (N = 61)
PCS Score				
CFB, LS Mean (SE)	3.4 (0.83)	6.2 (0.86)	5.9 (0.83)	6.9 (0.85)
Difference vs. Placebo,		2.9 (0.7, 5.0)	2.6 (0.4, 4.8)	3.6 (1.3, 5.8)
p-value vs. Placebo	---	0.011	0.022	0.002
MCS Score				
CFB, LS Mean (SE)	3.2 (1.22)	4.5 (1.26)	6.8 (1.20)	8.8 (1.25)
Difference vs. Placebo,		1.3 (-1.9, 4.5)	3.6 (0.4, 6.8)	5.6 (2.4, 8.9)
p-value vs. Placebo	---	0.429	0.028	<.001

Maintenance Period

Patients who achieved clinical response at Week 12 entered the blinded maintenance period. Patients who received mirikizumab in the induction period were re-randomised to either mirikizumab SC 200 mg Q4W, or mirikizumab SC 200 mg Q12W.

Patients who received placebo in the induction period received SC placebo Q4W.

Statistical comparisons were performed between each of the mirikizumab treatment groups. There were no statistical comparisons between either of the mirikizumab treatment groups and the placebo group. The inclusion of the placebo group was only intended to maintain the blind during the maintenance period of the study.

Overall, there were no significant differences between the main secondary endpoints related to the maintenance period.

Secondary Endpoint: Clinical Remission at Week 52

There was no significant difference in the proportion of patients who achieved clinical remission at Week 52 between either the mirikizumab SC Q4W treatment group and the mirikizumab SC Q12W treatment group

Results for the Secondary Endpoint: Clinical Remission at Week 52

	Placebo SC Q4W (N = 13)	Miri 200 mg SC Q4W (N = 47)	Miri 200 mg SC Q12W (N = 46)
Response, n (%)	1 (7.7%)	22 (46.8%)	17 (37.0%)
Difference vs. Miri 200 mg SC Q4W,			-9.9% (-29.8%, 10.1%)
p-value vs. Miri 200 mg SC Q4W	Not compared	---	0.332

2.6.5.2. Main study(ies)

Title of study

Induction study:

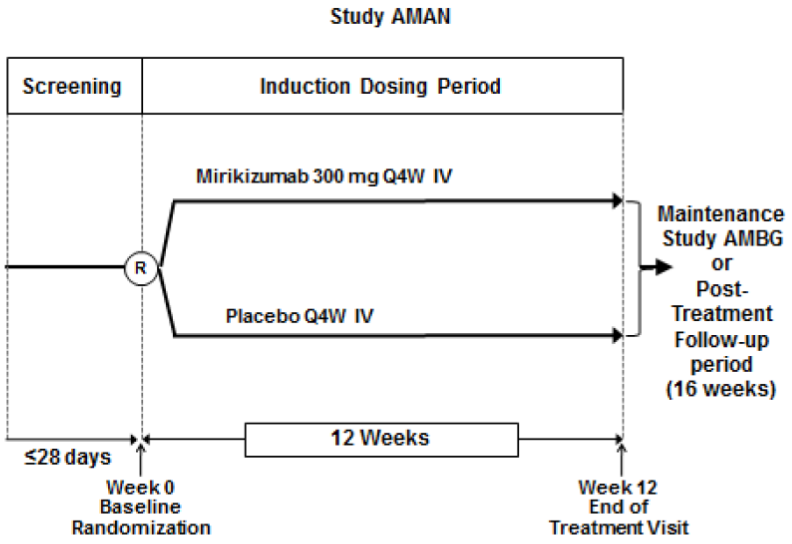
A Phase 3, Multicentre, Randomised, Double-Blind, Parallel, Placebo-Controlled Induction Study of Mirikizumab in Conventional-Failed and Biologic-Failed Patients with Moderately to Severely Active Ulcerative Colitis. (I6T-MC-AMAN).

Maintenance study

A Phase 3, Multicentre, Randomised, Double-blind, Parallel-arm, Placebo-controlled Maintenance Study of Mirikizumab in Patients with Moderately to Severely Active Ulcerative Colitis LUCENT 2: 6T-MC-AMBG

Methods

Study AMAN was a multicentre, randomised, double-blind, parallel-arm, placebo-controlled study designed to evaluate the safety and efficacy of mirikizumab, compared with placebo, over a 12-week Induction period. The study population included patients with moderately to severely active ulcerative colitis (UC) who had an inadequate response to, loss of response to, or are intolerant to conventional (nonbiologic) therapy for UC (conventional-failed), and those who had an inadequate response to, loss of response to, or are intolerant to biologic therapy for UC (biologic-failed).



Abbreviations: IV = intravenous; Q4W = every 4 weeks; R = randomization.

Figure AMAN.3.1. Study AMAN design.

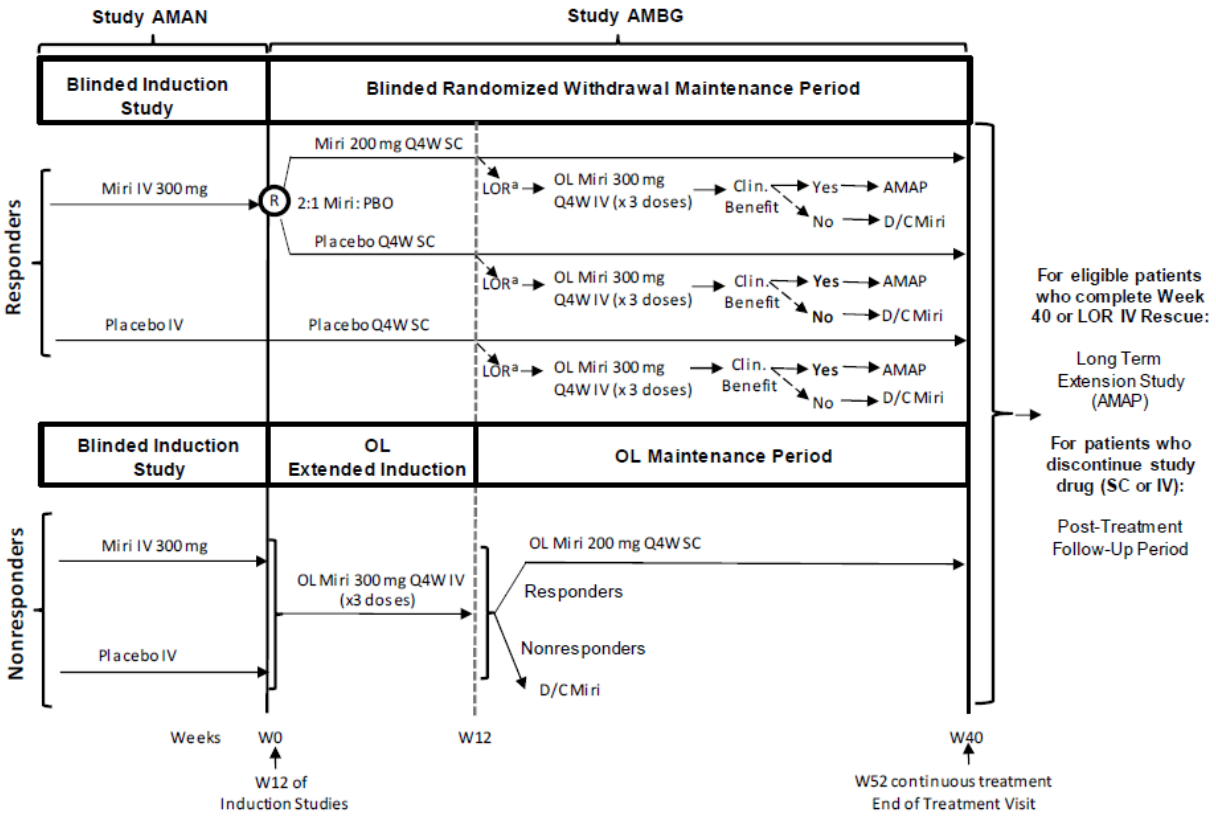
Induction period (Week 0 to Week 12): After a 4-week Screening period, at Visit 2 (Week 0), patients were randomised 3:1 to receive blinded intravenous (IV) administration of 300 mg mirikizumab or placebo every 4 weeks (Q4W) with stratification based on • biologic-failed status (yes/no) • baseline corticosteroid use (yes/no) • baseline disease activity (modified Mayo score [MMS]: [4-6] or [7-9]), and • geographic region (North America/Europe/Other).

Post-treatment follow-up period (16 weeks): At the end of Week 12 of the Induction period, patients could either • enter Study I6T-MC-AMBG (Study AMBG), a separate maintenance study of mirikizumab, or • discontinue study treatment and complete the post-treatment follow-up period. Coronavirus Disease 2019 (COVID-19) had limited impact on the conduct of Study AMAN. Mitigations or adjustments were required for a small number of patients during the trial. Operational delays due to COVID-19-related site closures, delayed or missed participant visits and database lock were noted.

Stratification factors: patients were stratified according to the following factors

Biologic- or JAKi-failed status
Baseline corticosteroid use
Baseline disease activity, and
Region (North America, Europe, or Other)

Study AMBG was a Phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel-arm study evaluating the safety and efficacy of 200 mg mirikizumab every 4 weeks (Q4W) subcutaneous (SC) in maintaining treatment response at Week 40 (that is, at Week 52 of continuous study drug treatment). This study was conducted at 368 centres that entered 1178 participants.



Abbreviations: D/C = discontinue; IV = intravenous; LOR = loss of response; Miri = mirikizumab; OL = open-label; PBO = placebo; Q4W = every 4 weeks; R = randomization; RB = rectal bleeding; SC = subcutaneous; SF = stool frequency; W = week.

Note: LOR is defined as ≥2-point increase from maintenance baseline in the combined SF + RB scores, AND combined SF + RB score of ≥4 on 2 consecutive visits, AND confirmed by an endoscopic subscore of 2 or 3.

a = Loss of response at or after Week 12 and up to and including Week 28.

Patients who achieved clinical response with blinded mirikizumab treatment during Study AMAN were randomised 2:1 to blinded 200 mg mirikizumab Q4W SC or blinded placebo.

Patients who responded to blinded placebo in their induction study remained on blinded placebo in Study AMBG. Open-label rescue therapy with 300 mg mirikizumab Q4W intravenously (IV) was administered for 3 doses if these patients lost response.

Patients who did not achieve clinical response with either blinded mirikizumab or blinded placebo during Study AMAN received open-label extended induction therapy with 300 mg mirikizumab Q4W IV administered for 3 doses.

Patients who achieved delayed clinical response (defined using induction study baseline) received open-label 200 mg mirikizumab Q4W SC.

Induction study non responders who did not achieve clinical response at Week 12 of Study AMBG were discontinued. Patients who completed Study AMBG were eligible for extension Study I6T-MC-AMAP (AMAP).

- **Study Participants**

Induction study AMAN key inclusion/exclusion criteria included the following

Inclusion criteria

- male or female patients ≥18 and ≤80 years of age at the time of initial screening.

Disease-Specific Inclusion Criteria included

- established diagnosis of UC of ≥3 months in duration before baseline (Week 0), which includes endoscopic evidence of UC and a histopathology report that supports a diagnosis of UC. Supportive endoscopy and histopathology reports must be available in the source documents.

- moderately to severely active UC as defined by a modified Mayo score (MMS) of 4 to 9 with an endoscopic subscore (ES) ≥2, with endoscopy performed within 10 days before baseline.

- evidence of UC extending proximal to the rectum (distal to the rectosigmoid junction, which lies approximately 10-15 cm from anal margin).

- have documentation of a surveillance colonoscopy (performed according to local standard) within 12 months before baseline for:
    - patients with pancolitis of >8 years' duration,
    - or patients with left-sided colitis of >12 years' duration, or
    - patients with primary sclerosing cholangitis.

OR

up-to-date colorectal cancer surveillance (performed according to local standard). At the discretion of the investigator, a colonoscopy (instead of a flexible sigmoidoscopy) can be performed as the screening endoscopy for this study. Patients who do not have a colonoscopy report available in source documentation will have a colonoscopy at screening.

Eligible patients had inadequate response, loss of response, or intolerance to either 1 or more corticosteroids or immunomodulators for UC, or to 1 or more biologic (TNF inhibitor or anti-integrin antibody) or JAKi (tofacitinib) approved for the treatment of UC.

Exclusion criteria

- Immunodeficiency syndrome or a known monogenic cause of UC-like colonic inflammation.
- Previous bowel resection or intestinal or intra-abdominal surgery:
- Current diagnosis of Crohn's disease, inflammatory bowel disease unclassified (IBD-U) (formerly known as indeterminate colitis), or UC proctitis (disease limited to the rectum, that is, distal to the recto-sigmoid junction, which lies approximately 10-15 cm from anal margin).
- Had evidence of toxic megacolon, intra-abdominal abscess, or stricture/stenosis within the small bowel or colon.
- Any history or current evidence of cancer of the gastrointestinal tract.
- Received or failed 3 or more biologic therapies (excluding tofacitinib) for UC.

For the **maintenance** study patients who achieved clinical response with blinded mirikizumab treatment during Study AMAN and not meeting any of the exclusion criteria were eligible to be enrolled into **study AMBG.**

Clinical response was defined as a decrease in the MMS of at least 2 points and at least a 30% decrease from baseline, and a decrease of at least a 1 point in the RB subscore from baseline or an RB score of 0 or 1.

- **Treatments**

For the **induction study** concomitant therapy was allowed under the following conditions

Throughout the study, stable doses of…	Were permitted if the prescribed dose…
oral 5-ASA	was stable for at least 2 weeks prior to the screening endoscopy
oral corticosteroids	was stable for at least 2 weeks prior to the screening endoscopy
AZA, 6-MP, and methotrexate	was stable for at least 8 weeks prior to the screening endoscopy

Study Intervention(s) Administered

Regimen Group	Dosing (IV)	Description
300 mg mirikizumab Q4W	300 mg mirikizumab (15 mL vial; 20 mg/mL)	• Administered at Weeks 0, 4, and 8 for patients randomized to mirikizumab during the Induction Period.
Placebo Q4W	Placebo	• Administered at Weeks 0, 4, and 8 for patients randomized to placebo during the Induction Period.

Abbreviations: IV = intravenous; Q4W = every 4 weeks.

Intravenous infusion of mirikizumab or placebo were administered over at least 30 minutes. All subjects were monitored for 1 hour or longer after dosing, according to investigator practice or local standard of care.

Investigational product was prepared at the site by blinded pharmacists or other trained and qualified personnel as designated by the investigator. Investigational product was administered at the site by blinded nurse, pharmacist, or other trained and qualified personnel as designated by the investigator.

There was no rescue arm in Study AMAN. However, patients who complete Study AMAN through Week 12 (with an acceptable safety profile) who did not achieve a clinical response to mirikizumab at Week 12 may be eligible to receive an induction dose of mirikizumab in Study AMBG.

For the maintenance study AMBG

The treatments to which patients were randomised or assigned were dependent upon their clinical response at Visit 5 (Week 12) of induction Study AMAN.

Table AMBG.7.1 Treatment Regimens: Induction Clinical Responders

Regimen		Dose Weeks 0-8	Dose Weeks 12-40
Responders to blinded mirikizumab in induction study			
Randomized 2:1	Blinded 200 mg mirikizumab Q4W SC	Weeks 0, 4, 8	• Continue **blinded** 200 mg mirikizumab SC at Weeks 12, 16, 20, 24, 28, 32, 36 **Or, if LOR anytime between Weeks 12 and 28 (inclusive):** • Change to **open-label 300 mg mirikizumab IV Q4W** for 3 doses **If no clinical benefit after 3 doses of rescue IV induction with mirikizumab, then discontinue mirikizumab** **If clinical benefit, may proceed to Study AMAP**
	Blinded Placebo Q4W SC	Weeks 0, 4, 8	• Continue **blinded** placebo at Weeks 12, 16, 20, 24, 28, 32, 36 **Or, if LOR anytime between Weeks 12 and 28 (inclusive):** • Change to **open-label 300 mg mirikizumab IV Q4W** for 3 doses **If no clinical benefit after 3 doses of rescue IV induction with mirikizumab, then discontinue mirikizumab** **If clinical benefit, may proceed to Study AMAP**
Responders to blinded placebo in induction study			
Blinded Placebo Q4W SC		Weeks 0, 4, 8	• Continue **blinded** placebo at Weeks 12, 16, 20, 24, 28, 32, 36 **Or, if LOR anytime between Weeks 12 and 28 (inclusive):** • Change to **open-label 300 mg mirikizumab IV Q4W** for 3 doses **If no clinical benefit after 3 doses of rescue IV induction with mirikizumab, then discontinue mirikizumab** **If clinical benefit, may proceed to Study AMAP**

Abbreviations: IV = intravenous; LOR = loss of response (defined as ≥2-point increase from maintenance baseline in the combined SF + RB scores, AND combined SF + RB score of ≥4 on 2 consecutive visits, AND confirmed by endoscopic subscore of 2 or 3); OL = open-label; Q4W = every 4 weeks; RB = rectal bleeding; SC = subcutaneous; SF = stool frequency.

Table AMBG.7.2. Treatment Regimens: Induction Clinical Nonresponders

Regimen	Dose Weeks 0-8	Dose Weeks 12-40
Nonresponders to blinded mirikizumab IV in induction study		
Open-label 300 mg mirikizumab IV	Weeks 0, 4, 8	**Week 12 Extended Induction Responders** • Open-label 200 mg mirikizumab SC at Weeks 12, 16, 20, 24, 28, 32, 36; then may proceed to Study AMAP • If clinical benefit is lost, discontinue mirikizumab and enter post-treatment follow-up period **Week 12 Extended Induction Nonresponders:** • Discontinue mirikizumab
Nonresponders to blinded placebo in induction study		
Open-label 300 mg mirikizumab IV	Weeks 0, 4, 8	**Week 12 Extended Induction Responders** • Open-label 200 mg mirikizumab SC at Weeks 12, 16, 20, 24, 28, 32, 36; then may proceed to Study AMAP • If clinical benefit is lost, discontinue mirikizumab and enter post-treatment follow-up period **Week 12 Extended Induction Nonresponders:** • Discontinue mirikizumab

Abbreviations: IV = intravenous; SC = subcutaneous.

- **Objectives / Endpoints**

Induction study AMAN

Primary objective

The primary objective of Study AMAN was to test the hypothesis that mirikizumab is superior to placebo in inducing clinical remission at Week 12 in patients with moderately to severely active *UC*

Ranked secondary efficacy variables (as per SAP)

- Alternate Clinical remission at week 12
- Clinical response at week 12
- Endoscopic remission at week 12
- Symptomatic remission at week 12
- Clinical response in biologic failed population at week 12
- Histologic-Endoscopic mucosal improvement at week 12
- Bowel movement urgency at week 12
- Symptomatic remission at week 4 .

The corresponding endpoints were

Primary endpoint: Clinical remission based on the MMS defined as Stool frequency subscore=0 or SF=1 with a ≥1 point decrease from baseline and, Rectal bleeding (RB) SUBSCORE=0 and Endoscopic subscore (ES) =0 or 1 (Excluding friability).

Ranked secondary endpoints

- Alternate Clinical remission at week 12: based on the MMS defined as Stool frequency subscore=0 or SF=1 and, Rectal bleeding (RB) SUBSCORE=0 and Endoscopic subscore (ES) =0 or 1 (Excluding friability).
- Clinical response based on MMS 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 an RB score of 0 or 1.
- Endoscopic remission: ES=0 or 1 (Excluding friability).
- Symptomatic remission: SF=0 or SF=1 with a ≥1 point decrease from baseline and RB=0
- Clinical response in biologic failed population: 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 an RB score of 0 or 1.
- Histologic-Endoscopic mucosal improvement: Geboes scoring system with neutrophil infiltration in 5% of crypts, no crypt destruction and no erosions, ulcerations or granulation tissue and Endoscopic remission ES=0 or 1 (Excluding friability
- Bowel urgency: the change form baseline in urgency numeric rating scale score.
- Symptomatic remission at week 4: SF=0 or SF=1 with a ≥1 point decrease from baseline and RB=0

Maintenance study AMBG

Primary objective
The primary objective of Study AMBG was to test the hypothesis that mirikizumab is superior to placebo in achieving clinical remission at Week 40 among patients induced into Clinical Response with mirikizumab in Study AMAN

Ranked secondary efficacy variables

- Alternate clinical remission at Week 40 among patients induced into **clinical response** with mirikizumab in Study AMAN.
- Endoscopic remission at week 40
- Histologic-Endoscopic mucosal improvement plus absence of neutrophil at week 40
- Bowel movement urgency improve,ment at week 40
- Corticosteroid free remission at week 40
- Urgency NRS of 0 or 1 AT WEEK 40
- Clinical remission at week 40 among clinical remitters in AMAN at week 12

The corresponding endpoints were

Primary endpoint

The proportion of patients in *clinical remission* at Week 40, defined as:
SF subscore = 0, or SF = 1 with a ≥1-point decrease from induction baseline, and RB subscore = 0, and ES = 0 or 1 (excluding friability).

Secondary endpoints

- Alternate clinical remission at Week 40, defined asc: SF subscore = 0, or SF = 1, and RB subscore = 0, and ES = 0 or 1 (excluding friability).
- The proportion of patients in endoscopic remission at Week 40, defined as: ES = 0 or 1 (excluding friability)
- **Histologic remission** with resolution of mucosal neutrophils, defined using the Geboes scoring system with subscores of 0 for grades: 2b (lamina propria neutrophils), 3 (neutrophils in epithelium), 4 (crypt destruction), and 5 (erosion or ulceration) **Endoscopic remission,** defined as ES = 0 or 1 (excluding friability)
- The change from induction baseline in the Urgency Numeric Rating Scale scoree.
- Corticosteroid-free remission without surgery at Week 40, defined as: Clinical remission at Week 40, Symptomatic remission at Week 28, and No corticosteroid use for ≥12 weeks prior to Week 40.
- The proportion of patients with Urgency Remission at Week 40, defined as: Urgency NRS = 0 or 1.
- The proportion of patients who were in *clinical remission* at Week 40 among patients in clinical remission at Week 12 in Study AMAN, with clinical remission is defined as: SF subscore = 0 or SF = 1 with a ≥1-point decrease from induction baseline, an RB subscore = 0, and ES = 0 or 1 (excluding friability).

Additional endpoints included (not controlled). health outcome endpoints, Effects on fatigue, abdominal pain, biomarkers CRP, Faecal calprotectin. symptomatic remission, symptomatic response

rates with rescue mirikizumab IV therapy in patients who loss of response, proportion of patients undergoing surgery for UC, colectomy, and hospitalisation for UC. (+ many others).

- **Sample size**

The applicant assumed that 90% of patients complete Study AMAN (which is expected to randomise approximately 1160 patients), anticipated that approximately 1044 patients will enrol in Study AMBG.

It was expected that approximately 459 of these patients would enter Study AMBG as clinical responders to mirikizumab and then will be randomised 2:1 to 200 mg mirikizumab SC (306 patients) and placebo (153 patients). Among the approximately 459 mirikizumab clinical responders, approximately 169 mirikizumab clinical remitters will be randomised to 200 mg mirikizumab SC (113 patients) and placebo (56 patients).

This assumed that:

The induction study (AMAN, which has a mixed population with approximately 60% biologic-failed patients) is expected to have an overall clinical remission rate of 21.6% and response rate of 58.6% with mirikizumab.

75% of induction patients receive treatment with mirikizumab, based on a 3:1 randomisation ratio for the induction study.

10% dropout rate from induction to maintenance.

The primary endpoint, maintenance of clinical remission, was to be assessed on patients who achieved remission to mirikizumab induction treatment. Assuming mirikizumab and placebo maintenance of clinical remission rates of 58.4% and 23.6%, respectively (biologic-failed patients: 44% and 13%; conventional-failed patients: 70% and 32%), this study based on the 169 mirikizumab induction remitters is expected to have >90% power to demonstrate that mirikizumab is superior to placebo by using a chi-square test with a 2-sided 0.05 significance level. This sample size also provides 80% power to evaluate clinical remission among induction remitters in the subgroup of biologic-failed patients. In addition, 459 mirikizumab induction clinical responders are expected to provide adequate power (>80%) to demonstrate that mirikizumab is superior to placebo for the major secondary endpoints (clinical remission, endoscopic remission, or corticosteroid-free remission) at Week 40, among responders to mirikizumab induction treatment by using a chi-square test with a 2-sided 0.05 significant level.

- **Randomisation and Blinding (masking)**

Study AMAN:

Eligible patients were randomly assigned in a 3:1 ratio to receive blinded IV administration of 300 mg mirikizumab or placebo Q4W.

Stratification factors AMAN

- Biologic- or JAKi-failed status
- Baseline corticosteroid use
- Baseline disease activity, and
- Region (North America, Europe, or Other).

Study AMBG

Mirikizumab clinical responders in Study AMAN were randomly assigned in Study AMBG to either continue receiving mirikizumab or be withdrawn from mirikizumab treatment (randomly assigned to placebo).

Patients treated with placebo in Study AMAN who met the endpoint of clinical response at Week 12 of Study AMAN remained in Study AMBG on blinded placebo SC Q4W.

Patients treated with either mirikizumab or placebo in Study AMAN who did not achieve clinical response at Week 12 of Study AMAN received open-label 300 mg mirikizumab IV Q4W for 3 doses in Study AMBG.

Stratification factors

- Biologic- or JAKi-failed status
- Baseline corticosteroid use
- Induction remission status, and Region (North America, Europe, or Other).

Interim safety analyses were conducted by an external DMC to review unblinded safety data and recommend changes to the study design if deemed necessary. Blinded study team was not involved in DMC data reviews or deliberations. DMC, histology, and endoscopy charters are on file.

Both AMAN and AMBG

According to the protocols,

Patients were randomised by an interactive web response system (IWRS) in a double blind manner.

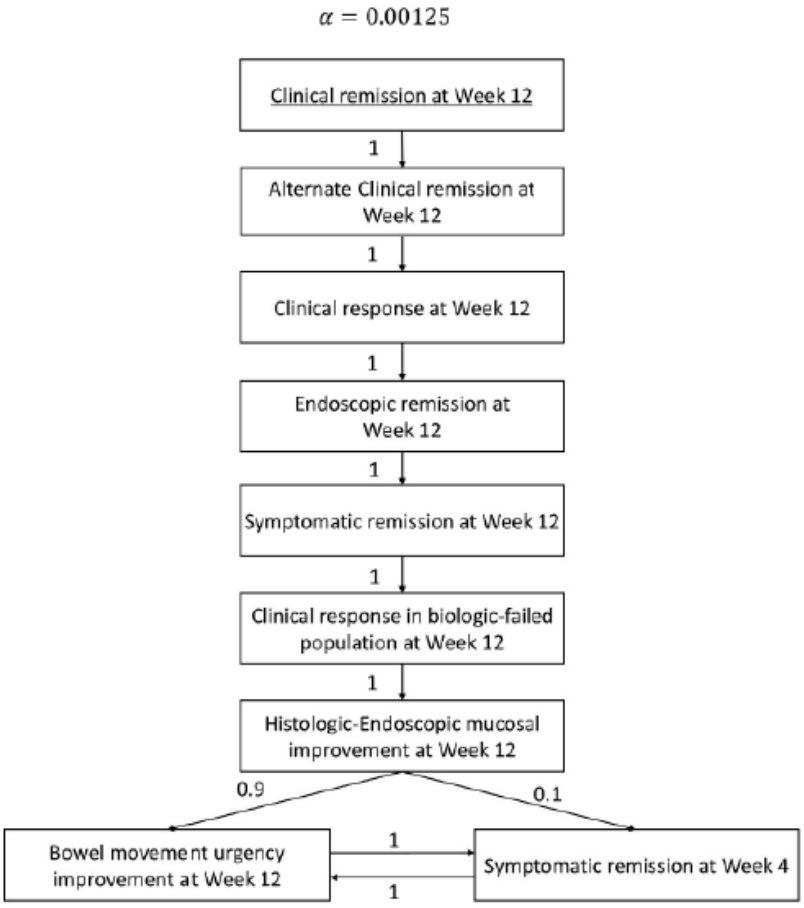
Investigational product will be prepared at the site by blinded pharmacists or other trained and qualified personnel as designated by the investigator. Investigational product will be administered at the site by a blinded nurse, pharmacist, or other trained and qualified personnel as designated by the investigator.

Mirikizumab could not be distinguished visually from placebo.

- **Statistical methods**

For both induction and maintenance trials, the statistical methods were appropriate. The populations for analyses were mITT; for both AMAN and AMBG: All randomised patients who received any amount of study treatment excluding patients impacted by the eCOA transcription error in Poland and Turkey (regardless, if the patient does not receive the correct treatment, or otherwise does not follow the protocol);

The statistical analyses methods for the primary efficacy endpoints were based on CMH tests, which are appropriate. Secondary endpoint analyses included the use of MMRM methods which required justification in terms of the missing at random assumptions. In Study AMAN, the family-wise type 1 error rates were controlled at a 2-sided alpha level of .00125 for the primary and all major secondary endpoints. The rationale for this alpha level was to demonstrate substantial evidence for the efficacy of mirikizumab within the single induction trial design. The graphical testing scheme for Study AMAN is presented.

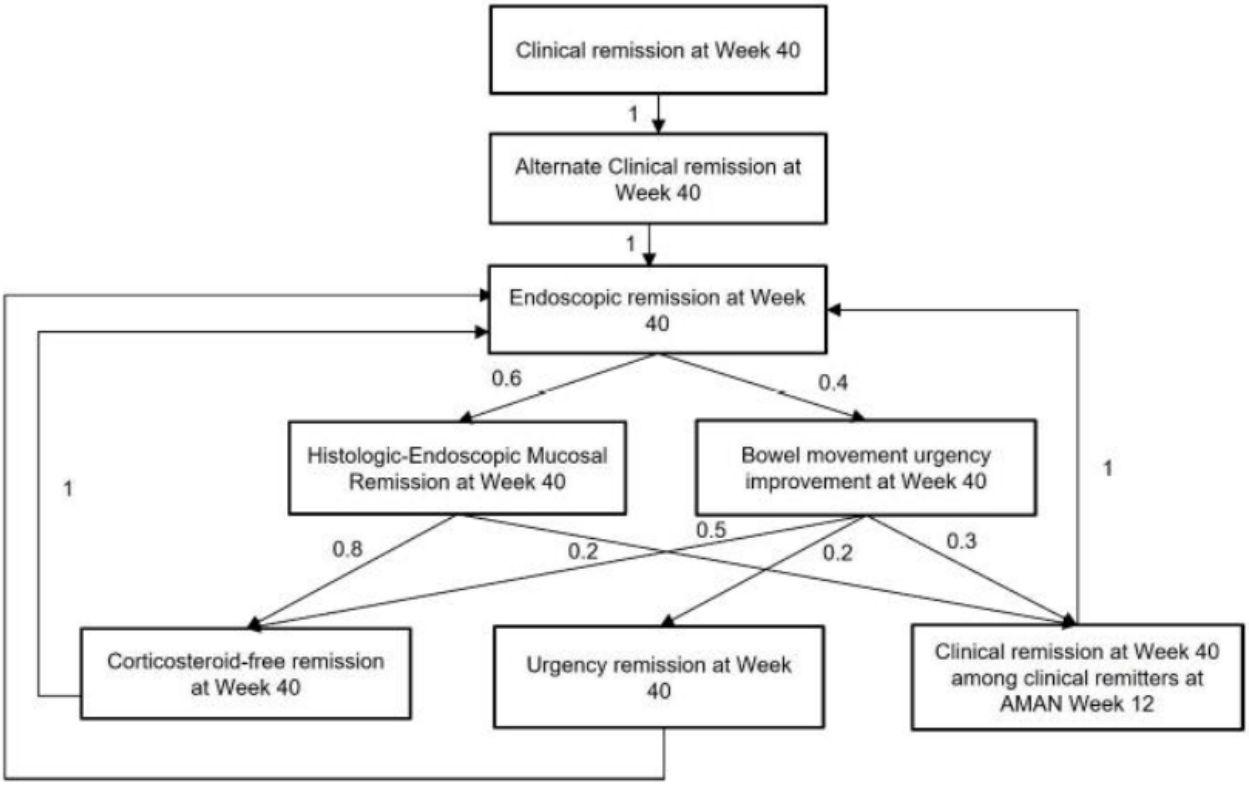


Note: The underlined endpoint is the primary endpoint.

Figure 2.7.3.6. Graphical scheme to control the overall type 1 error rate for Study AMAN.

Study AMBG

In Study AMBG, the family-wise type 1 error rates were controlled at a 2-sided alpha level of .05 for the primary and all major secondary endpoints. The graphical testing scheme for Study AMBG is presented.

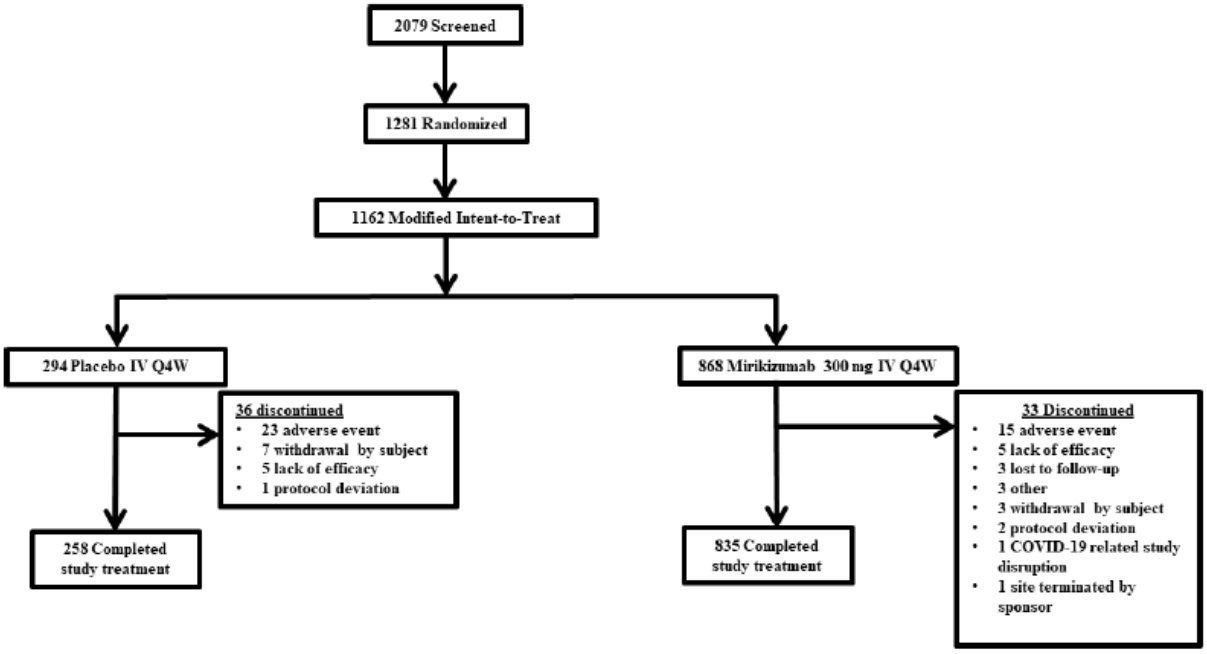


Note: The endpoints "Histologic-Endoscopic Mucosal Remission" and "Urgency Remission" are called "Histo-Endoscopic Mucosal Remission" and "Bowel Urgency Remission (Urgency NRS 0 or 1)," respectively, throughout this document.

Results

- **Participant flow**

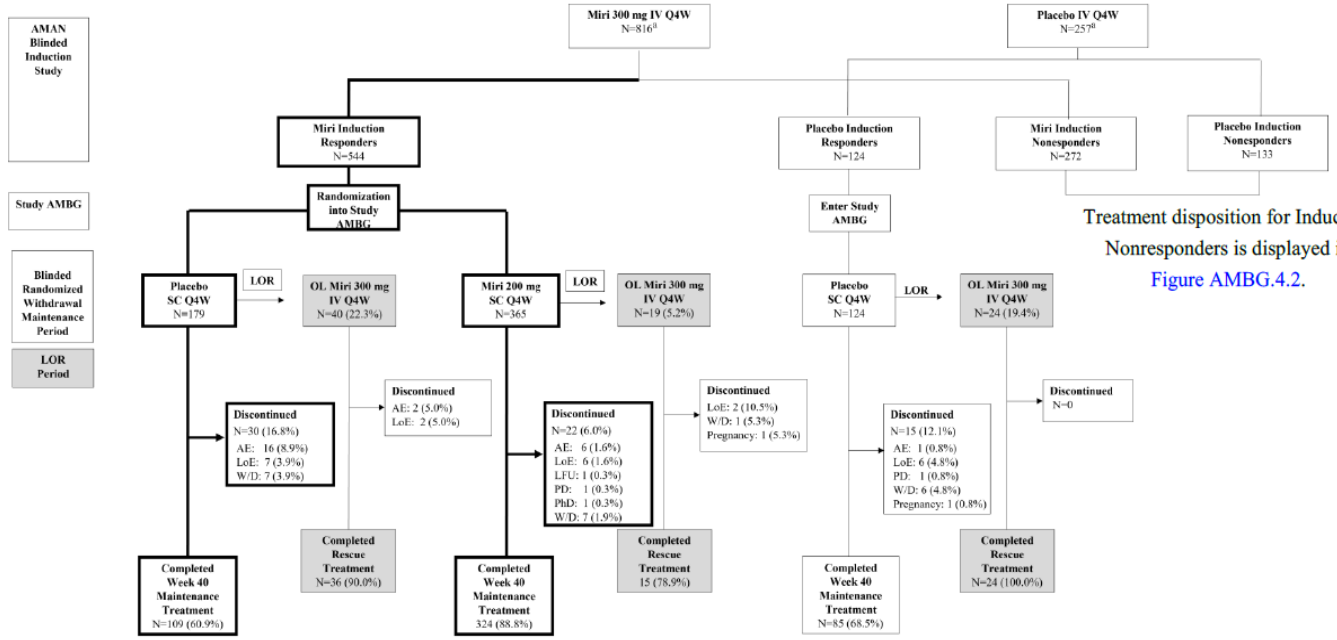
Study AMAN



Abbreviations: COVID-19 = Coronavirus Disease 2019; IV = intravenous; ITT = =intent-to-treat; Q4W = every 4 weeks.
Source: Table AMAN.8.1.

Figure AMAN.4.1. Study participant disposition figure modified ITT population.

Study AMBG



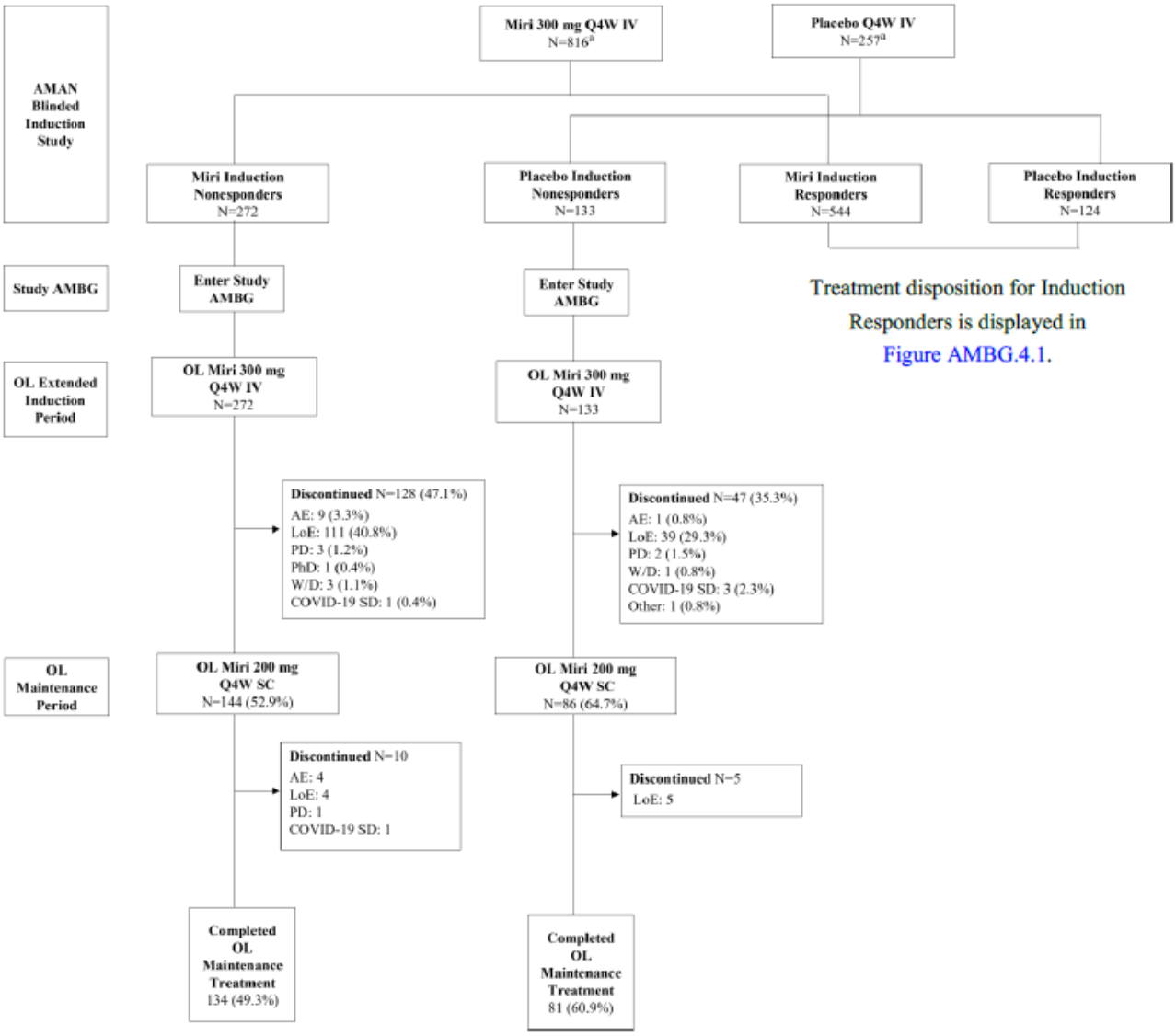
Abbreviations: AE = adverse event; IV = intravenous; Miri = mirikizumab; LFU = lost to follow up; LoE = lack of efficacy; LOR = loss of response; N = number of patients in the analysis population; n = number of patients in the specified category; PhD = physician decision; PD = protocol deviation; Q4W = every 4 weeks; SC = subcutaneous; W/D = withdrawal by subject.

a Patient numbers reflect only patients who entered into Study AMBG.

Note: Bolded lines highlight the re-randomized mirikizumab induction responders.

Source: Table AMBG.8.1.

Figure AMBG.4.1. Treatment disposition: placebo and mirikizumab induction responders, mITT population.



Abbreviations: AE = adverse event; COVID-19 = Coronavirus Disease 2019; IV = intravenous; Miri = mirikizumab; LFU = lost to follow up; LoE = lack of efficacy; N = number of patients in the analysis population; n = number of patients in the specified category; PhD = physician decision; PD = protocol deviation; Q4W = every 4 weeks; SC = subcutaneous; SD = study disruption; W/D = withdrawal by subject.

a Patient numbers reflect only patients who entered into Study AMBG.

Source: Table AMBG.8.1.

Figure AMBG.4.2. Treatment disposition: placebo and mirikizumab induction nonresponders, mITT population.

Recruitment

Study AMAN:

Study Initiation Date: 18 June 2018 first participant first visit

Study Completion Date: 21 January 2021 last participant last visit

The analyses presented in this report are based on a database lock date of 11 June 2021

Study AMBG:

Study Initiation Date: 19 October 2018 first participant first visit

Study Completion: 03 November 2021 last participant last visit date

The analyses presented in this report are based on a primary outcome database lock date of 06 December 2021

- **Conduct of the study**

The applicant states that the studies were in accordance with ICH GCP requirements.

Study AMAN was inspected

Study Identifier	Site of Inspection	Date of Inspection	Regulatory Authority That Conducted Inspection
I6T-MC-AMAN	Jilin Central General Hospital – Wang	24 Nov 2021 to 25 Nov 2021	China - Jilin FDA
I6T-MC-AMAN	Hôpital Beaujon – Treton	17 Dec 2019 to 19 Dec 2019	France - Regulatory Agency of France (ANSM)
I6T-MC-AMAN	Studiengesellschaft BSF GmbH – Fechner	10 Nov 2020 to 11 Nov 2020	Germany - Landesverwaltungsamt Sachsen-Anhalt

Study AMBG was also inspected

Study Identifier	Site of Inspection	Date of Inspection	Regulatory Authority That Conducted Inspection
I6T-MC-AMBG	Universitair Ziekenhuis Gasthuisberg - Ferrante	09 Jun 2021 to 11 Jun 2021	Belgium - Belgium Federal Agency for Medicines and Health Products (FAGG)

Protocol amendments:

Analysis considerations related to COVID-19 mitigations used in Studies AMAN and AMBG are presented.

Analysis Considerations for Efficacy Analyses Related to COVID-19 Mitigations

COVID-19 Mitigation	Efficacy Analysis	Study Affected	Analysis Consideration
An extended window for endoscopy	• Primary endpoint, and • Key secondary endpoints	Study AMAN Study AMBG	• Sensitivity analysis using mNRI to impute out of window endoscopies were implemented. • Sensitivity analysis using PP population was implemented.
Missing endoscopies	• Primary endpoint, and • Key secondary endpoints	Study AMBG	• Missing endoscopies were treated as nonresponders. • Sensitivity analysis using mNRI to impute out of window endoscopies were implemented. • Sensitivity analysis using PP population was implemented.
Other	• Primary endpoint, and • Key secondary endpoints	Study AMAN Study AMBG	• Efficacy analysis in the PP population.

Abbreviations: COVID-19 = coronavirus disease 2019; mNRI = modified nonresponder imputation; PP = per-protocol.

Description and impact of eCOA transcription error

Studies AMAN and AMBG used an eCOA device to record the PRO measures of SF and RB.

When the study was ongoing, the applicant noted that in Study AMAN the eCOA devices for patient daily diary assessment of RB and SF Mayo subscores initially contained errors in the wording in

answers to questions for patients in Poland and Turkey, respectively. RB scores in Poland and SF scores in Turkey in Study AMAN were therefore not accurately reported by patients on the eCOA devices.

Data from patients who were randomly assigned to Study AMAN on the basis of these erroneous entries could not be accurately used in the study as baseline assessment of these PROs as well as for assessment of efficacy postbaseline. These impacted patients in Poland and Turkey were excluded from primary efficacy analyses (but included in safety analyses).

The applicant considered these eCOA errors as important protocol deviations and they are reported in the Study AMAN CSR and Study AMBG CSR.

Addressing the eCOA transcription error

The applicant originally intended to randomly assign 1160 patients in study AMAN. To compensate for the 118 patients lost to the eCOA transcription error, additional patients were randomly assigned so that study power was maintained. Lilly aimed to enrol an additional 118 patients. A total of 121 additional patients were actually enrolled.

Data from patients impacted by the eCOA transcription error were excluded from the primary efficacy analysis but included in the primary safety analysis. The impact of removing these patients was assessed in a sensitivity analysis.

- **Baseline data**

Study AMAN

Overall, at baseline of study AMAN, patients in the mITT population had a mean (SD) age of 42.5 (13.9) years and were more likely to be male (59.8%). The majority of patients were White. Mean (SD) duration of disease was 7.1 (6.8) years, and 38.2% of patients had a disease duration of 7 years or more. Patients had a mean (SD) MMS of 6.5 (1.3), with 53.2% of patients in the severe disease category (MMS 7 to 9) and 66.7% had severe UC, defined by an Mayo ES of 3.

Demographic and disease characteristics were well balanced across treatment groups.

Summary of Demographic Characteristics, mITT Population, Study AMAN

		PBO IV Q4W (N = 294)	Miri 300 mg IV Q4W (N = 868)	Total (N = 1162)
Continuous Variables, mean (SD)				
Age (years)		41.3 (13.81)	42.9 (13.94)	42.5 (13.92)
Weight (kg)		70.9 (16.75)	72.6 (17.26)	72.1 (17.14)
BMI (kg/m^2)		24.5 (5.05)	25.0 (5.39)	24.9 (5.31)
Categorical Variables, n (%)				
Sex	Female	129 (43.9)	338 (38.9)	467 (40.2)
	Male	165 (56.1)	530 (61.1)	695 (59.8)
Race	White	219 (74.7)	614 (71.5)	833 (72.3)
	Asian	68 (23.2)	223 (26.0)	291 (25.3)
	Other[a]	6 (2.0)	22 (2.6)	28 (2.4)
Ethnicity[b]	Hispanic/Latino	9 (25.0)	22 (19.1)	31 (20.5)
	Non-Hispanic, non-Latino	27 (75.0)	92 (80.0)	119 (78.8)

	PBO IV Q4W (N = 294)	Miri 300 mg IV Q4W (N = 868)	Total (N = 1162)
Continuous Variables			
MMS, mean (SD)	6.5 (1.27)	6.5 (1.32)	6.5 (1.31)
Duration of UC (years), mean (SD)	6.9 (6.95)	7.2 (6.75)	7.1 (6.80)
Urgency NRS, mean (SD)	6.2 (2.22)	6.1 (2.16)	6.2 (2.18)
Abdominal Pain NRS, mean (SD)	5.1 (2.54)	4.9 (2.41)	5.0 (2.44)
CRP (mg/L), median (range)	4.2 (0, 173)	4.1 (0, 150)	4.1 (0, 173)
Fecal calprotectin (μg/g), median (range)	1472 (15, 31 680)	1559 (15, 31 680)	1524 (15, 31 680)
Categorical Variables, n (%)			
MMS 7-9 (severe UC)	155 (52.9)	463 (53.3)	618 (53.2)
ES 3 (severe disease)	200 (68.3)	574 (66.1)	774 (66.7)
Left-sided colitis	188 (64.2)	544 (62.7)	732 (63.0)
Prior biologic or JAKi failure	118 (40.1)	361 (41.6)	479 (41.2)
Baseline corticosteroid use	113 (38.4)	351 (40.4)	464 (39.9)
Baseline immunomodulator use	69 (23.5)	211 (24.3)	280 (24.1)

Abbreviations: CRP = C-reactive protein; ES = endoscopic subscore; IV = intravenous; JAKi = Janus kinase inhibitor; Miri = mirikizumab; mITT = modified intent-to-treat; MMS = modified Mayo score; n = number of patients in the specified category; N = number of patients in the mITT population; NRS = numeric rating scale; PBO = placebo; Q4W = every 4 weeks; UC = ulcerative colitis.

Disposition

Of the mITT population, 258 (87.8%) in the placebo group and 835 (96.2%) in the mirikizumab group completed the study. The most frequently stated reason for study discontinuation was due to AE in both placebo (n = 23; 7.8%) and mirikizumab (n = 15; 1.7%) groups.

Study AMBG

The mITT population comprised 1073 patients.

Of the 1073 patients, 544 were responders to mirikizumab induction, the cohort evaluated for the primary and major secondary objectives. Of these 544 responders to mirikizumab induction, 35% of patients had failed 1 or more prior biologic or JAKi therapy.

In the mITT population of Study AMBG who responded to mirikizumab during Study AMAN, patients had a mean (SD) age of 42.7 (13.8) years (at Week 0 of Study AMAN) and were more likely to be male (58.5%). The majority of patients were White

Mean (SD) duration of disease at Week 0 of Study AMAN was 6.8 (6.6) years, and 36.0% of patients had a disease duration of 7 years or more. Patients had a mean (SD) MMS at Week 0 of Study AMAN of 6.5 (1.3), with 52.6% of patients in the severe disease category (MMS 7 to 9) and 62.7% had severe UC, defined by a Mayo ES of 3.

Summary of Demographics, mITT Population, Study AMBG

		Induction Study Responders				Induction Study Nonresponders	
		Induction Study Miri			Induction Study PBO	Induction Study Miri	Induction Study PBO
Parameter		Maintenance PBO SC (N = 179)	Maintenance Miri 200 mg SC (N = 365)	Maintenance Total (N = 544)	Maintenance PBO SC (N = 124)	Miri 300 mg IV (N = 272)	Miri 300 mg IV (N = 133)
Continuous Variables, mean (SD)							
Age (years)		41.2 (12.80)	43.4 (14.22)	42.7 (13.80)	40.8 (13.43)	44.0 (14.23)	42.0 (13.76)
Weight (kg)		72.4 (17.20)	71.8 (17.29)	72.0 (17.24)	71.0 (18.17)	73.9 (17.18)	71.9 (15.47)
BMI (kg/m^2)		24.8 (5.18)	24.9 (5.39)	24.8 (5.32)	24.6 (5.29)	25.2 (5.23)	24.7 (4.88)
Categorical Variables, n (%)							
Sex	Female	75 (41.9)	151 (41.4)	226 (41.5)	57 (46.0)	90 (33.1)	55 (41.4)
	Male	104 (58.1)	214 (58.6)	318 (58.5)	67 (54.0)	182 (66.9)	78 (58.6)
Race	White	125 (70.6)	261 (71.9)	386 (71.5)	92 (74.2)	200 (74.3)	102 (77.3)
	Asian	51 (28.8)	93 (25.6)	144 (26.7)	28 (22.6)	59 (21.9)	28 (21.2)
	Other	1 (0.6)	9 (2.5)	10 (1.9)	4 (3.2)	10 (3.7)	2 (1.5)
Ethnicity[a]	Hispanic/Latino	2 (9.5)	12 (26.7)	14 (21.2)	2 (20.0)	4 (9.8)	7 (30.4)
	Non-Hispanic, non-Latino	18 (85.7)	33 (73.3)	51(77.3)	8 (80.0)	37 (90.2)	16 (69.6)

	Induction Study Responders				Induction Study Nonresponders	
	Induction Study Miri			Induction Study PBO	Induction Study Miri	Induction Study PBO
Parameter	Maintenance PBO SC (N = 179)	Maintenance Miri 200 mg SC (N = 365)	Maintenance Total (N = 544)	Maintenance PBO SC (N = 124)	Miri 300 mg IV (N = 272)	Miri 300 mg IV (N = 133)
Continuous Variables						
MMS, mean (SD)	6.6 (1.24)	6.5 (1.33)	6.5 (1.30)	6.5 (1.27)	6.5 (1.38)	6.3 (1.33)
Duration of UC (years), mean (SD)	6.7 (5.61)	6.9 (7.10)	6.8 (6.64)	6.1 (5.83)	7.6 (6.80)	7.5 (7.86)
Urgency NRS, mean (SD)	6.2 (1.91)	6.0 (2.23)	6.1 (2.13)	6.4 (2.04)	6.2 (2.19)	6.0 (2.37)
Abdominal Pain NRS, mean (SD)	5.3 (2.15)	4.9 (2.44)	5.0 (2.36)	5.5 (2.36)	4.7 (2.53)	4.9 (2.67)
CRP (mg/L), median (range)	3.0 (0, 150)	3.8 (0, 120)	3.6 (0, 150)	3.7 (0, 173)	5.5 (0, 80)	4.3 (0, 68)
Fecal calprotectin (µg/g), median (range)	1750 (15, 31680)	1482 (15, 31680)	1565 (15, 31680)	1164 (15, 18954)	1546 (15, 31680)	1540 (69, 31680)
Categorical Variables, n (%)						
MMS 7-9 (severe UC)	102 (57.0)	184 (50.4)	286 (52.6)	58 (46.8)	154 (56.6)	70 (52.6)
ES 3 (severe disease)	106 (59.2)	235 (64.4)	341 (62.7)	74 (59.7)	197 (72.4)	97 (72.9)
Left-sided colitis	119 (66.5)	234 (64.1)	353 (64.9)	85 (68.5)	154 (56.6)	90 (67.7)
Prior biologic or JAKi failure	64 (35.8)	128 (35.1)	192 (35.3)	35 (28.2)	147 (54.0)	61 (45.9)
Baseline corticosteroid use	68 (38.0)	135 (37.0)	203 (37.3)	53 (42.7)	118 (43.4)	46 (34.6)
Baseline immunomodulator use	39 (21.8)	78 (21.4)	117 (21.5)	31 (25.0)	77 (28.3)	33 (24.8)

Abbreviations: CRP = C-reactive protein; ES = endoscopic subscore; IV = intravenous; JAKi = Janus kinase inhibitor; Miri = mirikizumab; mITT= modified intent-to-treat; MMS = modified Mayo score; n = number of patients in the specified category; N = number of patients in the mITT population; NRS = numeric rating scale; PBO = placebo; SC = subcutaneous; SD = standard deviation; UC = ulcerative colitis.

Note: Patients who responded to mirikizumab in Study AMAN are the cohort used for the primary and major secondary objectives. These groups are marked in **bold**.

Source: t_dm_sum_mitt.rtf

Disposition *Overall study population*

Of the 1073 patients from the mITT population who entered Study AMBG (257 [87.4%] from AMAN placebo group and 816 [94.0%] from AMAN mirikizumab group),

544 (50.7%) had been Week 12 responders to mirikizumab in Study AMAN, and 124 (11.6%) had been Week 12 responders to placebo in Study AMAN.

272 (25.3%) had been Week 12 non-responders to mirikizumab in Study AMAN, and 133 (12.4%) had been Week 12 non-responders to placebo in Study AMAN.

- **Numbers analysed**

Study AMAN

Population	Description	Number of Patients
Screening Population	**Definition:** All patients who signed informed consent. **Purpose:** Used for disposition analysis.	2079
Modified Intent-to-Treat (mITT) Population	**Definition:** All randomized patients who received any amount of study treatment, excluding patients impacted by the eCOA transcription error in Poland and Turkey (regardless of whether the patient did not receive the correct treatment, or otherwise did not follow the protocol). **Purpose:** Used for efficacy and health outcomes analysis.	1162
Safety Population	**Definition:** All randomized patients who received any amount of study treatment (regardless of whether the patient did not receive the correct treatment, or otherwise did not follow the protocol). **Purpose:** Used for safety-related analysis.	1279
Intent-to-Treat (ITT) Population	**Definition:** All randomized patients. Patients will be analyzed according to the treatment to which they were assigned. **Purpose:** Used for sensitivity analysis for the primary and major secondary efficacy endpoints.	1281
Per-Protocol Population (PP)	**Definition:** All mITT patients who are not deemed noncompliant with treatment, who do not have significant protocol deviations, and whose investigator site does not have significant GCP deviations that require a report to regulatory agencies (regardless of study period). **Purpose:** Used for sensitivity analysis for the primary and major secondary efficacy endpoints.	955

Abbreviations: eCOA = electronic clinical outcome assessment; GCP = good clinical practice.

Study AMBG

Table AMBG.4.1. Number of Patients in Each Analysis Population

Population	Number of patients
All entered patients	1178
Modified Intent-to-treat (mITT) Population	1073
Safety Population	1177
Intent-to-treat (ITT) Population	1177
Per-protocol (PP) Population	897

Source: Table AMBG.8.1.

- **Outcomes and estimation**

Results of Primary and Major Secondary Endpoints Modified Intent-to-Treat Population Study I6T-MC-AMAN

	PBO IV Q4W (N = 294)	Miri 300 mg IV Q4W (N = 868)	P-value
Clinical Remission at Week 12 (Primary Endpoint)[a]			
Response, n (%)	39 (13.3)	210 (24.2)	
Common Risk Difference (99.875% CI)[b]	11.1 (3.2, 19.1)		.00006
Alternate Clinical Remission at Week 12 (Major Secondary Endpoint)[c]			
Response, n (%)	43 (14.6)	222 (25.6)	
Common Risk Difference (99.875% CI)[b]	11.1 (3.0, 19.3)		.00007
Clinical Response at Week 12 (Major Secondary Endpoint)[d]			
Response, n (%)	124 (42.2)	551 (63.5)	
Common Risk Difference (99.875% CI)[b]	21.4 (10.8, 32.0)		<.00001
Endoscopic Improvement at Week 12 (Major Secondary Endpoint)[e]			
Response, n (%)	62 (21.1)	315 (36.3)	
Common Risk Difference (99.875% CI)[b]	15.4 (6.3, 24.5)		<.00001
Symptomatic Remission at Week 4 (Major Secondary Endpoint)[f]			
Response, n (%)	38 (12.9)	189 (21.8)	
Common Risk Difference (99.875% CI)[b]	9.2 (1.4, 16.9)		.00064
Symptomatic Remission at Week 12 (Major Secondary Endpoint)[f]			
Response, n (%)	82 (27.9)	395 (45.5)	
Common Risk Difference (99.875% CI)[b]	17.5 (7.5, 27.6)		<.00001
Clinical Response at Week 12 in Patients Who Failed Biologic or JAKi Therapy for UC (Major Secondary Endpoint)[d]			
Response, n/N (%)	35/118 (29.7)	197/361 (54.6)	
Common Risk Difference (99.875% CI)[b]	25.0 (9.0, 41.1)		<.00001
Histo-Endoscopic Mucosal Improvement at Week 12 (Major Secondary Endpoint)[g]			
Response, n (%)	41 (13.9)	235 (27.1)	
Common Risk Difference (99.875% CI)[b]	13.4 (5.5, 21.4)		<.00001
Bowel Urgency Severity at Week 12 (Major Secondary Endpoint)[h]			
LSM Change from Baseline (SE)	-1.63 (0.141)	-2.59 (0.083)	
LSM Difference (99.875% CI)	-0.95 (-1.47, -0.44)		<.00001

Mirikizumab demonstrated clinically meaningful efficacy across clinical, symptomatic, and endoscopic endpoints both in patients who were naive to biologic and JAKi therapy, and in patients who had failed at least 1 biologic or JAKi therapy.

Health-Related Quality of Life

<u>IBDQ total score</u>

Patients enrolled in the Phase 3 mirikizumab UC programme had a mean IBDQ total baseline score of 130.5 out of 224, indicating substantial impact on the 4 domains of bowel symptoms, systemic symptoms, emotional function, and social function.

Patients in the mirikizumab treatment group showed a nominally significantly greater LSM improvement in IBDQ total score at Week 12 compared with the placebo group: 38.4 in the mirikizumab group compared with 25.2 in the placebo group (LSM difference = 13.2; p<.001).

At Week 12, over half of the total number of patients treated with mirikizumab (57.5%) achieved IBDQ remission. In comparison, only 39.8% of patients in the placebo group achieved IBDQ remission (common risk difference = 18.1%; p<.001).

EQ-5D-5L VAS score

Patients in the mirikizumab treatment group showed a nominally significantly greater LSM improvement in EQ-5D-5L score at Week 12, compared with the placebo group: 14.6 in the mirikizumab group compared with 9.4 in the placebo group (LSM difference = 5.2; p<.001).

C-reactive protein in all mITT patients

Patients enrolled in the Phase 3 mirikizumab UC programme had mean and median CRP levels at baseline of 9.4 mg/L and 4.1 mg/L, respectively.

Patients in the mirikizumab treatment group showed a nominally significantly greater LSM reduction in CRP from baseline at Week 12 compared with the placebo group: -4.6 mg/L in the mirikizumab group compared with -0.9 mg/L in the placebo group (LSM difference = -3.7; p<.001)

Fecal calprotectin in mITT patients with a baseline value over 250 mg/kg

Among patients with a baseline fecal calprotectin level over 250 mg/kg, a post hoc analysis noted that 34.3% of those in the mirikizumab group had a fecal calprotectin level at Week 12 of 250 mg/kg or less, compared with 20.1% in the placebo group (common risk difference = 14.6%; p<.001)

Study AMBG

Results of Primary and Major Secondary Endpoints Modified Intent-to-Treat Population – Mirikizumab Induction Responders Study I6T-MC-AMBG.

	PBO SC Q4W (N = 179)	Miri 200 mg SC Q4W (N = 365)	P-value
Clinical Remission at (Primary Endpoint) Week 40 in Patients who had achieved Clinical Response with mirikizumab in Study AMAN (Primary Endpoint)[a]			
Response, n (%)	45 (25.1)	182 (49.9)	
Common Risk Difference (95% CI)[b]	23.2 (15.2, 31.2)		<.001
Alternate Clinical Remission at Week 40 in Patients who had achieved Clinical Response with mirikizumab in Study AMAN (Major Secondary Endpoint)[c]			
Response, n (%)	47 (26.3)	189 (51.8)	
Common Risk Difference (95% CI)[b]	24.1 (16.0, 32.2)		<.001
Clinical Remission at Week 40 in Patients who had Achieved Clinical Remission with mirikizumab in Study AMAN (Major Secondary Endpoint)[a]			
Response, n/N (%)	24/65 (36.9)	91/143 (63.6)	
Common Risk Difference (95% CI)[b]	24.8 (10.4, 39.2)		<.001
Endoscopic Improvement at Week 40 in Patients who had Achieved Clinical Response with mirikizumab in Study AMAN (Major Secondary Endpoint)[d]			
Response, n (%)	52 (29.1)	214 (58.6)	
Common Risk Difference (95% CI)[b]	28.5 (20.2, 36.8)		<.001
Corticosteroid-Free Remission Without Surgery at Week 40 in Patients who had Achieved Clinical Response with mirikizumab in Study AMAN (Major Secondary Endpoint)[e]			
Response, n (%)	39 (21.8)	164 (44.9)	
Common Risk Difference (95% CI)[b]	21.3 (13.5, 29.1)		<.001
Histo-Endoscopic Mucosal Remission at Week 40 in Patients who had Achieved Clinical Response with mirikizumab in Study AMAN (Major Secondary Endpoint)[f]			
Response, n (%)	39 (21.8)	158 (43.3)	
Common Risk Difference (95% CI)[b]	19.9 (12.1, 27.6)		<.001
Bowel Urgency Severity at Week 40 in Patients who had Achieved Clinical Response with mirikizumab in Study AMAN (Major Secondary Endpoint)[g]			
LSM Change from Baseline (SE)	-2.74 (0.202)	-3.80 (0.139)	
LSM Difference (95% CI)	-1.06 (-1.51, -0.61)		<.001
Bowel Urgency Remission (Urgency NRS 0 or 1) at Week 40 in Patients who had Achieved Clinical Response with mirikizumab in Study AMAN and an Urgency NRS ≥ 3 at Study AMAN Baseline (Major Secondary Endpoint)			
Response, n/N (%)	43/172 (25.0)	144/336 (42.9)	
Common Risk Difference (95% CI)[b]	18.1 (9.8, 26.4)		<.001

Health-Related Quality of Life

IBDQ total score

At Week 40 of Study AMBG, patients in the mirikizumab treatment group who responded to mirikizumab in Study AMAN sustained a nominally significantly greater LSM improvement from Week 0 of Study AMAN on the IBDQ total score compared with the placebo group: 49.8 in the mirikizumab group compared with 24.5 in the group of patients withdrawn from mirikizumab treatment (LSM difference = 25.2; p<.001).

At Week 40 of the study, 72.3% of patients in the mirikizumab group responded to mirikizumab in Study AMAN compared with 43.0% in the placebo group who achieved IBDQ remission (common risk difference = 28.5%; p<.001)

EQ-5D-5L VAS score

Patients in the mirikizumab treatment group who responded to mirikizumab in Study AMAN showed a nominally significantly greater LSM improvement in EQ-5D-5L VAS score from Week 0 of Study AMAN at Week 40 of Study AMBG, compared with the placebo group: 20.1 in the mirikizumab group compared with 8.8 in the placebo group (LSM difference = 11.3; p<.001)

C-reactive protein in all mITT patients

At Week 40 of Study AMBG, patients in the mirikizumab treatment group who responded to mirikizumab in Study AMAN showed a nominally significantly greater LSM reduction in CRP from baseline (Week 0 of Study AMAN), compared with patients who were randomly assigned to withdrawal from mirikizumab (randomly assigned to placebo) at Week 0 of Study AMBG: - 4.7 mg/L in the mirikizumab group compared with -1.4 mg/L in the placebo group (LSM difference = -3.3; p<.001)

Fecal calprotectin in mITT patients with a baseline value over 250 mg/kg

Among patients with a fecal calprotectin level over 250 mg/kg at baseline of Study AMAN, a post hoc analysis noted that 50.7% of those in the mirikizumab group had a fecal calprotectin level at Week 40 of Study AMBG of 250 mg/kg or less, compared with 19.3% in the placebo group who were randomly assigned to withdrawal from mirikizumab (randomly assigned to placebo) at Week 0 of Study AMBG (common risk difference = 29.1%; p<.001)

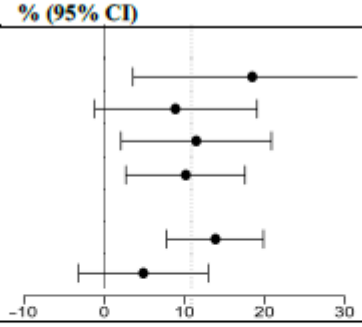
- **Ancillary analyses**

Baseline Demographic and Disease Characteristics Subgroups

Clinical Remission for Study AMAN by Select Demographic and Baseline Disease Characteristics Subgroups Modified Intent-to-Treat Population Study I6T-MC-AMAN – Induction Period

	Risk Difference % (95% CI)	PBO n (%)	Miri n (%)	Diff. %
All Patients		39 (13.3)	210 (24.2)	10.9
Age (years)				
<40		23 (15.5)	109 (27.7)	12.2
≥40		16 (11.0)	101 (21.3)	10.3
Sex				
Male		20 (12.1)	105 (19.8)	7.7
Female		19 (14.7)	105 (31.1)	16.3
Baseline BMI[a]				
Normal (≥18.5 and <25 kg/m^2)		19 (12.8)	125 (27.7)	15.0
Overweight (≥25 and <30 kg/m^2)		9 (11.8)	46 (19.5)	7.6
Obese (≥30 and <40 kg/m^2)		6 (15.4)	22 (19.3)	3.9
Prior biologic or tofacitinib failure				
Failed		10 (8.5)	55 (15.2)	6.8
Not failed		29 (16.5)	155 (30.6)	14.1
Prior biologic failure[b]				
Failed		10 (8.5)	55 (15.3)	6.7
Not failed		29 (16.4)	155 (30.5)	14.1
Prior anti-TNF failure				
Failed		9 (9.3)	51 (15.7)	6.4
Not failed		30 (15.2)	159 (29.3)	14.1
Prior vedolizumab failure				
Failed		2 (3.4)	18 (11.3)	7.9
Not failed		37 (15.7)	192 (27.1)	11.3
Number of prior failures[c]				
0		29 (16.5)	155 (30.6)	14.1
1		7 (10.8)	31 (17.2)	6.5
≥2		3 (5.7)	24 (13.3)	7.6
Baseline corticosteroid use				
Yes		19 (16.8)	71 (20.2)	3.4
No		20 (11.0)	139 (26.9)	15.8
Baseline immunomodulator use				
Yes		11 (15.9)	40 (19.0)	3.0
No		28 (12.4)	170 (25.9)	13.4

	Risk Difference % (95% CI)	PBO n (%)	Miri n (%)	Diff. %
Duration of UC				
<1 years[d]		4 (12.1)	26 (30.6)	18.5
≥1 to <3 years		13 (16.7)	54 (25.6)	8.9
≥3 to <7 years		10 (13.2)	58 (24.7)	11.5
≥7 years		12 (11.2)	72 (21.4)	10.2
Baseline disease location				
Left-sided colitis		24 (12.8)	145 (26.7)	13.9
Pancolitis		15 (14.6)	62 (19.5)	4.9



Abbreviations: BMI = body mass index; CI = confidence interval; Diff. = unadjusted risk difference; Miri = mirikizumab SC Q4W; n = number of patients in the specified category; PBO = placebo SC Q4W; SC = subcutaneous; Q4W = every 4 weeks; TNF = tumor necrosis factor; UC = ulcerative colitis.

[a] Data from 83 underweight (<18.5 kg/m^2) patients and 14 extremely obese (≥40 kg/m^2) patients not shown due to small sample size.

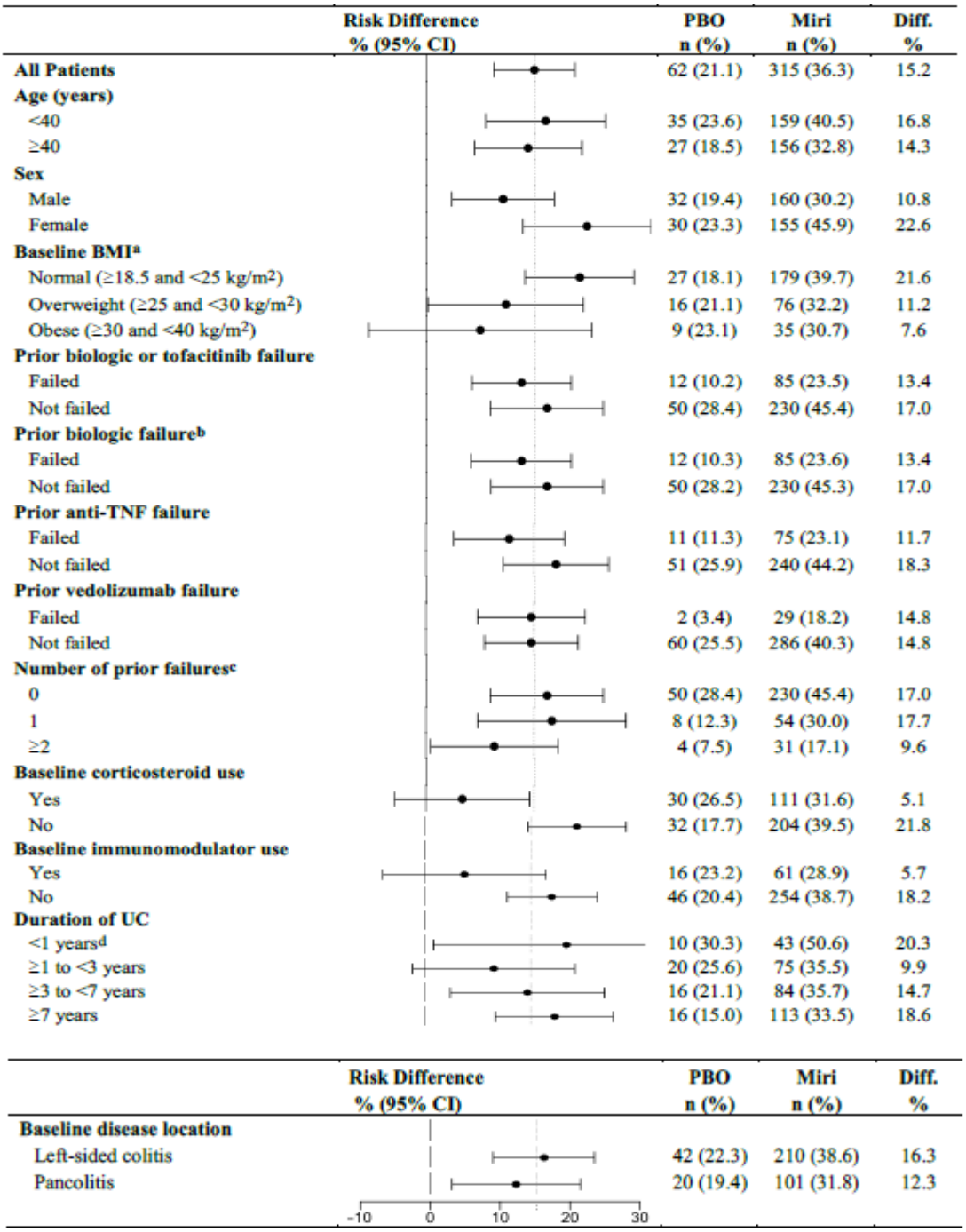
[b] Excludes tofacitinib.

[c] Number of failed biologics or tofacitinib.

[d] Upper limit of the CI was cutoff in the graph.

Note: Dotted line represents the estimated risk difference for all patients.

Endoscopic Improvement for Study AMAN by Select Demographic and Baseline Disease Characteristics Subgroups Modified Intent-to-Treat Population Study I6T-MC-AMAN – Induction Period



Abbreviations: BMI = body mass index; CI = confidence interval; Diff. = unadjusted risk difference; Miri = mirikizumab SC Q4W; n = number of patients in the specified category; PBO = placebo SC Q4W; SC = subcutaneous; Q4W = every 4 weeks; TNF = tumor necrosis factor; UC = ulcerative colitis.

[a] Data from 83 underweight (<18.5 kg/m2) patients and 14 extremely obese (≥40 kg/m2) patients not shown due to small sample size.

[b] Excludes tofacitinib.

[c] Number of failed biologics or tofacitinib.

[d] Upper limit of the CI was cutoff in the graph.

Note: Dotted line represents the estimated risk difference for all patients.

Primary Endpoint Clinical Remission for Study AMAN by Baseline Corticosteroid and

Immunomodulator Use Subgroups

Subgroup	PBO IV Q4W (N = 294)	Miri 300 mg IV Q4W (N = 868)	Risk Difference (95% CI)
Clinical Remission at Week 12 (Primary Endpoint)[a], n/Ns (%)			
No baseline corticosteroid use subgroup	20/181 (11.0)	139/517 (26.9)	15.8 (9.9, 21.8)
Baseline corticosteroid use subgroup	19/113 (16.8)	71/351 (20.2)	3.4 (-4.7, 11.5)
No baseline immunomodulator use subgroup	28/225 (12.4)	170/657 (25.9)	13.4 (8.0, 18.9)
Baseline immunomodulator use subgroup	11/69 (15.9)	40/211 (19.0)	3.0 (-7.1, 13.1)

Abbreviations: CI = confidence interval; ES = endoscopic subscore; IV = intravenous; n = number of patients in the specified category; N = number of patients in the mITT population; Ns = number of patients within the specific subgroup; PBO = placebo; Q4W = every 4 weeks; RB = rectal bleeding; SF = stool frequency.

[a] Clinical Remission is defined as follows: SF subscore = 0 or 1 with at least a 1-point decrease from baseline; RB subscore = 0; and ES = 0 or 1 (excluding friability).

Sensitivity Analyses

Several predefined sensitivity analyses, including a tipping-point analysis, were conducted to assess the robustness of the primary and major secondary results. All the additional sensitivity analyses provided directionally consistent and nominally statistically significant results, confirming the primary analyses.

The tipping-point analysis of the primary endpoint demonstrated that if 20% of the missing placebo-treated patients were imputed as responders, while all the missing mirikizumab-treated patients were treated as non-responders, the p-value would have been .0054.

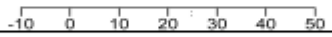
Baseline Demographic and Disease Characteristics Subgroups

Subgroup analyses by demographic and baseline disease characteristics were conducted study AMBG.

Clinical Remission for Study AMBG by Select Demographic and Baseline Disease Characteristics Subgroups Modified Intent-to-Treat Population – Mirikizumab Induction Responders Study I6T-MC-AMBG – Randomized Withdrawal Maintenance Period

	Risk Difference % (95% CI)	PBO n (%)	Miri n (%)	Diff. %
All Patients		45 (25.1)	182 (49.9)	24.7
Age (years)				
<40		23 (24.7)	81 (51.3)	26.5
≥40		22 (25.6)	101 (48.8)	23.2
Sex				
Male		25 (24.0)	109 (50.9)	26.9
Female		20 (26.7)	73 (48.3)	21.7
Baseline BMI[a]				
Normal (≥18.5 and <25 kg/m^2)		26 (26.8)	100 (51.0)	24.2
Overweight (≥25 and <30 kg/m^2)		8 (17.4)	45 (46.4)	29.0
Obese (≥30 and <40 kg/m^2)		9 (34.6)	20 (51.3)	16.7
Prior biologic or tofacitinib failure				
Failed		10 (15.6)	59 (46.1)	30.5
Not failed		35 (30.4)	123 (51.9)	21.5
Prior biologic failure[b]				
Failed		10 (15.6)	59 (46.1)	30.5
Not failed		35 (30.4)	123 (51.9)	21.5
Prior anti-TNF failure				
Failed		9 (15.5)	52 (46.4)	30.9
Not failed		36 (29.8)	130 (51.4)	21.6
Prior vedolizumab failure				
Failed		3 (13.0)	21 (44.7)	31.6
Not failed		42 (26.9)	161 (50.6)	23.7
Number of prior failures[c]				
0		35 (30.4)	123 (51.9)	21.5
1		6 (17.1)	34 (44.2)	27.0
≥2		4 (13.8)	25 (49.0)	35.2
Baseline corticosteroid use				
Yes		12 (17.6)	61 (45.2)	27.5
No		33 (29.7)	121 (52.6)	22.9
Baseline immunomodulator use				
Yes		11 (28.2)	39 (50.0)	21.8
No		34 (24.3)	143 (49.8)	25.5

	Risk Difference % (95% CI)	PBO n (%)	Miri n (%)	Diff. %
Duration of UC				
<1 year		4 (23.5)	22 (52.4)	28.9
≥1 to <3 years		9 (25.0)	50 (50.5)	25.5
≥3 to <7 years		12 (20.3)	54 (56.8)	36.5
≥7 years		20 (29.9)	56 (43.4)	13.6
Baseline disease location				
Left-sided colitis		37 (31.1)	122 (52.1)	21.0
Pancolitis		8 (13.6)	59 (46.1)	32.5



Abbreviations: BMI = body mass index; CI = confidence interval; Diff. = unadjusted risk difference; Miri = mirikizumab SC Q4W; n = number of patients in the specified category; PBO = placebo SC Q4W; SC = subcutaneous; Q4W = every 4 weeks; TNF = tumor necrosis factor; UC = ulcerative colitis.

[a] Data from 34 underweight (<18.5 kg/m^2) patients and 9 extremely obese (≥40 kg/m^2) patients not shown due to small sample size.

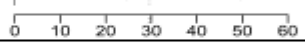
[b] Excludes tofacitinib.

[c] Number of failed biologics or tofacitinib.

Note: Dotted line represents the estimated risk difference for all patients.

Endoscopic Improvement for Study AMBG by Select Demographic and Baseline Disease Characteristics Subgroups Modified Intent-to-Treat Population – Mirikizumab Induction Responders Study I6T-MC-AMBG – Randomized Withdrawal Maintenance Period

	Risk Difference % (95% CI)	PBO n (%)	Miri n (%)	Diff. %
All Patients		52 (29.1)	214 (58.6)	29.6
Age (years)				
<40		26 (28.0)	96 (60.8)	32.8
≥40		26 (30.2)	118 (57.0)	26.8
Sex				
Male		28 (26.9)	121 (56.5)	29.6
Female		24 (32.0)	93 (61.6)	29.6
Baseline BMI[a]				
Normal (≥18.5 and <25 kg/m^2)		30 (30.9)	113 (57.7)	26.7
Overweight (≥25 and <30 kg/m^2)		10 (21.7)	60 (61.9)	40.1
Obese (≥30 and <40 kg/m^2)		10 (38.5)	23 (59.0)	20.5
Prior biologic or tofacitinib failure				
Failed		13 (20.3)	65 (50.8)	30.5
Not failed		39 (33.9)	149 (62.9)	29.0
Prior biologic failure[b]				
Failed		13 (20.3)	65 (50.8)	30.5
Not failed		39 (33.9)	149 (62.9)	29.0
Prior anti-TNF failure				
Failed		12 (20.7)	57 (50.9)	30.2
Not failed		40 (33.1)	157 (62.1)	29.0
Prior vedolizumab failure				
Failed		3 (13.0)	24 (51.1)	38.0
Not failed		49 (31.4)	190 (59.7)	28.3
Number of prior failures[c]				
0		39 (33.9)	149 (62.9)	29.0
1		9 (25.7)	37 (48.1)	22.3
≥2		4 (13.8)	28 (54.9)	41.1
Baseline corticosteroid use				
Yes		14 (20.6)	73 (54.1)	33.5
No		38 (34.2)	141 (61.3)	27.1
Baseline immunomodulator use				
Yes		12 (30.8)	47 (60.3)	29.5
No		40 (28.6)	167 (58.2)	29.6
Duration of UC				
<1 year		5 (29.4)	27 (64.3)	34.9
≥1 to <3 years		10 (27.8)	61 (61.6)	33.8
≥3 to <7 years		17 (28.8)	65 (68.4)	39.6
≥7 years		20 (29.9)	61 (47.3)	17.4
Baseline disease location				
Left-sided colitis		43 (36.1)	146 (62.4)	26.3
Pancolitis		9 (15.3)	67 (52.3)	37.1



Abbreviations: BMI = body mass index; CI = confidence interval; Diff. = unadjusted risk difference; Miri = mirikizumab SC Q4W; n = number of patients in the specified category; PBO = placebo SC Q4W; SC = subcutaneous; Q4W = every 4 weeks; TNF = tumor necrosis factor; UC = ulcerative colitis.

[a] Data from 34 underweight (<18.5 kg/m^2) patients and 9 extremely obese (≥40 kg/m^2) patients not shown due to small sample size.

[b] Excludes tofacitinib.

[c] Number of failed biologics or tofacitinib.

Note: Dotted line represents the estimated risk difference for all patients.

Primary Endpoint Clinical Remission for Study AMBG by Baseline Corticosteroid and Immunomodulator Use Subgroups Modified Intent-to-Treat Population – Mirikizumab Induction Responders Study I6T-MC-AMBG

Subgroup	PBO SC Q4W (N = 179)	Miri 200 mg SC Q4W (N = 365)	Risk Difference (95% CI)
Clinical Remission at Week 40 in Patients who had achieved Clinical Response with mirikizumab in Study AMAN[a]			
No baseline corticosteroid use subgroup	33/111 (29.7)	121/230 (52.6)	22.9 (12.2, 33.6)
Baseline corticosteroid use subgroup	12/68 (17.6)	61/135 (45.2)	27.5 (15.2, 39.9)
No baseline immunomodulator use subgroup	34/140 (24.3)	143/287 (49.8)	25.5 (16.4, 34.7)
Baseline immunomodulator use subgroup	11/39 (28.2)	39/78 (50.0)	21.8 (3.8, 39.8)

Abbreviations: CI = confidence interval; ES = endoscopic subscore; mITT = modified intent-to-treat; n = number of patients in the specified category; N = number of patients in the mITT population; PBO = placebo; RB = rectal bleeding; SF = stool frequency.

[a] Clinical Remission is defined as follows: SF subscore = 0 or SF subscore = 1 with at least a 1-point decrease from baseline; RB subscore = 0; and ES = 0 or 1 (excluding friability).

Sensitivity Analyses

Several predefined sensitivity analyses, including a tipping-point analysis, were conducted to assess the robustness of the primary and major secondary results. All these analyses provided directionally consistent and nominally statistically significant results, confirming the primary analyses. Impacted data were imputed using multiple imputation

The tipping-point analysis of the primary endpoint demonstrated that if 20% of the missing mirikizumab induction responder patients withdrawn from mirikizumab (randomly assigned to placebo) were imputed as responders, while all the missing mirikizumab induction responder patients randomly assigned to mirikizumab were treated as non-responders, the p-value would have been .003.

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 1: Summary of Efficacy for trial I6T-MC-AMAN

Title: A Phase 3, Multicentre, Randomised, Double-blind, Parallel, Placebo-controlled Induction Study of Mirikizumab in Conventional-failed and Biologic-failed Patients with Moderately to Severely Active Ulcerative Colitis			
Study identifier	I6T-MC-AMAN		
Design	Phase 3, multicentre, randomised, double-blind, parallel, placebo-controlled induction study		
	Duration of main phase:		12 weeks
Hypothesis	Superiority		
Treatment groups	Placebo IV Q4W		Administered at Weeks 0, 4, and 8. Number randomised = 294
	300 mg mirikizumab IV Q4W		Administered at Weeks 0, 4, and 8. Number randomised = 868
Endpoints and definitions	Primary endpoint	Clinical Remission at Week 12	The proportion of patients in clinical remission at Week 12. Clinical remission is based on the MMS and is defined as • SF subscore = 0 or SF = 1 with a ≥1 point decrease from baseline • RB subscore = 0, and • ES = 0 or 1 (excluding friability)
	Major secondary endpoint	Alternate Clinical Remission at Week 12	The proportion of patients in alternate clinical remission at Week 12. Alternate clinical remission is based on the MMS and is defined as • SF subscore = 0 or SF = 1 • RB subscore = 0, and • ES = 0 or 1 (excluding friability)
	Major secondary endpoint	Clinical Response at Week 12	The proportion of patients in clinical response at Week 12. Clinical response is 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 an RB score of 0 or 1
	Major secondary endpoint	Endoscopic Improvement at Week 12	The proportion of patients with endoscopic remission at Week 12, defined as • ES = 0 or 1 (excluding friability)

	Major secondary endpoint	Symptomatic Remission at Week 4	The proportion of patients in symptomatic remission at Week 4, defined as: • SF= 0 or SF = 1 with a ≥1 point decrease from baseline, and • RB = 0
	Major secondary endpoint	Symptomatic Remission at Week 12	The proportion of patients in symptomatic remission at Week 12, defined as: • SF = 0 or SF = 1 with a ≥1 point decrease from baseline, and • RB = 0
	Major secondary endpoint	Clinical Response at Week 12 in Patients Who Failed Biologic or JAKi Therapy for UC	The proportion of patients in the biologic-failed population in clinical response at Week 12. Clinical response is 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 an RB score of 0 or 1
	Major secondary endpoint	Bowel Urgency Severity at Week 12	The change from baseline in the Urgency Numeric Rating Scale score
	Major secondary endpoint	Histo-endoscopic Mucosal Improvement at Week 12	The proportion of patients with histologic-endoscopic mucosal improvement at Week 12, defined as achieving both • Histologic improvement, defined using Geboes scoring system with neutrophil infiltration in 5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue, and • Endoscopic improvement, defined as ES = 0 or 1 (excluding friability)
Database lock	11 Jun 2021		
Results and analysis			
Analysis description	**Primary analysis:** Clinical Remission at Week 12		
Analysis population, time point description, and statistical model	Modified Intent-to-Treat population Week 12 CMH test with NRI		

Descriptive statistics and estimate variability	Treatment group		Placebo	Mirikizumab
	Number of patients		294	868
	Proportion of patients in clinical remission at Week 12, n (%)		39 (13.3)	210 (24.2)
Effect estimate per comparison	Primary endpoint: Clinical Remission at Week 12	Comparison groups	Placebo versus mirikizumab	
		Common risk difference (99.875% CI)	11.1 (3.2, 19.1)	
		p-value	.00006	
Results and analysis				
Analysis description	**Major secondary analysis:** Alternate clinical remission at Week 12			
Analysis population, time point description, and statistical model	Modified Intent-to-Treat population Week 12 CMH test with NRI			
Descriptive statistics and estimate variability	Treatment group		Placebo	Mirikizumab
	Number of patients		294	868
	Proportion of patients in alternate clinical remission at Week 12, n (%)		43 (14.6)	222 (25.6)
Effect estimate per comparison	Major secondary endpoint: Alternate clinical remission at Week 12	Comparison groups	Placebo versus mirikizumab	
		Common risk difference (99.875% CI)	11.1 (3.0, 19.3)	
		p-value	.00007	
Results and analysis				
Analysis description	**Major secondary analysis:** Clinical Response at Week 12			
Analysis population, time point description, and statistical model	Modified Intent-to-Treat population Week 12 CMH test with NRI			

Descriptive statistics and estimate variability	Treatment group		Placebo	Mirikizumab
	Number of patients		294	868
	Proportion of patients in clinical response at Week 12, n (%)		124 (42.2)	551 (63.5)
Effect estimate per comparison	Major secondary endpoint: Clinical Response at Week 12	Comparison groups	Placebo versus mirikizumab	
		Common risk difference (99.875% CI)	21.4 (10.8, 32.0)	
		p-value	<.00001	
Results and analysis				
Analysis description	**Major secondary analysis:** Endoscopic Improvement at Week 12			
Analysis population, time point description, and statistical model	Modified Intent-to-Treat population Week 12 CMH test with NRI			
Descriptive statistics and estimate variability	Treatment group		Placebo	Mirikizumab
	Number of patients		294	868
	Proportion of patients in endoscopic improvement at Week 12, n (%)		62 (21.1)	315 (36.3)
Effect estimate per comparison	Major secondary endpoint: Endoscopic Improvement at Week 12	Comparison groups	Placebo versus mirikizumab	
		Common risk difference (99.875% CI)	15.4 (6.3, 24.5)	
		p-value	<.00001	
Results and analysis				
Analysis description	**Major secondary analysis:** Symptomatic Remission at Week 4			
Analysis population, time point description, and statistical model	Modified Intent-to-Treat population Week 4 CMH test with NRI			

Descriptive statistics and estimate variability	Treatment group		Placebo	Mirikizumab
	Number of patients		294	868
	Proportion of patients in symptomatic remission at Week 4, n (%)		38 (12.9)	189 (21.8)
Effect estimate per comparison	Major secondary endpoint: Symptomatic Remission at Week 4	Comparison groups	Placebo versus mirikizumab	
		Common risk difference (99.875% CI)	9.2 (1.4, 16.9)	
		p-value	.00064	
Results and analysis				
Analysis description	**Major secondary analysis:** Symptomatic Remission at Week 12			
Analysis population, time point description, and statistical model	Modified Intent-to-Treat population Week 12 CMH test with NRI			
Descriptive statistics and estimate variability	Treatment group		Placebo	Mirikizumab
	Number of patients		294	868
	Proportion of patients in symptomatic remission at Week 12, n (%)		82 (27.9)	395 (45.5)
Effect estimate per comparison	Major secondary endpoint: Symptomatic Remission at Week 12	Comparison groups	Placebo versus mirikizumab	
		Common risk difference (99.875% CI)	17.5 (7.5, 27.6)	
		p-value	<.00001	
Results and analysis				
Analysis description	**Major secondary analysis:** Clinical Response at Week 12 in patients who failed biologic or JAKi therapy for UC			
Analysis population, time point description, and statistical model	Modified Intent-to-Treat population who failed biologic or JAKi therapy for UC Week 12 CMH test with NRI			

Descriptive statistics and estimate variability	Treatment group		Placebo	Mirikizumab
	Number of patients		118	361
	Proportion of patients in clinical response at Week 12, n (%)		35 (29.7)	197 (54.6)
Effect estimate per comparison	Major secondary endpoint: Clinical Response at Week 12 in patients who failed biologic or JAKi therapy for UC	Comparison groups	Placebo versus mirikizumab	
		Common risk difference (99.875% CI)	25.0 (9.0, 41.1)	
		p-value	<.00001	
Results and analysis				
Analysis description	**Major secondary analysis:** Bowel urgency severity at Week 12			
Analysis population, time point description, and statistical model	Modified Intent-to-Treat population Week 12 MMRM			
Descriptive statistics and estimate variability	Treatment group		Placebo	Mirikizumab
	Number of patients (with nonmissing data)		258	829
	LSM Change from Baseline at Week 12 (SE)		-1.63 (0.141)	-2.59 (0.083)
Effect estimate per comparison	Major secondary endpoint: Bowel urgency severity at Week 12	Comparison groups	Placebo versus mirikizumab	
		LSM difference (99.875% CI)	-0.95 (-1.47, -0.44)	
		p-value	<.00001	
Results and analysis				
Analysis description	**Major secondary analysis:** Histo-endoscopic mucosal improvement at Week 12			
Analysis population, time point description, and statistical model	Modified Intent-to-Treat population Week 12 CMH test with NRI			

Descriptive statistics and estimate variability	Treatment group		Placebo	Mirikizumab
	Number of patients		294	868
	Proportion of patients in histo-endoscopic mucosal improvement at Week 12, n (%)		41 (13.9)	235 (27.1)
Effect estimate per comparison	Major secondary endpoint: Histo-endoscopic mucosal improvement at Week 12	Comparison groups	Placebo versus mirikizumab	
		Common risk difference (99.875% CI)	13.4 (5.5, 21.4)	
		p-value	<.00001	

Abbreviations: CMH = Cochran-Mantel-Haenzel; CI = confidence interval; ES = endoscopic subscore; IV = intravenous; JAKi = Janus kinase inhibitor; LSM = least squares mean; MMRM = mixed-model repeated measures; MMS = modified Mayo score; n = number of patients in the specified category; NRI = nonresponder imputation; Q4W = every 4 weeks; RB = rectal bleeding; SE = standard errorSF = stool frequency; UC = ulcertive colitis.

Note: In Study AMAN, the family-wise type 1 error rates were controlled at a 2-sided alpha level of .00125 for the primary and all major secondary endpoints.

Table 2: Summary of efficacy for trial Study I6T-MC-AMBG

Title: A Phase 3, Multicenter, Randomized, Double-Blind, Parallel-Arm, Placebo-Controlled Maintenance Study of Mirikizumab in Patients with Moderately to Severely Active Ulcerative Colitis			
Study identifier	I6T-MC-AMBG		
Design	Phase 3, multicentre, randomised, double-blind, parallel-arm, placebo-controlled maintenance study		
	Duration of main phase:		40 weeks (52 weeks of continuous study drug treatment)
Hypothesis	Superiority		
Treatment groups (for primary and major secondary endpoints)	Placebo SC Q4W		Number randomised = 179
	200 mg mirikizumab SC Q4W		Number randomised = 365
Endpoints and definitions	Primary endpoint	Clinical Remission at Week 40 in patients induced into clinical response with mirikizumab in Study AMAN	The proportion of mirikizumab induction responders in clinical remission at Week 40. Clinical remission is based on the MMS and is defined as: • SF subscore = 0 or SF = 1 with a ≥1 point decrease from baseline • RB subscore = 0, and • ES = 0 or 1 (excluding friability)
	Major secondary endpoint	Alternate Clinical Remission at Week 40 in patients induced into clinical response with mirikizumab in Study AMAN	The proportion of mirikizumab induction responders in alternate clinical remission at Week 40. Alternate clinical remission is based on the MMS and is defined as: • SF subscore = 0 or SF = 1 • RB subscore = 0, and • ES = 0 or 1 (excluding friability)
	Major secondary endpoint	Clinical Remission at Week 40 in patients induced into clinical remission with mirikizumab in Study AMAN	The proportion of mirikizumab induction remitters in clinical remission at Week 40. Clinical remission is based on the MMS and is defined as: • SF subscore = 0 or SF = 1 with a ≥1 point decrease from baseline • RB subscore = 0, and • ES = 0 or 1 (excluding friability)
	Major secondary endpoint	Endoscopic Improvement at Week 40 in patients induced into clinical response with mirikizumab in Study AMAN	The proportion of mirikizumab induction responders with endoscopic remission at Week 40, defined as: • ES = 0 or 1 (excluding friability)
	Major secondary endpoint	Corticosteroid-free Remission at Week 40 in patients induced into clinical response with mirikizumab in Study AMAN	The proportion of mirikizumab induction responders in corticosteroid-free remission at Week 40, defined as: • Clinical Remission at Week 40 • Symptomatic Remission at Week 28 (SF = 0 or SF = 1 with a ≥1 point decrease from baseline and RB = 0), and • No corticosteroid use for at least 12 weeks prior to Week 40.

	Major secondary endpoint	Histo-endoscopic Mucosal Remission at Week 40 in patients induced into clinical response with mirikizumab in Study AMAN	The proportion of mirikizumab induction responders in histo-endoscopic mucosal remission at Week 40, defined as achieving both:
			• Histologic remission with resolution of mucosal neutrophils, defined using the Geboes scoring system with subscores of 0 for Grades
			  ○ 2b (lamina propria neutrophils)
			  ○ 3 (neutrophils in epithelium)
			  ○ 4 (crypt destruction), and
			  ○ 5 (erosion or ulceration), and
			• Endoscopic improvement, defined as ES = 0 or 1 (excluding friability).

	Major secondary endpoint	Bowel Urgency Severity at Week 40 in patients induced into clinical response with mirikizumab in Study AMAN	The change from baseline in the Urgency Numeric Rating Scale score in mirikizumab induction responders
	Major secondary endpoint	Bowel Urgency Remission at Week 40 in patients induced into clinical response with mirikizumab in Study AMAN	The proportion of mirikizumab induction responders with a baseline (AMAN Week 0) Urgency NRS of at least 3 with Bowel Urgency Remission (an Urgency NRS score of 0 or 1) at Week 40
Database lock	06 Dec 2021		
Results and analysis			
Analysis description	**Primary analysis:** Clinical Remission at Week 40 in patients induced into clinical response with mirikizumab in Study AMAN		
Analysis population, time point description, and statistical model	Modified Intent-to-Treat population Week 40 CMH test with NRI		
Descriptive statistics and estimate variability	Treatment group	Placebo	Mirikizumab
	Number of patients	179	365
	Proportion of mirikizumab induction responders in clinical remission at Week 40, n (%)	45 (25.1)	182 (49.9)

Effect estimate per comparison	Primary endpoint: Clinical Remission at Week 40 in patients induced into clinical response with mirikizumab in Study AMAN	Comparison groups	Placebo versus mirikizumab
		Common risk difference (95% CI)	23.2 (15.2, 31.2)
		p-value	<.001
Results and analysis			
Analysis description	**Major secondary analysis:** Alternate Clinical Remission at Week 40 in patients induced into clinical response with mirikizumab in Study AMAN		
Analysis population, time point description, and statistical model	Modified Intent-to-Treat population Week 40 CMH test with NRI		

Descriptive statistics and estimate variability	Treatment group	Placebo	Mirikizumab
	Number of patients	179	365
	Proportion of mirikizumab induction responders in alternate clinical remission at Week 40, n (%)	47 (26.3)	189 (51.8)

Effect estimate per comparison	Major secondary endpoint: Alternate Clinical Remission at Week 40 in patients induced into clinical response with mirikizumab in Study AMAN	Comparison groups	Placebo versus mirikizumab
		Common risk difference (95% CI)	24.1 (16.0, 32.2)
		p-value	<.001
Results and analysis			
Analysis description	**Major secondary analysis:** Clinical Remission at Week 40 in patients induced into clinical remission with mirikizumab in Study AMAN		
Analysis population, time point description, and statistical model	Modified Intent-to-Treat Population Week 40 CMH test with NRI		

Descriptive statistics and estimate variability	Treatment group		Placebo	Mirikizumab
	Number of patients		65	143
	Proportion of mirikizumab induction remitters in clinical remission at Week 40, n (%)		24 (36.9)	91 (63.6)
Effect estimate per comparison	Major secondary endpoint: Clinical Remission at Week 40 in patients induced into clinical remission with mirikizumab in Study AMAN	Comparison groups	Placebo versus mirikizumab	
		Common risk difference (95% CI)	24.8 (10.4, 39.2)	
		p-value	<.001	
Results and analysis				
Analysis description	**Major secondary analysis:** Endoscopic Improvement at Week 40 in patients induced into clinical response with mirikizumab in Study AMAN			
Analysis population, time point description, and statistical model	Modified Intent-to-Treat population Week 40 CMH test with NRI			
Descriptive statistics and estimate variability	Treatment group		Placebo	Mirikizumab
	Number of patients		179	365
	Proportion of mirikizumab induction responders with endoscopic improvement at Week 40, n (%)		52 (29.1)	214 (58.6)
Effect estimate per comparison	Major secondary endpoint: Endoscopic Improvement at Week 40 in patients induced into clinical response with mirikizumab in Study AMAN	Comparison groups	Placebo versus mirikizumab	
		Common risk difference (95% CI)	28.5 (20.2, 36.8)	
		p-value	<.001	
Results and analysis				
Analysis description	**Major secondary analysis:** Corticosteroid-free Remission at Week 40 in patients induced into clinical response with mirikizumab in Study AMAN			

Analysis population, time point description, and statistical model	Modified Intent-to-Treat population patients receiving corticosteroids at AMAN baseline Week 40 CMH test with NRI			
Descriptive statistics and estimate variability	Treatment group		Placebo	Mirikizumab
	Number of patients		179	365
	Proportion of mirikizumab induction responders in corticosteroid-free remission at Week 40, n (%)		39 (21.8)	164 (44.9)
Effect estimate per comparison	Major secondary endpoint: Corticosteroid-free Remission at Week 40 in patients induced into clinical response with mirikizumab in Study AMAN	Comparison groups	Placebo versus mirikizumab	
		Common risk difference (95% CI)	21.3 (13.5, 29.1)	
		p-value	<.001	
Results and analysis				
Analysis description	**Major secondary analysis:** Histo-endoscopic Mucosal Remission at Week 40 in patients induced into clinical response with mirikizumab in Study AMAN			
Analysis population, time point description, and statistical model	Modified Intent-to-Treat population Week 40 CMH test with NRI			
Descriptive statistics and estimate variability	Treatment group		Placebo	Mirikizumab
	Number of patients		179	365
	Proportion of mirikizumab induction responders with histo-endoscopic mucosal remission at Week 40, n (%)		39 (21.8)	158 (43.3)

Effect estimate per comparison	Major secondary endpoint: Histo-endoscopic Mucosal Remission at Week 40 in patients induced into clinical response with mirikizumab in Study AMAN	Comparison groups	Placebo versus mirikizumab
		Common risk difference (95% CI)	19.9 (12.1, 27.6)
		p-value	<.001
Results and analysis			
Analysis description	**Major secondary analysis:** Bowel Urgency Severity at Week 40 in patients induced into clinical response with mirikizumab in Study AMAN		
Analysis population, time point description, and statistical model	Modified Intent-to-Treat population Week 40 MMRM		
Descriptive statistics and estimate variability	Treatment group	Placebo	Mirikizumab
	Number of patients (with nonmissing data)	104	316
	LSM Change from Baseline at Week 40 (SE)	-2.74 (0.202)	-3.80 (0.139)
Effect estimate per comparison	Major secondary endpoint: Bowel Urgency Severity at Week 40 in patients induced into clinical response with mirikizumab in Study AMAN	Comparison groups	Placebo versus mirikizumab
		LSM difference (95% CI)	-1.06 (-1.51, -0.61)
		p-value	<.00001
Results and analysis			
Analysis description	**Major secondary analysis:** Bowel Urgency Remission at Week 40 in patients induced into clinical response with mirikizumab in Study AMAN		
Analysis population, time point description, and statistical model	Modified Intent-to-Treat population Week 40 CMH test with NRI		
	Treatment group	Placebo	Mirikizumab
Descriptive statistics and estimate variability	Number of patients	172	336
	Proportion of mirikizumab induction responders with a baseline (AMAN Week 0) Urgency NRS of at least 3 with Bowel Urgency Remission at Week 40, n (%)	43 (25.0)	144 (42.9)
Effect estimate per comparison	Major secondary endpoint: Bowel Urgency Remission at Week 40 in patients induced into clinical response with mirikizumab in Study AMAN	Comparison groups	Placebo versus mirikizumab
		Common risk difference (95% CI)	18.1 (9.8, 26.4)
		p-value	<.001

Abbreviations: CI = confidence interval; CMH = Cochran-Mantel-Haenzel; ES = endoscopic subscore; LSM = least squares mean; MMRM = mixed-model repeated measures; MMS = modified Mayo score; n = number of patients in the specified category; NRI = nonresponder imputation; NRS = numeric rating scale; Q4W = every 4 weeks; RB = rectal bleeding; SC = subcutaneous; SF = stool frequency; UC = ulcertive colitis.

Note: In Study AMBG, the family-wise type 1 error rates were controlled at a 2-sided alpha level of .05 for the primary and all major secondary endpoints.

Table 3: Clinical studies in special populations

	Age 65-74 years (Number of subjects in this age range /total number of subjects)	Age 75-84 year (Number of subjects in this age range/total number of subjects)	Age 85+ years (Number of subjects in this age range/total number of subjects)
Controlled trials[a]	296/3822 (7.7%)	42/3822 (1.1%)	0
Non-controlled trials	NA	NA	NA

Abbreviation: NA = not applicable.

[a] Ulcerative colitis Studies I6T-MC-AMAC and I6T-MC-AMAN, psoriasis Studies I6T-MC-AMAJ, I6T-MC-AMAK, and I6T-MC-AMAF, and Crohn's disease study I6T-MC-AMAG.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The mirikizumab UC Phase 3 programme comprised 3 trials:

- 12-week induction Study I6TMC- AMAN (AMAN),
- 40-week maintenance Study 16T-MC-AMBG (AMBG),
- long term extension Study I6T-MC-AMAP.

A phase 2 dose finding study also provides some supportive evidence.

As stated in the EMA Guideline (CHMP/EWP/18463/2006 Rev.1 *Guideline on the development of new medicinal products for the treatment of Ulcerative Colitis*) "to fulfil a claim for the treatment of ulcerative colitis, it is expected that at least two confirmatory trials are provided.
The applicant received Scientific Advice from CHMP (EMEA/H/SAH/079/1/2017/III) 22 June 2017.

The advice was on the pre-clinical and clinical pharmacology and phase studies in UC and safety monitoring. The development mostly followed the advice however the applicant at that time proposed 2 separate induction studies (AMAN) and (AMAO) both of which planned to enrol 408 patients and test two separate regimens in UC patients who failed or were intolerant to conventional or biological therapies. This is in line with the EMA Guideline (CHMP/EWP/18463/2006 Rev.1 *Guideline on the development of new medicinal products for the treatment of Ulcerative Colitis*) *"to fulfil a claim for the treatment of ulcerative colitis, it is expected that at least two confirmatory trials are provided".*

The applicant only conducted a single induction study (AMAN) however, this study enrolled more patients (1162) compared to the planned enrolment of 816 patients. This study was well powered, >90% power to demonstrate that mirikizumab is superior to placebo in achieving this endpoint, as assessed using a chi-square test with a 2-sided significance level of 0.00125.

The applicant presented the results of a **Phase 2 dose finding study (AMAC)** in which 3 doses of mirikizumab were compared to placebo to assess the induction of endoscopic remission at Week 12 following induction treatment. The primary objective of this study was to test the hypothesis that treatment with mirikizumab is superior to placebo in inducing clinical remission at Week 12. The study was in principle well designed with appropriate inclusion and exclusion criteria assessment endpoints and while the method used for the calculation of the sample size seemed unusual, the numbers recruited to the study were sufficient to adequately power the study for the primary endpoint.

The induction study (AMAN) consisted of a 4-week screening period, followed by a **12 week dosing period.** Following this phase, patients could then enter the maintenance study AMBG, or post treatment follow up period of 16 weeks.

Patients were randomised 3:1 to receive blinded intravenous (IV) administration of 300 mg mirikizumab or placebo every 4 weeks (Q4W) with stratification based on • biologic-failed status (yes/no) • baseline corticosteroid use (yes/no) • baseline disease activity (modified Mayo score [MMS]: [4-6] or [7-9]), and • geographic region (North America/Europe/Other).
There was no rescue arm in Study AMAN. However, patients who completed Study AMAN through Week 12 (with an acceptable safety profile) who did not achieve a clinical response to mirikizumab at Week 12 were eligible to receive an induction dose of mirikizumab in Study AMBG.

The study (AMAN) enrolled patients who had an established diagnosis of UC of ≥3 months in duration before baseline (Week 0), which includes endoscopic evidence of UC and a histopathology report that supports a diagnosis of UC. They had moderately to severely active UC as defined by a modified Mayo score (MMS) of 4 to 9 with an endoscopic subscore (ES) ≥2, with endoscopy performed within 10 days before baseline. Both Male and female patients were enrolled and were aged 8 to 80 years old.
It would have been preferred to have a definition of moderate and severe UC more in line with the EMA UC guideline, therefore *the interchangeability with the full Mayo score should be demonstrated convincingly with a view on common clinical practice and external validity of trial results"*. However, the applicant has reported the number and proportion of patients that fulfilled the full Mayo score definition (Mayo Score of 6 to 12 and endoscopy subscore of 2 to 3) at baseline and clarified that the results can be generalised also to these patients**.**

Patients must have had an inadequate response to, loss of response to, or intolerance to at least a conventional treatment which included corticosteroids, immunomodulatory treatments (oral AZA, 6-MP or a combination of a thiopurine and allopurinol) or biological agents (such as anti- TNF antibodies or anti-integrin antibodies) or to Janus kinase (JAK) inhibitors (such as tofacitinib). Patients had to be on stable doses of oral 5-ASA therapy or steroids for at least 2 weeks before screening endoscopy. Patients receiving AZA, 6-MP, and methotrexate: were required to be on a stable dose for at least 8 weeks before the screening.

The primary endpoint used in the studies "clinical remission per adapted mayo score" is a composite endpoint evaluating symptoms and endoscopic features of UC, using 3 parts of the validated Mayo Score, however with exclusion of the physician global scale. To be a responder the patient should have had a stool frequency subscore (SF) =0, or SF =1 with a ≥1 point decrease from baseline and not greater than baseline, a rectal bleeding score (RB) of 0, and endoscopic subscore =0 or 1 (excluding friability).

The composite endpoint utilised in this study is not fully in line with the EMA UC GL (CHMP/EWP/18463/2006 rev 1), which states that clinical (symptoms) and endoscopic remission should be evaluated as co-primary endpoints to ensure a beneficial effect over placebo in both parts. However similar endpoints have been accepted by CHMP in approved treatments for UC. Furthermore, the composite primary endpoint was agreed by CHMP during the scientific advice with the condition that the individual components of the score were also tested and controlled for. Additionally, the sub-scoring levels chosen are consistent with the guideline, which states that a score of 0 or 1 may be used for defining endoscopic healing and symptomatic remission should include cessation of rectal bleeding.

Two protocols were submitted one dated 13-Mar-2018 and an amended version (protocol a) dated 12-Sep-2019. The endpoints listed in the version dated 12-Sep-2019 do not follow the same order as those stated in the SAP provided nor in the study report submitted for this trial. As the first key secondary endpoint alternate clinical response at week 12 was removed. This assessment report is presented in the order in which present in the SAP. Conduct of the study was stated to be in line with GCP. This trial was previously inspected by Belgian and French regulators, no critical issues were identified, however corrective actions were requested.

The applicant utilised an eCOA device to electronically capture patient daily diary entries regarding PRO questions for SF and RB, which are components of the MMS. A transcription error (i.e., copy and paste error) in the eCOA devices in Turkey was reported to Eli Lilly and Company (Lilly). Further investigation

of the programming for the eCOA devices for all languages revealed a similar transcription error in Polish, and no other languages. As these were considered important errors by the applicant the 117 impacted patients from Turkey and Poland, whose baseline data was collected using incorrectly transcribed PRO questions on the eCOA devices, were excluded from the primary efficacy analysis but included in the primary safety analysis.

The statistical methods were in general acceptable.

Study AMBG was a phase 3 multicentre, randomised, double-blind, placebo-controlled, withdrawal design, parallel-arm study evaluating the safety and efficacy of 200 mg mirikizumab every 4 weeks (Q4W) subcutaneous (SC) in **maintaining treatment response** at Week 40 (that is, at Week 52 of continuous study drug treatment).

There were 2 main cohorts, those who were responders from AMAN and the non-responders The responders from AMAN who had received Mirikizumab were re randomised to continue with mirikizumab at a lower dose of 200 mg Q4W or receive placebo blinded for 40 weeks. This is the main aspect of the efficacy analysis and was controlled for. Any of the patients in the placebo or treatment arm who lost their response were treated open label with 300 mg Q4W.

Patients entering into the study who were non responders were treated in open label with 300 mg q4w regimen for as long as they were achieving clinical benefit.

The primary endpoint was the proportion of patients who were in clinical remission at week 12 form AMAN study and maintained this at week 40. This is acceptable. Key secondary endpoints included proportion of patients who achieved clinical remission and entered into the study with clinical response. Endoscopic remission, corticosteroid free remission without surgery and clinical remission at week 40 in the subgroup of patients in whom biological treatments failed or were intolerant to. Which are all accepted as clinically relevant.

544 Patients responders from the preceding study AMAN were enrolled. 179 patients were randomised to placebo. 365 were randomised to Mirikizumab.

There was a high compliance rate achieved in the study 88.8% completed treatment in Mirikizumab arm, whereas 60.9% completed in the placebo arm.

There were a number of protocol amendments (covid related), and the majority these appeared acceptable.

Similar to the AMAN study, Study AMBG utilised an eCOA device to electronically capture patient daily diary entries regarding PRO questions for SF and RB, which are components of the MMS. A transcription error (i.e., copy and paste error) in the eCOA devices in Turkey was reported to Lilly. Further investigation of the programming for the eCOA devices for all languages revealed a similar transcription error in Polish.

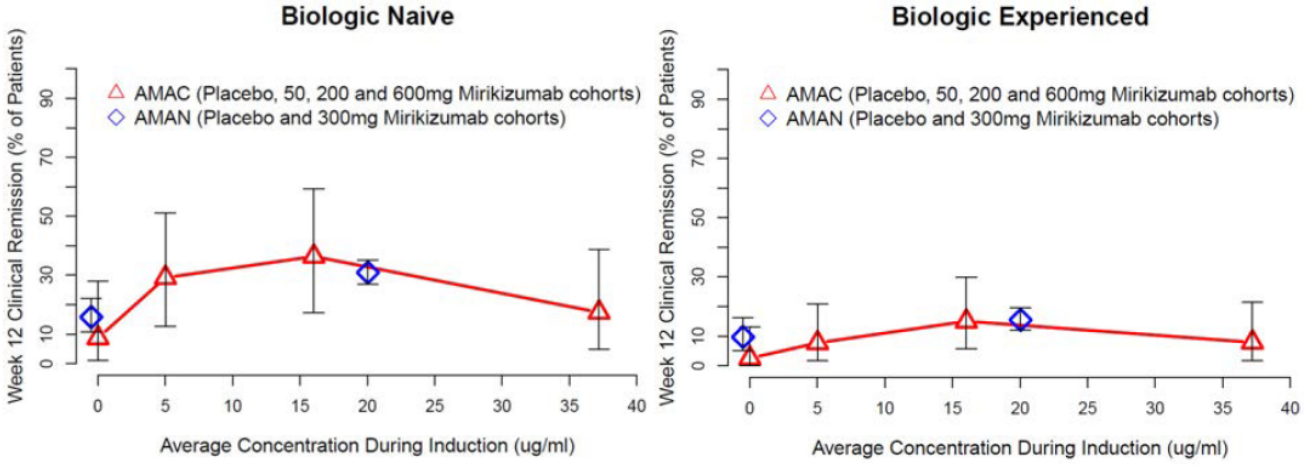
Overall, 104 impacted patients from Turkey (4) and Poland (100), Sensitivity analyses for efficacy were performed on primary and selected key secondary endpoints at Week 40 by including impacted patients using the ITT population with the mNRI method.

Furthermore, following completion of the pivotal trial clinical study report for the Study AMBG, it was identified that 6 sensitivity analyses (using mNRI) were not fully aligned with the final version of the SAP. The covariate of "treatment" was inadvertently omitted from the multiple imputation model in the mNRI sensitivity analyses of the primary and some major secondary endpoints as reported in the CSR. This was then amended by the applicant. The applicant provided the primary efficacy and key secondary endpoint (endoscopic remission) results without this covariate; no meaningful differences were observed between the two analyses.

Efficacy data and additional analyses

Dose finding

The results of the **dose finding study AMAC** are somewhat ambiguous. The trial did not meet its primary objective as no statistically significant difference was seen in any of the treatment arms compared to placebo. There was a trend seen in the secondary endpoints towards higher efficacy in the two higher dose arms, but these results are inconsistent. However, it is accepted that the results of this study are intended to be indicative only.



Abbreviations: AMAC = I6T-MC-AMAC; AMAN = I6T-MC-AMAN.

Note: AMAC data points represent the percentage of patients that achieved clinical remission in each of the study cohorts, from left to right: Placebo, 50 mg, 200 mg, and 600 mg mirikizumab. The points for both AMAC and AMAN are plotted along the x-axis at the median time-averaged concentration for each cohort. Due to the application of exposure-based dose adjustments, the overall average induction dose received by patients in AMAC in the 50-mg and 200-mg cohorts were 100 mg and 250 mg, respectively.

Figure 2.5.3.2 **Exposure-response relationship for clinical remission at the end of induction treatment in bio-naïve and bio-experienced patients with UC in Phase 2 and Phase 3 studies.**

Patients who achieved remission in the induction phase were enrolled into the 52-week maintenance phase of the trial. Here, patients who had received induction doses of mirikizumab were randomised to receive maintenance mirikizumab treatment at two doses, either 200 mg Q4W or 200 mg Q12W, while patients who received placebo continued doing so. The results of this phase are indicative only, as the study was not designed to formally assess efficacy. However, it was seen that there was no difference in maintenance of remission between the two treatment arms, although as there was no comparison against the response in the placebo arm it is difficult to interpret this maintenance response.

Overall, the trial has provided some information regarding efficacy in patients with UC, showing a possible trend towards increased efficacy in the higher doses selected, although the results are not pivotal.

Table 4: Results for the Secondary Endpoint: Clinical Remission at Week 52

	Placebo SC Q4W (N = 13)	Miri 200 mg SC Q4W (N = 47)	Miri 200 mg SC Q12W (N = 46)

Response, n (%)	1 (7.7%)	22 (46.8%)	17 (37.0%)
Difference vs. Miri 200 mg SC Q4W,			-9.9% (-29.8%, 10.1%)
p-value vs. Miri 200 mg SC Q4W	Not compared	---	0.332

Induction of efficacy

The statistical results of the induction study (AMAN) were considered to be reasonably compelling in providing evidence of treatment effect.

Sensitivity analysis for efficacy were performed on primary and selected key secondary endpoints by including impacted patients using the ITT population with mNRI multiple imputation method 117 reports. These did not show any differences from the primary analysis.

The baseline demographics in terms of age, gender, weight, and disease duration were well balanced between the cohorts. Also, the background disease severity (moderate and severe) was also well matched and background treatment.

The primary endpoint clinical remission MMS for the entire population was achieved p=0.00006) risk difference from placebo 11.1, (99.857% CI: 3.2, 19.1). The applicant also tested the subgroups based on prior UC therapy these were statistically significant in the biologic and tofacitinib naive subgroup Risk Diff 15.1 (8.3, 21.9). Statistical significance was not demonstrated in the at least 1 biologic or tofacitinib failed subgroup (P=0.065) (Risk Diff 6.8 (0.5, 13.0) or in the more than 1 biologic or tofacitinib failed subgroup (P=0.149), (Risk Diff 7.6 (-0.3, 15.5) however trended positive for the mirikizumab-treatment group compared to the placebo.

For endoscopic remission a significantly greater percentage of patients achieved endoscopic remission at Week 12 in the mirikizumab-treatment group compared placebo (p <0.00001) risk difference 15.4 (99.857% CI; 6.3, 24.5). For the subgroups analysis based on prior UC therapy biologic and tofacitinib naive subgroup, endoscopic remission was significantly higher in the mirikizumab-treatment group compared to the placebo group (p<0.001). Risk diff 17.9 (95% CI 9.8, 25.9). Also, in the at least 1 biologic or tofacitinib failed subgroup a significantly higher effect in the mirikizumab-treatment group compared to the placebo group was demonstrated (p = 0.001). Risk diff 13.4 (95% CI 6.4, 20.4). However, within the more than 1 biologic or tofacitinib failed subgroup, the response was numerically higher but not statistically significant (p = 0.123).

For symptomatic remission a significantly greater percentage of patients achieved symptomatic remission at Weeks 4 and 12 in the mirikizumab-treatment group compared to the placebo group. At week 4; P =0.00064, risk diff was 9.2 (99.875% CI 1.4, 16.9) and at week 12 p< 0.00001 risk diff 17.5 (99.875% CI 17.5 27.6). Statistical significance was seen in each subgroup p< 0.001.

According to the definition of Clinical remission and the clinical response at Week 12, the change of mean SF and RB subscores seem to be clinically relevant in the mirikizumab group and are not far from clinical relevance in PBO group at Week 12. The difference between them is both statistically significant and clinically relevant.

Mirikizumab also demonstrated statistically significance for histological improvement and histological remission at 12 weeks compared to placebo.

In the induction study (Study AMAN), remarkably high response/remission rates were found for Primary efficacy endpoint (Clinical remission rate at W12) and for some Major secondary efficacy endpoints in the mITT population as well as in "Biologic and JAKi naïve" patients in the placebo group when compared to the response rates observed in the mirikizumab group. Response rates between 15-50% in PBO group with response rates not higher than 70% in miri 300 mg group were observed.

Mirikizumab also demonstrated improvement on QoL scales a greater mean increase (improvement) from baseline in IBDQ total score (p< 0.001) compared to placebo for response and remission and improvement in EQ-5D-5L score (p<0.001). Analyses on the subgroups were provided in the responses.

During the Induction period, 290 patients (98.6%) in the placebo group and 851 patients (98.0%) in the mirikizumab-treatment group were compliant with treatment (which was defined as missing no doses prior to discontinuing study treatment).

The induction study AMAN overall met its primary and key secondary endpoints. While there was no active comparator in this trial the clinical effect size is similar to other authorisations in UC. However, the effect size on the primary endpoint was relatively small.

Also, while the study was not powered for individual prior UC treatment subgroups, a lower effect is seen in patients failing at least 1 biological treatment prior to entering into the study. In the subgroup of patients who failed following more than 1 biological treatment statistical significance for some endpoints was not demonstrated.

Additionally in patients who had used corticosteroids at baseline statistical significance was not in for clinical remission, endoscopic or symptomatic remission or for histologic-endoscopic improvement.

For part of the intended indication the applicant was seeking a claim in patients who have failed, or were intolerant to Janus kinase inhibitors however, it seems that the only member of this class of medications investigated was tofacitinib. The number of patients who had failed tofacitinib alone at baseline was rather low (6 placebo, 34 mirikizumab). Further justification was required by the applicant to support this aspect of the indication in the day 120 LoQs.

In addition, the applicant was seeking to include "(…), or, have medical contraindications to such therapies" in the indication statement. The applicant was asked to delete this text as any such statement is considered inappropriate in this section of the SmPC. The applicant was also asked to remove the reference to section 5.1 in the day 180 LoOI.

All of these aspects have been addressed satisfactorily as the applicant agreed to amend the indication initially sought as follows:

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 ~~or a Janus kinase (JAK) inhibitor, or have medical contraindications to such therapies~~ (see section 5.1).

This is in line with the data from the development Programme as discussed above.

Maintenance of efficacy

Overall, the data from maintenance study AMBG demonstrated a statistically significant improvement in clinical response over time compared to placebo. The proportions of patients achieving clinical remission were: 49.9% in patients randomly assigned to 200 mg mirikizumab SC Q4W, and 25.1% in patients randomly assigned to placebo (common risk difference = 23.2%; p<.001).

Also, the key secondary endpoints also demonstrated statistically significant better results compared to placebo over time. These included endoscopic remission at week 40 showed a risk difference (RD) 28.5% P < 0.001, maintenance of clinical remission at Week 40 RD 24.8% p< 0.001.

A significantly greater percentage of patients achieved corticosteroid-free remission without surgery at Week 40 in the mirikizumab-treatment group compared to the placebo group (p<0.001), histologic-endoscopic mucosal remission (p<0.001), Bowel Movement Urgency NRS (p<0.001) AND Urgency Remission (Urgency NRS = 0 or 1).

Subgroup analysis based on demographic, previous treatment, duration of disease etc demonstrated a consistent beneficial effect for both clinical remission and endoscopic improvement. The only variable in question is patients who are obese, BMI ≥ 30 and ≤ 40 kg/m^2**.** The lower limit crosses zero, however the number of patients was relatively low compared to the normal and overweight cohorts and patients with severe UC generally have lower BMI's.

The secondary endpoints were further supported by improvements in clinical remission in patients with or without steroids at baseline, abdominal pain and fatigue all $p < 0.001$.

There was also a statistically significant difference for inflammatory biomarkers seen with treatment for both CRP and Faecal calprotectin with mirikizumab treatment compared to placebo.

Health related outcomes: Among the mirikizumab induction responders at Week 40, patients in the mirikizumab-treatment group achieved a significantly greater ($p<0.001$) mean increase (improvement) from baseline in IBDQ total score, IBDQ response, IBDQ remission, compared to the placebo group. Also, mirikizumab-treatment group achieved a significantly greater improvement from baseline in EQ-5D-5L VAS score, SF-36 PCS component score SF-36 MCS component score versus placebo.

Of the 365 mirikizumab responders from Study AMAN randomly assigned to mirikizumab maintenance treatment, 19 (5.2%) experienced a loss of response during maintenance and received at least 1 dose of rescue therapy with open-label 300 mg mirikizumab IV Q4W for up to 3 doses. Of the rescued patients, 12 (63.2%) patients regained symptomatic response and 7 (36.8%) achieved Symptomatic Remission after 12 weeks of rescue therapy. These patients were treated in open label rescue and the efficacy data was not therefore controlled for type 1 error. The rescued patients who achieved a clinical response were then given 200mg Q4W. Accordingly, the SmPC recommends considering a total of 3 doses of 300mg intravenous infusion and, if clinical benefit is achieved to resume the maintenance dosing. Which is acceptable.

The applicant has added a wording to the SmPC to recommend an additional 12 weeks' treatment for patients who did not achieve induction remission. This is agreed however as it is unclear what percentage of these patients can then be maintained on 200 mg Q4W the SmPC now also clarifies that Mirikizumab should be discontinued if no therapeutic benefit to extended induction therapy materialises by week 24.

2.6.7. Conclusions on the clinical efficacy

Overall, the applicant has demonstrated through the clinical trials submitted that mirikizumab is an efficacious treatment for induction and maintenance of patients with UC in the proposed indication.

2.6.8. Clinical safety

The main safety data supporting this MAA come from 2 pivotal Phase 3 studies in participants with UC:

- I6T-MC-AMAN (AMAN), and
- I6T-MC-AMBG (AMBG).

Supportive safety data provide context to the 2 pivotal Phase 3 studies, UC studies and includes safety data from the entire mirikizumab clinical development programme encompassing 11 studies:

- 4 studies in participants with moderately-to-severely active UC, including the 2 pivotal trials and the supportive

o Phase 2 Study I6T-MC-AMAC (AMAC), and

o Phase 3 long-term extension Study I6T-MC-AMAP (AMAP).

- 2 studies in participants with moderate-to-severe CD
- 5 studies in participants with moderate-to-severe plaque psoriasis

2.6.8.1. Patient exposure

UC Induction Placebo-Controlled Analysis Set

In the safety population that includes all participants who received 1 dose, there were **1281** participants in the UC Induction Placebo-Controlled Analysis Set.

- 322 placebo IV Q4W, and
- 959 mirikizumab 300 mg IV Q4W.

The number and percentage of participants who completed 12 weeks of study treatment was 285 (88.5%) placebo group participants, and 920 (95.9%) mirikizumab treatment participants.

UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Set

There were **581** participants in the UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Set

- 192 placebo SC Q4W, and
- 389 mirikizumab 200 mg SC Q4W.

The number and percentage of participants who completed 40 weeks of study treatment was

- 119 (62.0%) placebo group participants, and

347 (89.2%) mirikizumab treatment participants

Overall exposure is based on the data from participants who received at least 1 dose of study drug during the mirikizumab clinical studies. The All UC Mirikizumab Integrated Analysis Set, which includes all mirikizumab exposures in the UC clinical programs, includes 2250.9 total PYE and is of primary interest to characterise the safety profile of mirikizumab in UC. The All Mirikizumab Exposures Integrated Analysis Set, which includes all mirikizumab exposures across the UC, CD, and psoriasis clinical programs, includes a total of 7801.3 total PYE; the majority of this exposure to mirikizumab was accrued in patients with psoriasis.

Table 5: Total Exposure to Mirikizumab UC Induction Placebo-Controlled, UC Maintenance Mirikizumab Responder Placebo-Controlled, UC Treatment Regimen Integrated, All UC Mirikizumab Integrated, and All Mirikizumab Exposures Integrated Analysis Sets

	Induction (Weeks 0-12)		Maintenance (Weeks 12-52)		UC Treatment Regimen (Weeks 0-52)	All UC Mirikizumab	All Mirikizumab Exposures
	placebo IV Q4W N=321	miri 300 mg IV Q4W N=958	placebo SC Q4W N=192	miri 200 mg SC Q4W N=389	miri N=389	miri N=1442	miri N=3798
Patient weeks of exposure, mean (SD)	11.7 (2.1)	12.1 (1.4)	32.4 (11.6)	38.4 (7.1)	52.6 (7.7)	81.5 (62.7)	107.2 (59.7)
Weeks of Exposure, n (%)							
>0	321 (100.0)	958 (100.0)	192 (100.0)	389 (100.0)	389 (100.0)	1442 (100.0)	3798 (100.0)
≥4	315 (98.1)	952 (99.4)	187 (97.4)	389 (100.0)	389 (100.0)	1432 (99.3)	3763 (99.1)
≥8	301 (93.8)	938 (97.9)	185 (96.4)	386 (99.2)	389 (100.0)	1410 (97.8)	3728 (98.2)
≥12	211 (65.7)	725 (75.7)	178 (92.7)	383 (98.5)	389 (100.0)	1376 (95.4)	3673 (96.7)
≥16	--	--	170 (88.5)	374 (96.1)	389 (100.0)	1258 (87.2)	3542 (93.3)
≥24	--	--	144 (75.0)	360 (92.5)	383 (98.5)	1208 (83.8)	3431 (90.3)
≥32	--	--	124 (64.6)	352 (90.5)	368 (94.6)	1022 (70.9)	3198 (84.2)
≥40	--	--	91 (47.4)	263 (67.6)	--	--	--
≥52	--	--	--	--	346 (88.9)	926 (64.2)	3025 (79.6)
≥104	--	--	--	--	--	450 (31.2)	2061 (54.3)
Total patient years[a]	72.1	221.8	119.4	286.0	391.8	2250.9	7801.3

2.6.8.2. Adverse events

General information

Table 6: Overview of Adverse Events by Frequency (On Treatment) UC Treatment Regimen, All UC Mirikizumab, and All Mirikizumab Exposures Integrated Analysis Sets

Event, n (%) [IR]	UC Induction (Weeks 0-12)		Maintenance (Weeks 12-52)		UC Treatment Regimen	All UC Mirikizumab	All Mirikizumab Exposures
	placebo IV Q4W N = 321 PYE = 72.1	miri 300 mg IV Q4W N = 958 PYE = 221.8	placebo SC Q4W N = 192 PYE = 119.3	miri 200 mg SC Q4W N = 389 PYE = 286	miri N = 389 PYE = 391.8	miri N = 1442 PYE = 2250.9	miri N = 3798 PYE = 7801.3
Participants with at least 1 TEAE	148 (46.1) [280.6]	426 (44.5) [261.0]	132 (68.8) [196.8]	251 (64.5) [160.1]	278 (71.5) [150.1]	1052 (73.0) [135.2]	3048 (80.3) [131.1]
Deaths	0 (0) [0]	0 (0) [0]	1 (0.5) [0.8]	0 (0) [0]	0 (0) [0]	1 (0.1) [0]	11 (0.3) [0.1]
SAEs	17 (5.3) [24.0]	27 (2.8) [12.3]	15 (7.8) [12.8]	13 (3.3) [4.6]	18 (4.6) [4.7]	123 (8.5) [5.7]	385 (10.1) [5.2]
Discontinuations from study treatment due to AE	23 (7.2) [32.4]	15 (1.6) [6.8]	16 (8.3) [13.6]	6 (1.5) [2.1]	7 (1.8) [1.8]	69 (4.8) [3.1]	182 (4.8) [2.3]

Abbreviations: AE = adverse event; IR = incidence rate; IV = intravenous; miri = mirikizumab; N = number of participants in the safety analysis set; n = number of participants within each specific category; PYE = patient-years of exposure; Q4W = once every 4 weeks; SAE = serious adverse event; SC = subcutaneous; TEAE = treatment-emergent adverse event; UC = ulcerative colitis.

Table 7: Overview of Adverse Events by Frequency (On- and Off-Treatment) UC Treatment Regimen, All UC Mirikizumab, and All Mirikizumab Exposures Integrated Analysis Sets

	UC Treatment Regimen Integrated Analysis Set (N=389)		UC Miri Exposures Integrated Analysis Set (N=1442)		All Miri Exposures Integrated Analysis Set (N=3798)	
Category	During miri treatment*a (Weeks 0-52) n (%)	During miri treatment and off miri*b n (%)	During miri treatment*a n (%)	During miri treatment and off miri*b n (%)	During miri treatment*a n (%)	During miri treatment and off miri*b n (%)
Treatment-emergent Adverse Events (TEAE)	278 (71.5)	279 (71.7)	1052 (73.0)	1107 (76.8)	3048 (80.3)	3112 (81.9)
TEAE by severity *c						
Mild	144 (37.0)	144 (37.0)	466 (32.3)	467 (32.4)	1236 (32.5)	1231 (32.4)
Moderate	114 (29.3)	115 (29.6)	482 (33.4)	517 (35.9)	1484 (39.1)	1529 (40.3)
Severe	20 (5.1)	20 (5.1)	104 (7.2)	123 (8.5)	328 (8.6)	352 (9.3)
Deaths	0	0	1 (0.1)	4 (0.3)	11 (0.3)	14 (0.4)
Serious Adverse Events	18 (4.6)	18 (4.6)	123 (8.5)	146 (10.1)	385 (10.1)	417 (11.0)
Discontinuations from Study Treatment due to Adverse Event	7 (1.8)	7 (1.8)	69 (4.8)	86 (6.0)	182 (4.8)	199 (5.2)

Common AEs by SOC

TEAEs within SOCs reported by more than 10% of the participants in either treatment group were infections and infestations and gastrointestinal disorders.

A numerically higher percentage of mirikizumab-treated participants compared with placebo-treated participants reported a TEAE in the Infections and infestations SOC. Several PTs in the Infections and infestations SOC showed a higher frequency in the mirikizumab treatment group compared with placebo (nasopharyngitis, URTI, and rhinitis). The frequency of events reported in the Infections and infestations SOC may be due to the increased risk of infections in people with UC and people treated with immunomodulatory therapies such as mirikizumab.

A numerically higher percentage of placebo group participants compared with mirikizumab treated participants reported a TEAE in the gastrointestinal disorders SOC. The most frequently reported TEAE in the gastrointestinal disorders SOC was UC. Notably, a higher frequency of participants in the placebo group reported a TEAE of UC compared with mirikizumab, clinically indicative of a lack of improvement of UC in the placebo group. There was a higher frequency of TEAEs reported from the Blood and lymphatic system disorders SOC in placebo group compared with the mirikizumab group due in large part to increased frequency of anaemia and iron deficiency anaemia. There was a higher frequency of Skin and subcutaneous tissue disorders SOC in mirikizumab compared with placebo due to the numerical increase in several TEAEs within the Rash cluster.

Table 8: System Organ Class by Decreasing Frequency in the Mirikizumab Treatment Group UC Induction Placebo-Controlled Analysis Set

System Organ Class, n (%)	placebo IV Q4W N = 321	miri 300 mg IV Q4W N = 958
Participants with at least 1 TEAE	148 (46.1)	426 (44.5)
Infections and infestations	45 (14.0)	145 (15.1)
Gastrointestinal disorders	48 (15.0)	101 (10.5)
Blood and lymphatic system disorders	30 (9.3)	60 (6.3)
Skin and subcutaneous tissue disorders	16 (5.0)	58 (6.1)
Musculoskeletal and connective tissue disorders	17 (5.3)	52 (5.4)
Nervous system disorders	19 (5.9)	52 (5.4)
General disorders and administration site conditions	17 (5.3)	50 (5.2)
Investigations	12 (3.7)	40 (4.2)
Respiratory, thoracic, and mediastinal disorders	13 (4.0)	32 (3.3)
Metabolism and nutrition disorders	7 (2.2)	28 (2.9)
Injury, poisoning, and procedural complications	6 (1.9)	24 (2.5)
Vascular disorders	5 (1.6)	20 (2.1)
Eye disorders	7 (2.2)	19 (2.0)
Psychiatric disorders	8 (2.5)	18 (1.9)
Cardiac disorders	5 (1.6)	9 (0.9)
Reproductive system and breast disorders	1 (0.3)	9 (0.9)
Immune system disorders	1 (0.3)	6 (0.6)
Hepatobiliary disorders	2 (0.6)	5 (0.5)
Renal and urinary disorders	3 (0.9)	5 (0.5)
Ear and labyrinth disorders	1 (0.3)	4 (0.4)
Neoplasms benign, malignant and unspecified	1 (0.3)	4 (0.4)
Congenital, familial, and genetic disorders	0 (0)	1 (0.2)
Endocrine disorders	2 (0.6)	1 (0.1)
Surgical and medical procedures	1 (0.3)	0 (0)

Abbreviations: IV = intravenous; miri = mirikizumab; N = number of participants in the safety analysis set; n = number of participants in specified category; Q4W = once every 4 weeks; TEAE = treatment-emergent adverse event; UC = ulcerative colitis.

UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Set

TEAEs within SOCs reported by more than 10% of the participants in either treatment group were

- Infections and infestations
- Gastrointestinal disorders
- General disorders and administration site conditions,
- Musculoskeletal and connective tissue disorders, and
- Skin and subcutaneous tissue disorders.

In the General disorders and administration site conditions, a higher percentage of TEAEs were reported in mirikizumab-treated participants compared with placebo, with injection site pain being the most frequently reported TEAE in the mirikizumab-treatment group (4.4%). This may be due in part to the higher frequency of injection site pain and other injection site-related AE terms reported for mirikizumab-treated participants compared with placebo. In the Musculoskeletal disorders SOC, most events reported were arthralgia which contributed to the higher frequency of SOC Musculoskeletal disorders reported in mirikizumab compared with placebo. No other PTs reported contributed similarly. In the Skin and subcutaneous tissue disorders, a higher percentage of TEAEs were reported in

mirikizumab-treated participants compared with placebo, with rash being the most frequently reported TEAE in the mirikizumab treatment group (3.6%). In Nervous system disorders, a higher percentage of TEAEs were reported in mirikizumab-treated participants compared with placebo, with headache being the most frequently reported TEAE in the mirikizumab treatment group (4.1%). In Respiratory, thoracic and mediastinal disorders, a higher percentage of TEAEs were reported in mirikizumab-treated participants compared with placebo, with cough and oropharyngeal pain being the most frequently reported TEAEs in the mirikizumab treatment group (1.3% for both).

In the Vascular disorders SOC, most reported events were hypertension, and these events contributed to the higher frequency reported for mirikizumab-treated participants compared with placebo. No other reported PTs contributed similarly. In the remaining SOCs reported more frequently in the mirikizumab treatment group compared with placebo, the numerical differences observed were evaluated and none of the others were considered clinically meaningful.

Among those SOCs reported more frequently by the placebo group, the higher frequency of TEAEs reported in the Gastrointestinal disorders SOC for placebo compared with mirikizumab-treated participants was due in large part to the higher frequency of reported colitis ulcerative.

This finding is similar to SOC evaluation of the UC Induction Placebo-Controlled Analysis Set and is considered clinically indicative of lack of improvement in the placebo group.

Table 9 System Organ Class by Decreasing Frequency in the Mirikizumab Treatment Group

UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Set

System Organ Class, n (%)	placebo SC Q4W N = 192	miri 200 mg SC Q4W N = 389
Participants with at least 1 TEAE	132 (68.8)	251 (64.5)
Infections and infestations	44 (22.9)	93 (23.9)
Gastrointestinal disorders	70 (36.5)	83 (21.3)
General disorders and administration site conditions	19 (9.9)	65 (16.7)
Musculoskeletal and connective tissue disorders	24 (12.5)	57 (14.7)
Skin and subcutaneous tissue disorders	13 (6.8)	44 (11.3)
Investigations	18 (9.4)	33 (8.5)
Nervous system disorders	9 (4.7)	31 (8.0)
Respiratory, thoracic, and mediastinal disorders	6 (3.1)	27 (6.9)
Metabolism and nutrition disorders	11 (5.7)	19 (4.9)
Injury, poisoning, and procedural complications	5 (2.6)	16 (4.1)
Blood and lymphatic system disorders	12 (6.3)	15 (3.9)
Vascular disorders	5 (2.6)	15 (3.9)
Psychiatric disorders	4 (2.1)	13 (3.3)
Eye disorders	2 (1.0)	12 (3.1)
Surgical and medical procedures	0 (0)	8 (2.1)
Immune system disorders	4 (2.1)	7 (1.8)
Neoplasms, benign, malignant, and unspecified	3 (1.6)	6 (1.5)
Reproductive system and breast disorders	0 (0)	6 (1.5)
Hepatobiliary disorders	1 (0.5)	5 (1.3)
Ear and labyrinth disorders	0 (0)	4 (1.0)
Cardiac disorders	2 (1.0)	3 (0.8)
Renal and urinary disorders	4 (2.1)	3 (0.8)
Congenital, familial, and genetic disorders	1 (0.5)	2 (0.5)
Endocrine disorders	1 (0.5)	1 (0.3)
Social circumstances	1 (0.5)	0 (0)

Abbreviations: miri = mirikizumab; N = number of participants in the safety analysis set; n = number of participants in the specified category; Q4W = once every 4 weeks; SC = subcutaneous; TEAE = treatment-emergent adverse event; UC = ulcerative colitis.

TEAEs considered related to study drug by the investigator

Common Treatment-Emergent Adverse Events

Common TEAEs are defined as events reported at a frequency of at least 1.0%, before rounding, of participants in the mirikizumab treatment group.

UC Induction Placebo-Controlled Analysis Set

Table 10 TEAEs Occuring in at least 1% of Mirikizumab-Treated Participants by Decreasing Frequency UC Induction Placebo-Controlled Analysis Set

Preferred Term	placebo IV Q4W (N=321) n (%)	300 miri IV Q4W (N=958) n (%)	Total (N=1279) n (%)	p-values*a 300 miri IV Q4W vs. placebo IV Q4W	Odds ratio*b 300 miri IV Q4W/ placebo IV Q4W
Subjects with >= 1 TEAE	148 (46.1)	426 (44.5)	574 (44.9)	0.650	0.94
Nasopharyngitis	10 (3.1)	39 (4.1)	49 (3.8)	0.505	1.32
Anaemia	19 (5.9)	32 (3.3)	51 (4.0)	0.048	0.55
Headache	9 (2.8)	32 (3.3)	41 (3.2)	0.718	1.20
Arthralgia	4 (1.2)	20 (2.1)	24 (1.9)	0.476	1.69
Colitis ulcerative	24 (7.5)	17 (1.8)	41 (3.2)	<0.001	0.22
Pyrexia	3 (0.9)	14 (1.5)	17 (1.3)	0.585	1.57
Upper respiratory tract infection	2 (0.6)	13 (1.4)	15 (1.2)	0.381	2.19
Fatigue	2 (0.6)	12 (1.3)	14 (1.1)	0.537	2.02
Pruritus	5 (1.6)	12 (1.3)	17 (1.3)	0.778	0.80
Hypertension	3 (0.9)	11 (1.1)	14 (1.1)	>0.999	1.23
Iron deficiency anaemia	7 (2.2)	10 (1.0)	17 (1.3)	0.156	0.47
Nausea	4 (1.2)	10 (1.0)	14 (1.1)	0.759	0.84
Oral herpes	2 (0.6)	10 (1.0)	12 (0.9)	0.741	1.68

Abbreviations: miri = mirikizumab; Q4W = every 4 weeks; TEAE = treatment emergent adverse event; N = number of subjects in the analysis population; n = number of subjects in the specified category.
See complete footnote on last page of the output.

Dataset: /lillyce/prd/ly3074828/i6t_mc_aman/final/data/analysis/restricted/adsl,adae.sas7bdat
Program: /lillyce/prd/ly3074828/i6t_mc_aman/final/programs/tfl/t_a_teae_gt_opcmiri_trt_pt_saf_i.sas
Output: /lillyce/prd/ly3074828/i6t_mc_aman/final/output/restricted/tfl/t_a_teae_gt_opcmiri_trt_pt_saf_i.rtf

Based on the thorough review of summary and participant-level data of common TEAEs reported in the UC Induction Placebo-Controlled Analysis Set, the TEAEs including headache, URTI, and fatigue were identified for further evaluation, as they were reported more frequently in the mirikizumab treatment group compared with the placebo group. Review of the other common TEAEs reported more frequently in the mirikizumab treatment group compared with placebo did not indicate clinically meaningful differences including, but not limited to, the frequency, severity or pattern in the time-to-onset of the events.

Headache was reported more frequently in the mirikizumab treatment group compared with placebo. All headache events were mild or moderate. None were reported as serious or led to study treatment discontinuation. No pattern in the time-to-onset, duration of the events, or common underlying aetiology was observed. URTI was reported more frequently in the mirikizumab treatment group compared with placebo. Most URTIs were reported as mild in severity. No URTIs were serious or led to study treatment discontinuation.

Fatigue was reported more frequently in the mirikizumab treatment group compared with placebo. The majority of mirikizumab-treated participants reporting fatigue were non-responders to treatment at the end of Study AMAN. Most fatigue events were reported as mild in severity. One participant reported a severe TEAE of fatigue after developing facial swelling and erythema a few hours after the first infusion of study drug. No fatigue events were reported as serious or resulted in study treatment discontinuation.

Anaemia, colitis ulcerative, and iron-deficiency anaemia were reported more frequently in the placebo group compared with the mirikizumab treatment group. These observed imbalances are clinically indicative of a lack of improvement of UC in the placebo group.

UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Set

Table 11 TEAEs Occuring in at least 1% of Mirikizumab-Treated Participants by Decreasing Frequency Safety Population – Induction Responder I6T-MC-AMBG- Maintenance Period

Preferred Term	Placebo Responder placebo SC (N=135) n (%)	Miri Responder placebo SC (N=192) n (%)	Miri Responder 200 miri SC (N=389) n (%)	Miri Responder Total (N=581) n (%)	p-values*b Miri Responder 200 miri SC vs. Miri Responder placebo SC	Odds ratio*c Miri Responder 20 miri SC/ Miri Responder placebo SC
Subjects with >= 1 TEAE	82 (60.7)	132 (68.8)	251 (64.5)	383 (65.9)	0.352	0.83
Nasopharyngitis	9 (6.7)	11 (5.7)	28 (7.2)	39 (6.7)	0.599	1.28
Arthralgia	4 (3.0)	8 (4.2)	26 (6.7)	34 (5.9)	0.263	1.65
Colitis ulcerative	18 (13.3)	40 (20.8)	26 (6.7)	66 (11.4)	<0.001	0.27
Injection site pain	2 (1.5)	6 (3.1)	17 (4.4)	23 (4.0)	0.652	1.42
Headache	5 (3.7)	2 (1.0)	16 (4.1)	18 (3.1)	0.045	4.08
Rash	2 (1.5)	0	14 (3.6)	14 (2.4)	0.007	NA
Pyrexia	6 (4.4)	5 (2.6)	13 (3.3)	18 (3.1)	0.801	1.29
Abdominal pain	3 (2.2)	4 (2.1)	11 (2.8)	15 (2.6)	0.783	1.37
Blood creatine phosphokinase increased	5 (3.7)	5 (2.6)	10 (2.6)	15 (2.6)	>0.999	0.99
Diarrhoea	3 (2.2)	1 (0.5)	10 (2.6)	11 (1.9)	0.111	5.04
Fatigue	1 (0.7)	4 (2.1)	10 (2.6)	14 (2.4)	>0.999	1.24
Gastrooesophageal reflux disease	0	1 (0.5)	10 (2.6)	11 (1.9)	0.111	5.04
Injection site reaction	1 (0.7)	1 (0.5)	10 (2.6)	11 (1.9)	0.111	5.04
Hypertension	1 (0.7)	1 (0.5)	9 (2.3)	10 (1.7)	0.177	4.52
Anaemia	8 (5.9)	9 (4.7)	8 (2.1)	17 (2.9)	0.113	0.43
COVID-19	5 (3.7)	4 (2.1)	8 (2.1)	12 (2.1)	>0.999	0.99
Injection site erythema	1 (0.7)	2 (1.0)	8 (2.1)	10 (1.7)	0.509	1.99
Back pain	4 (3.0)	4 (2.1)	7 (1.8)	11 (1.9)	0.758	0.86
Pain in extremity	1 (0.7)	3 (1.6)	7 (1.8)	10 (1.7)	>0.999	1.15
Upper respiratory tract infection	2 (1.5)	5 (2.6)	7 (1.8)	12 (2.1)	0.543	0.69

Abbreviations: miri = mirikizumab; SC = subcutaneous; TEAE = treatment emergent adverse event; N = number of subjects in the analysis population; n = number of subjects in the specified category.
See complete footnote on last page of the output.

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Treatment-Emergent Adverse Events Occurring in >=1% of Miri Treated Patients — Page 2 of 4
MedDRA Preferred Term by Decreasing Frequency — 10:15 09DEC2021
Safety Population - Induction Responder — PDPM
I6T-MC-AMBG - Maintenance period

Preferred Term	Placebo Responder placebo SC (N=135) n (%)	Miri Responder placebo SC (N=192) n (%)	Miri Responder 200 miri SC (N=389) n (%)	Miri Responder Total (N=581) n (%)	p-values*b Miri Responder 200 miri SC vs. Miri Responder placebo SC	Odds ratio*c Miri Responder 200 miri SC/ Miri Responder placebo SC
Dyspepsia	2 (1.5)	0	6 (1.5)	6 (1.0)	0.185	NA
Gastroenteritis	2 (1.5)	2 (1.0)	6 (1.5)	8 (1.4)	>0.999	1.49
Cough	1 (0.7)	1 (0.5)	5 (1.3)	6 (1.0)	0.669	2.49
Haemorrhoids	2 (1.5)	3 (1.6)	5 (1.3)	8 (1.4)	0.723	0.82
Hypoaesthesia	0	0	5 (1.3)	5 (0.9)	0.177	NA
Influenza like illness	1 (0.7)	1 (0.5)	5 (1.3)	6 (1.0)	0.669	2.49
Migraine	0	0	5 (1.3)	5 (0.9)	0.177	NA
Oropharyngeal pain	1 (0.7)	1 (0.5)	5 (1.3)	6 (1.0)	0.669	2.49
Urinary tract infection	0	1 (0.5)	5 (1.3)	6 (1.0)	0.669	2.49
Vulvovaginal mycotic infection*a	0	0	2 (1.3)	2 (0.8)	>0.999	NA
Alanine aminotransferase increased	1 (0.7)	1 (0.5)	4 (1.0)	5 (0.9)	>0.999	1.98
Bronchitis	0	0	4 (1.0)	4 (0.7)	0.308	NA
Gamma-glutamyltransferase increased	2 (1.5)	1 (0.5)	4 (1.0)	5 (0.9)	>0.999	1.98
Herpes zoster	0	0	4 (1.0)	4 (0.7)	0.308	NA
Hyperglycaemia	3 (2.2)	1 (0.5)	4 (1.0)	5 (0.9)	>0.999	1.98
Nausea	2 (1.5)	5 (2.6)	4 (1.0)	9 (1.5)	0.165	0.39
Pharyngitis	1 (0.7)	0	4 (1.0)	4 (0.7)	0.308	NA
Pruritus	2 (1.5)	4 (2.1)	4 (1.0)	8 (1.4)	0.450	0.49
Respiratory tract infection viral	1 (0.7)	0	4 (1.0)	4 (0.7)	0.308	NA
Rhinitis	0	0	4 (1.0)	4 (0.7)	0.308	NA
SARS-CoV-2 test positive	1 (0.7)	0	4 (1.0)	4 (0.7)	0.308	NA
Seasonal allergy	0	2 (1.0)	4 (1.0)	6 (1.0)	>0.999	0.99

Abbreviations: miri = mirikizumab; SC = subcutaneous; TEAE = treatment emergent adverse event; N = number of subjects in the analysis population; n = number of subjects in the specified category.
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Treatment-Emergent Adverse Events Occurring in >=1% of Miri Treated Patients
MedDRA Preferred Term by Decreasing Frequency
Safety Population - Induction Responder
I6T-MC-AMBG - Maintenance period

Preferred Term	Placebo Responder placebo SC (N=135) n (%)	Miri Responder placebo SC (N=192) n (%)	Miri Responder 200 miri SC (N=389) n (%)	Miri Responder Total (N=581) n (%)	p-values*b Miri Responder 200 miri SC vs. Miri Responder placebo SC	Odds ratio*c Miri Responder 200 miri SC/ Miri Responder placebo SC
Stomatitis	1 (0.7)	1 (0.5)	4 (1.0)	5 (0.9)	>0.999	1.98

Abbreviations: miri = mirikizumab; SC = subcutaneous; TEAE = treatment emergent adverse event; N = number of subjects in the analysis population; n = number of subjects in the specified category.
See complete footnote on last page of the output.

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Output: /lillyce/prd/ly3074828/i6t_mc_ambg/intrm1/output/restricted/tfl/t_a_teae_gtopcmiri_pfdf_saf_ir_m.rtf

Based on thorough review of summary and participant-level data of common TEAEs reported in the UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Set, the numerical imbalances between mirikizumab and placebo for TEAEs of headache, rash, injection site reaction, and oropharyngeal pain were identified for further evaluation. Review of the other common TEAEs reported more frequently in the mirikizumab treatment group compared with placebo did not indicate clinically meaningful differences in the frequency, severity, or pattern in the time-to-onset of the events.

Headache

Similar to the UC Induction Placebo-Controlled Analysis Set, a higher frequency o mirikizumab-treated participants (4.1%) reported headache TEAEs compared with placebo participants (1.0%) in the UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Set. All headache events were reported as mild or moderate. None were reported as serious or led to study treatment discontinuation. No pattern in the time-to-onset, or duration of the events, or common underlying aetiology was observed.

Rash

An imbalance in the frequency of reported rash TEAEs in the mirikizumab-treated participants (3.6%) compared with placebo (0) was observed. All rash events were reported as mild or moderate. None were reported as serious or led to study treatment discontinuation. There was no apparent temporal relationship between mirikizumab administration and onset of rash, as event start ranged from Days 30 to 250. No consistent duration in events was observed, as events lasted from Days 1 to 228.

Injection site reaction (PT)

Injection site reaction TEAEs were more frequently reported in mirikizumab-treated participants (2.6%) compared with placebo (0.5%). All injection site reaction events were reported as mild or moderate. None were reported as serious or led to study treatment discontinuation. Duration was 1 to 9 days in the majority of participants. Six of the 10 mirikizumab participants with events reported an injection site reaction at more than 1 dosing visit.

Oropharyngeal pain

Oropharyngeal pain within the URTI cluster occurred notably more frequently in mirikizumab treated

Participants' (1.3%) compared with placebo (0.5%).

Common AEs reported more frequently in placebo compared with mirikizumab

The frequency of colitis ulcerative and anaemia remained higher in placebo compared with the mirikizumab treatment group, and this consistent finding in the UC Induction and UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Set is suggestive of the lack of improvement of UC in the placebo group.

UC Treatment Regimen, All UC Mirikizumab, and All Mirikizumab Exposures Integrated Analysis Sets

In the All UC Mirikizumab Integrated Analysis Set, the majority of common TEAEs were reported at a lower IR compared with the UC Treatment Regimen Integrated Analysis Set.

TEAEs reported at a higher IR in the All UC Mirikizumab Integrated Analysis Set compared with the UC Treatment Regimen Integrated Analysis Set were colitis ulcerative, COVID-19, and upper respiratory tract infection.

The higher IR for colitis ulcerative in the All UC Mirikizumab Integrated Analysis Set likely reflects the inclusion of UC non-responders and participants with LOR who, based on their more active UC and refractory nature of their disease to treatment, would be expected to report colitis ulcerative TEAEs.

The higher incidence rate for COVID-19 in the All UC Mirikizumab Integrated Analysis Set is not unexpected in a participant population that includes UC non-responders and participants with LOR, as such participants may be at increased risk to develop an infection due to UC, comorbidities or concomitant UC medications. The higher incidence rate for COVID-19 may also be related to the ongoing spread of COVID-19 as the global pandemic matured and infected a greater proportion of the world's population.

A comparison of incidence rates of common TEAEs reported in the UC Treatment Regimen and All UC Mirikizumab Integrated Analysis Sets demonstrates that longer duration of mirikizumab exposure in participants with UC does not increase the IR of these common TEAEs. The IR of the most common TEAEs appeared to be stable or decreased with continued exposure. The higher IR of colitis ulcerative, COVID-19, and upper respiratory tract infection TEAEs in the All UC Mirikizumab Integrated Analysis Set likely reflects inclusion of participants with more severely active UC and the maturation of the COVID-19 global pandemic

Table 12 Common Treatment-Emergent Adverse Events Occurring in at least 3% of Participants by Decreasing Frequency in the All UC Mirikizumab Integrated Analysis Set

Event, n (%) [IR]	UC Treatment Regimen Integrated Analysis Set	All UC Mirikizumab Integrated Analysis Set
	miri N = 389	miri N = 1442
Participants with at least 1 TEAE	278 (71.5) [150.1]	1052 (73.0) [135.2]
Colitis ulcerative	27 (6.9) [7.1]	176 (12.2) [8.4]
Nasopharyngitis	46 (11.8) [12.7]	167 (11.6) [8.4]
Headache	26 (6.7) [6.9]	126 (8.7) [6.1]
Arthralgia	33 (8.5) [8.9]	124 (8.6) [5.9]
Anaemia	20 (5.1) [5.3]	80 (5.5) [3.7]
COVID-19	10 (2.6) [2.6]	76 (5.3) [3.5]
Upper respiratory tract infection	11 (2.8) [2.9]	67 (4.6) [3.1]
Pyrexia	19 (4.9) [5.0]	65 (4.5) [3.0]
Hypertension	18 (4.6) [4.7]	51 (3.5) [2.3]
Nausea	10 (2.6) [2.6]	50 (3.5) [2.3]
Back pain	10 (2.6) [2.6]	47 (3.3) [2.2]
Fatigue	13 (3.3) [3.4]	48 (3.3) [2.2]
Abdominal pain	16 (4.1) [4.2]	48 (3.3) [2.2]
Injection site pain	17 (4.4) [4.5]	44 (3.1) [2.0]

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

Treatment-Emergent Adverse Events by Cluster

The percentages of participants with TEAEs are summarised by treatment using the MedDRA PT nested within the predefined event clusters. Event clusters were defined by medical representatives after a blinded review of the MedDRA PTs reported by any participant in the safety population. PTs that are essentially synonymous and refer to the same clinical concept were grouped as a cluster.

Table 13 Definitions of Event Clusters Cluster Preferred Terms Included in Cluster

Cluster	Preferred Terms Included in Cluster
Abdominal pain	abdominal pain, abdominal pain upper, abdominal pain lower, and abdominal discomfort.
Diarrhoea	diarrhoea and frequent bowel movements.
Fatigue	fatigue, malaise, and asthenia.
Gastroenteritis	gastroenteritis, gastroenteritis rotavirus, and gastroenteritis viral.
Headache	headache and tension headache
Herpes simplex infection	oral herpes, genital herpes, herpes simplex reactivation, and herpes simplex.
Hypertension	hypertension, accelerated hypertension, blood pressure increased, and essential hypertension.
Hypertriglycerdaemia	blood triglycerides increased and hypertriglyceridaemia.
Infusion site reaction	infusion site erythema, infusion site pain, infusion site paraesthesia, and infusion site pruritus.
Leukopenia	leukopenia and white blood cell count decreased.
Neutropenia	neutropenia and neutrophil count decreased.
Rash	rash, rash pruritic, rash macular, rash maculo-papular, and rash papular.
Tinea infection	body tinea, tinea cruris, and tinea infection.
Upper respiratory tract infection	nasopharyngitis, upper respiratory tract infection, oropharyngeal pain, rhinitis, pharyngitis, sinusitis, tonsillitis, oropharyngeal discomfort, acute sinusitis, and viral URTI.

Table 14 Event Clusters by Decreasing Frequency in the Induction Mirikizumab Treatment Group UC Induction and UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Sets

Cluster, n (%)	Induction (Weeks 0-12)		Maintenance (Weeks 12-52)	
	placebo IV Q4W N = 321	miri 300 mg IV Q4W N = 958	placebo SC Q4W N = 192	miri 200 mg SC Q4W N = 389
Upper respiratory tract infection	19 (5.9)	76 (7.9)	19 (9.9)	46 (11.8)
Headache	9 (2.8)	32 (3.3)	2 (1.0)	16 (4.1)
Fatigue	6 (1.9)	18 (1.9)	5 (2.6)	14 (3.6)
Abdominal pain	8 (2.5)	17 (1.8)	7 (3.6)	13 (3.3)
Hypertension	4 (1.2)	14 (1.5)	1 (0.5)	10 (2.6)
Herpes simplex infection	3 (0.9)	13 (1.4)	1 (0.5)	5 (1.3)
Rash	2 (0.6)	11 (1.1)	1 (0.5)	16 (4.1)
Leukopenia	2 (0.6)	8 (0.8)	3 (1.6)	3 (0.8)
Neutropenia	1 (0.3)	8 (0.8)	2 (1.0)	1 (0.3)
Diarrhoea	0 (0)	7 (0.7)	2 (1.0)	12 (3.1)
Gastroenteritis	1 (0.3)	7 (0.7)	3 (1.6)	7 (1.8)
Infusion site reaction	1 (0.3)	4 (0.4)	--	--
Tinea infection	2 (0.6)	3 (0.3)	0 (0)	4 (1.0)
Hypertriglycerdaemia	1 (0.3)	2 (0.2)	0 (0)	3 (0.8)

Based on an evaluation of the individual PTs and the predefined clusters, there were 3 clusters where data supported a plausible association with mirikizumab treatment:

- Upper respiratory tract infection
- Rash, and
- Headache.

Upper respiratory tract infection cluster

UC Induction Placebo-Controlled Analysis Set

There were no severe or serious TEAEs reported, and no participants discontinued mirikizumab treatment due to an AE within the Upper respiratory tract infection cluster.

UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Set

One mirikizumab-treated participant reported a severe URTI TEAE of nasopharyngitis. No SAEs were reported, and no participants discontinued study treatment due to an AE within the cluster. Nasopharyngitis, upper respiratory tract infection and oropharyngeal pain were reported more frequently as individual PTs compared to other events included in the cluster.

Based on small but consistently higher frequency of events reported for mirikizumab-treated participants and the immunomodulatory mode of action of mirikizumab, there is biologic plausibility for an association between mirikizumab and the occurrence of URTI in the UC Induction Placebo-Controlled and UC Maintenance Mirikizumab Responder Analysis Sets.

Rash cluster

UC Induction Placebo-Controlled Analysis Set: All events reported within the Rash cluster were mild or moderate. None were reported as serious or led to study treatment discontinuation. No pattern in the time-to-onset or duration of the events was observed. None of the events occurred on a study drug dosing day (that is, none were immediate reactions). Ten mirikizumab participants had a past medical history of atopy, skin disorder, or food or drug hypersensitivity. Rash was reported as related to mirikizumab treatment by the investigator for 5 participants.

UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Set: Rash was reported more frequently as an individual PT compared with other events included in the cluster. Within the Rash cluster, all events reported were mild or moderate. None were reported as serious or led to study treatment discontinuation. No pattern in the time-to-onset or duration of the events was observed.

Seven participants had a past medical history of rash or a drug allergy/hypersensitivity to another medication. Four participants reported a rash in UC Induction Placebo-Controlled Analysis Set. Rash was reported as related to mirikizumab treatment by the investigator for 2 participants. While there was no distinct pattern in time-to-onset or duration of the rash events, the frequency of reports of rash notably increased in the mirikizumab-treated group during maintenance compared with induction with no increase in the placebo group. There is biologic plausibility for an association between the administration of mirikizumab and the occurrence of rash. Therefore, these observations were considered clinically meaningful.

Headache cluster

UC Induction and UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Set

In the Headache cluster, the majority of events reported were headache, which contributed to the higher frequency of the Headache cluster reported in the mirikizumab group compared with placebo.

Treatment-Emergent Adverse Events by Maximum Severity

In the UC clinical trials, severity of AEs was determined by the investigator based on their medical judgement.

UC Induction Placebo-Controlled Analysis Set

The frequency of severe TEAEs was higher in the placebo group than the mirikizumab treatment group. The Gastrointestinal disorders SOC had the highest frequency of severe events reported:

- 4.7% (n = 15) placebo, and

- 0.8% (n = 8) mirikizumab.

Of the severe TEAEs reported within the Gastrointestinal disorders SOC, a majority were colitis ulcerative (14 placebo; 6 mirikizumab). These observed imbalances are clinically indicative of more improvement of UC in the mirikizumab treatment group relative to the placebo group.

The frequency of severe TEAEs in the Infections and infestations SOC was higher in the mirikizumab group (0.5%, n = 5) than the placebo group (0.3%, n = 1). There was no pattern in the type of severe infection TEAEs, as each PT was reported by 1 participant.

Table 15 Treatment-Emergent Adverse Events by Maximum Severity UC Induction Placebo-Controlled Analysis Set Severity, n (%) placebo IV Q4W

Severity, n (%)	placebo IV Q4W N = 321	miri 300 mg IV Q4W N = 958
Participants with at least 1 TEAE	148 (46.1)	426 (44.5)
Mild	78 (24.3)	262 (27.3)
Moderate	47 (14.6)	143 (14.9)
Severe	23 (7.2)	21 (2.2)

UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Set

The frequency of severe TEAEs was higher in the placebo group than the mirikizumab treatment group. Gastrointestinal disorders SOC was the most frequently reported severe SOC in the placebo group compared with mirikizumab:

- 3.1% (n = 6) placebo, and
- 0.8% (n = 3) mirikizumab.

Similar to UC Induction Placebo-Controlled Analysis Set, most of the severe TEAEs reported with the Gastrointestinal disorders SOC were colitis ulcerative (6, placebo; 2 mirikizumab). These observed imbalances are clinically indicative of more improvement of UC in the mirikizumab treatment group relative to the placebo group. The frequency of severe TEAEs in the General disorders and administration conditions SOC was higher in the mirikizumab group (0.5%, n = 2) than in the placebo group (0%). The 2 severe TEAEs reported were injection site pain. The frequency of severe TEAEs in the Infections and infestations SOC was similar in the placebo group (2.1%, n = 4) than in the mirikizumab treatment group (0.8%, n = 3).

There were no other severe TEAE PTs reported in 2 or more participants in either the placebo or mirikizumab treatment groups.

Table 16 Treatment-Emergent Adverse Events by Maximum Severity UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Set

Severity, n (%)	placebo SC Q4W N = 192	miri 200 mg SC Q4W N = 389
Participants with at least 1 TEAE	132 (68.8)	251 (64.5)
Mild	71 (37.0)	148 (38.0)
Moderate	49 (25.5)	87 (22.4)
Severe	12 (6.3)	16 (4.1)

UC Treatment Regimen, All UC Mirikizumab, and All Mirikizumab Exposures Integrated Analysis Sets

The Gastrointestinal disorders SOC had the highest frequency of severe events reported among participants in the UC Treatment Regimen, All UC Mirikizumab, and All Mirikizumab

In the Gastrointestinal disorders SOC, the most frequently reported severe TEAE was colitis ulcerative. The frequency of participants reporting severe colitis ulcerative was

- 0.5% in the UC Treatment Regimen Integrated Analysis Set
- 1.9% in the All UC Mirikizumab Integrated Analysis Set, and
- 0.7% in the All Mirikizumab Exposures Integrated Analysis Set.

These frequencies likely reflect the UC disease activity in the populations comprising the different analysis sets. The frequency of participants reporting severe TEAEs in the remaining SOCs was consistent with the placebo-controlled analysis set data and reflected the longer duration of exposure to mirikizumab in the UC Treatment Regimen

Table 17 All UC Mirikizumab, and All Mirikizumab Exposures Integrated Analysis Sets.

Event, n (%)	UC Treatment Regimen Integrated Analysis Set	All UC Mirikizumab Integrated Analysis Set	All Mirikizumab Exposures Integrated Analysis Set
	miri N = 389	miri N = 1442	miri N = 3798
Participants with at least 1 TEAE	278 (71.5)	1052 (73.0)	3048 (80.3)
Mild	144 (37.0)	466 (32.3)	1235 (32.5)
Moderate	113 (29.0)	482 (33.4)	1482 (39.0)
Severe	21 (5.4)	104 (7.2)	331 (8.7)

Hepatic Treatment-Emergent Adverse Events

UC Induction Placebo-Controlled Analysis Set

Based on the hepatic disorders SMQ (narrow terms), the percentage of participants that reported at least 1 TE hepatic disorder was

- 1.6% (n = 5) placebo, and
- 1.6% (n = 15) mirikizumab.

In the placebo group, the most frequently reported TE hepatic disorder was GGT increased:

- 0.6% (n = 2) placebo, and

- 0.4% (n = 4) mirikizumab.

In the mirikizumab treatment group, the most frequently reported TE hepatic disorder was AST increased:

- 0.5% (n = 5) mirikizumab, and
- 0.3% (n = 1) placebo.

UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Set

Based on the hepatic disorders SMQ (narrow terms), the percentage of participants that reported at least 1 TE hepatic disorder was

- 2.1% (n = 4) placebo, and
- 3.1% (n = 12) mirikizumab.

In the placebo group, each hepatic event was reported for 1 participant (0.5%). In the mirikizumab treatment group, the most frequently reported TE hepatic disorders were

ALT increased and GGT increased:

- 0.5% (n = 1) placebo, and
- 1.0% (n = 4) mirikizumab.

The frequency of hepatic TEAEs (narrow terms) was similar between the placebo and mirikizumab treatment groups and was also similar between treatments for broad and narrow scope terms combined.

UC Treatment Regimen, All UC Mirikizumab, and All Mirikizumab Exposures Integrated Analysis Sets

The IRs of TE hepatic disorders in the UC Treatment Regimen and All UC Mirikizumab Integrated Analysis Sets did not suggest an increase in hepatic AEs with increased exposure and duration of treatment.

In the All Mirikizumab Exposures Integrated Analysis Set, 3 TEAEs of drug induced liver injury were reported in the Hepatobiliary disorders SOC in participants with psoriasis. Two of the events were related to treatment with isoniazid for latent tuberculosis and were moderate in severity. In 1 participant, ALT was elevated to ≥5xULN and in the other, ALT was increased to ≥10xULN.

One participant with baseline dyslipidaemia, **hepatic steatosis**, and alcohol use had ALT elevation to 6.49xULN and AST elevation to 3.22xULN fourteen days after the first dose of mirkizumab (250 mg SC Q4W). Although, the patient had no liver-related symptoms, the event was reported as DILI of moderate severity. ALT and AST improved without discontinuation of mirkizumab. On Day 40, a second event of DILI (mild in severity) was reported with ALT 1.67xULN and AST 0.92xULN. Thereafter, ALT and AST fluctuated between normal and 1.5xULN without discontinuation of mirkizumab and normalised on Day 334 only to fluctuate again between below normal and 2xULN while continuing mirkizumab treatment. Although the elevations were possibly related to mirikizumab, the Lilly internal assessment was that these changes were consistent with non-alcoholic fatty liver disease and that alcohol, cefaclor, tramadol, and acetaminophen (administered for an upper respiratory infection) may have contributed to the elevations.

Table 18 Exposure-Adjusted Incidence Rate of at least 2 per 100 Patient Years in the UC Induction, UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Sets, UC Treatment Regimen, and All UC Mirikizumab Integrated Analysis Sets

UC Mirikizumab Integrated Analysis Sets

Event, n (%) [IR]	Induction (Weeks 0-12)	Maintenance (Weeks 12-52)	UC Treatment Regimen (Weeks 0-52)	All UC Mirikizumab
	miri 300 mg IV Q4W N = 958 PYE = 221.8	miri 200 mg SC Q4W N = 389 PYE = 286	miri N = 389 PYE = 391.8	miri N = 1442 PYE = 2250.9
Participant with at least 1 reported narrow scope TEAE	15 (1.6) [6.8]	12 (3.1) [4.3]	17 (4.4) [4.5]	65 (4.5) [3.0]
ALT increased	4 (0.4) [1.8]	4 (1.0) [1.4]	6 (1.5) [1.5]	21 (1.5) [0.9]
GGT increased	4 (0.4) [1.8]	4 (1.0) [1.4]	5 (1.3) [1.3]	19 (1.3) [0.9]
AST increased	5 (0.5) [2.3]	3 (0.8) [1.1]	5 (1.3) [1.3]	19 (1.3) [0.9]
Hepatic enzyme increased	0 (0) [0]	1 (0.3) [0.4]	1 (0.3) [0.3]	3 (0.2) [0.1]
Liver function test increased	1 (0.1) [0.5]	2 (0.5) [0.7]	3 (0.8) [0.8]	6 (0.4) [0.3]
Blood bilirubin increased	3 (0.3) [1.4]	2 (0.5) [0.7]	4 (1.0) [1.0]	7 (0.5) [0.3]

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase;

GGT = gamma-glutamyltransferase; IR = incidence rate; IV = intravenous; miri = mirikizumab; N = number of participants in the safety analysis set; n = number of participants in specified category; PYE = patient-years of exposure; Q4W = once every 4 weeks; SC = subcutaneous; TEAE = treatment-emergent adverse event; UC = ulcerative colitis.

Treatment-Emergent Shifts in Hepatic Laboratory Values

TE elevations in hepatic enzymes were reported at a low frequency in the placebo-controlled periods of studies AMAN and AMBG.

Table 19 Postbaseline Values

Maximum Postbaseline Category, n (%)	Induction (Weeks 0-12)		Maintenance (Weeks 12-52)	
	placebo IV Q4W N = 321 Nx = 312	miri 300 mg IV Q4W N = 958 Nx = 947	placebo SC Q4W N = 192 Nx = 191	miri 200 mg SC Q4W N = 389 Nx = 387
ALT				
≥3xULN	2 (0.6)	4 (0.4)	1 (0.5)	3 (0.8)
≥5xULN	1 (0.3)	1 (0.1)	0 (0)	3 (0.8)
≥10xULN	0 (0)	0 (0)	0 (0)	0 (0)
AST				
≥3xULN	0 (0)	4 (0.4)	1 (0.5)	4 (1.0)
≥5xULN	0 (0)	2 (0.2)	0 (0)	3 (0.8)
≥10xULN	0 (0)	0 (0)	0 (0)	0 (0)
ALP				
≥2xULN	2 (0.6)	2 (0.2)	4 (2.1)	2 (0.5)
Total Bilirubin				
≥2xULN	1 (0.3)	6 (0.6)	4 (2.1)	2 (0.5)

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; IV = intravenous; miri = mirikizumab; N = number of participants in the safety analysis set; n = number of participants in specified category; Nx = number of participants in the baseline category and that have at least 1postbaseline measurement; Q4W = once every 4 weeks; SC = subcutaneous; UC = ulcerative colitis; ULN =upper limit of normal.

UC Treatment Regimen, All UC Mirikizumab, and All Mirikizumab Exposures Integrated Analysis Sets

Table 20 Participants Meeting Elevated Hepatic Criteria Maximum Postbaseline Values (ALT and AST) UC Placebo group, UC Treatment Regimen, All UC Mirikizumab, All Placebo group, and All Mirikizumab Exposures Integrated Analysis Sets

Maximum Postbaseline Category, n (%) [IR]	UC Placebo	UC Treatment Regimen	All UC Mirikizumab	All Placebo	All Mirikizumab Exposures
	N = 384 Nx = 377 PYE = 197.2	N = 389 Nx = 389 PYE = 391.8	N = 1442 Nx = 1427 PYE = 2250.9	N = 719 Nx = 711 PYE = 298.6	N = 3798 Nx = 3773 PYE = 7801.3
ALT					
≥3xULN	4 (1.1) [2.0]	5 (1.3) [1.3]	28 (2.0) [1.2]	9 (1.3) [3.0]	115 (3.0) [1.5]
≥5xULN	2 (0.5) [1.0]	4 (1.0) [1.0]	10 (0.7) [0.4]	5 (0.7) [1.7]	24 (0.6) [0.3]
≥10xULN	0 (0) [0]	0 (0) [0]	3 (0.2) [0.1]	0 (0) [0]	8 (0.2) [0.1]
AST					
≥3xULN	2 (0.5) [1.0]	5 (1.3) [1.3]	30 (2.1) [1.3]	4 (0.6) [1.3]	104 (2.8) [1.3]
≥5xULN	0 (0) [0]	4 (1.0) [1.0]	15 (1.1) [0.7]	1 (0.1) [0.3]	42 (1.1) [0.5]
≥10xULN	0 (0) [0]	0 (0) [0]	2 (0.1) [0.1]	0 (0) [0]	9 (0.2) [0.1]

Interpretation of the exposure-adjusted IRs for laboratory changes are influenced by differences in the frequency of sample collection during the induction Study AMAN, the maintenance Study AMBG, and the long-term extension Study AMAP.

Frequency and incidence rate

The frequency and IRs of ALT or AST shifts to ≥3x and, ≥5xULN in the UC Treatment Regimen, All UC Mirikizumab, and All Mirikizumab Exposures Integrated Analysis Sets did not show an increase in clinically relevant changes in ALT or AST compared with the UC Placebo and All Placebo treatment groups over longer duration of treatment.

The frequencies and IRs of ALT or AST shifts to ≥10xULN in the All UC Mirikizumab (0.2%, IR 0.1; 0.1%, IR 0.1) and All Mirikizumab Exposures (0.2%, IR 0.1) Integrated Analysis Sets were low. No participants in the UC Placebo or All Placebo group had ALT or AST elevations to ≥10xULN, although the lower sample size, limited duration of treatment, and few PYE for the UC Placebo and All Placebo participants may have contributed to fewer events detected.

Infections and Opportunistic Infections

UC Induction Placebo-Controlled Analysis Set

Based on the infections SMQ (narrow terms), the percentage of participants that reported at least 1 TE infection was 14.0% (n = 45) in placebo, and 15.1% (n = 145) in mirikizumab. In the placebo and mirikizumab treatment group, the most frequently reported TE infection was nasopharyngitis 3.1% (n = 10) in placebo, and 4.1% (n = 39) in mirikizumab. The frequency of reported TE infections was similar between the placebo and mirikizumab treatment groups.

UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Set

Based on the infections SMQ (narrow terms), the percentage of participants that reported at least TE infection was 22.9% (n = 44) in placebo, and 23.9% (n = 93) in mirikizumab. In the placebo and mirikizumab treatment group, the most frequently reported TE infection was nasopharyngitis: 5.7% (n = 11) in placebo, and 7.2% (n = 28) in mirikizumab.

All UC Mirikizumab Integrated Analysis Set

There was a transient increase in TE infections at Week 156. All participants who reported TE infections at Week 156 were in Study AMAP after having completed Study AMAC. The majority of these events were mild, and there was no pattern

observed in the types or duration of infections reported. All participants recovered from their infection, and none of these infections resulted in discontinuation of mirikizumab

Opportunistic infections

UC Induction Placebo-Controlled Analysis Set

Based on the OIs SMQ (narrow terms), the percentage of participants that reported at least 1 TE opportunistic infection was0.3% (n = 1) in placebo (1 HZ), and 0.5% (n = 5) in mirikizumab (1 oesophageal candidiasis, 2 cytomegalovirus colitis, 1 HZ, 1 intestinal tuberculosis). One participant (0.1%) in the mirikizumab treatment group reported cytomegalovirus colitis as a SAE.

Overall, the frequency of reported TE opportunistic infections was low in the placebo and mirikizumab treatment groups, although the majority of reported opportunistic infections were in the mirikizumab treatment group.

UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Set

Based on the OIs SMQ (narrow terms), the percentage of participants that reported at least 1 TE opportunistic infection was 0 in placebo, and 1.3% (n = 5) in mirikizumab. The 5 OIs reported in the UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Set were oral candidiasis (n=1) mirikizumab and HZ 1.0% (n=4) mirikizumab.

The frequency of TE OIs was low in the mirikizumab treatment group, with HZ reported as severe in 1 mirikizumab-treated participant. All other OIs were reported as mild to moderate in severity, and none resulted in discontinuation of mirikizumab.

Serious Infections

The frequencies of serious infections were low and similar between the UC Induction (n = 7, 0.7%) and UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Sets (n = 3, 0.8%), and did not demonstrate a clinically meaningful difference between mirikizumab treatment and placebo.

The IRs of serious infections in the UC Treatment Regimen, All UC Mirikizumab, and All Mirikizumab Exposures Integrated Analysis Sets were comparable to the Induction and Maintenance Analysis Sets and did not suggest an increase in reports of serious infections with increased duration of treatment

MACE

UC Induction Placebo-Controlled Analysis Set

No TE MACE were reported in the UC Induction Placebo-Controlled Analysis Set.

UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Set

The percentage of participants that reported at least 1 TE MACE was 0.5% (n = 1) in placebo, and 0% in mirikizumab. The event was reported by the investigator as ischaemic stroke Cerebrovascular event (nonfatal stroke) in the placebo group.

UC Treatment Regimen Integrated Analysis Set

No TE MACE were reported in the UC Treatment Regimen Integrated Analysis Set

All UC Mirikizumab and All Mirikizumab Exposures Integrated Analysis Set

The IR of TE MACE in the All UC Mirikizumab (0.2) and All Mirikizumab Exposures Integrated Analysis Set (0.3) were low although numerically higher compared to the UC Induction Placebo-Controlled and UC Maintenance Mirikizumab Responder Placebo-Controlled, and UC Treatment Regimen Integrated Analysis Sets.

The higher IR in the All Mirikizumab Exposures was related to the inclusion of psoriasis participants who have a higher risk and background IR for MACE (Gottlieb et al. 2014). In the placebo-controlled period of the mirikizumab psoriasis development programme, a numerical imbalance for MACE (placebo = 0; mirikizumab = 5; 0.4% [1.2 IR]) was observed. Across all treatment periods of the mirikizumab psoriasis development programme, 21 psoriasis participants reported TE MACE (2 cardiovascular death, 14 nonfatal MI, and 6 nonfatal stroke).

The MACE IR for the All Mirikizumab Exposures Analysis Set (0.3) was within published background IRs for each respective population and for other approved IL-23p19 inhibitors (0.2-0.6).

Table 21 Exposure-Adjusted Incidence Rates of Adjudicated and Confirmed Major Adverse Cardiovascular Events by Subcategory UC Induction Placebo-Controlled, UC Maintenance Mirikizumab Responder Placebo-Controlled, UC Treatment Regimen Integrated, All UC Mirikizumab Integrated, and All Mirikizumab Exposures Integrated Analysis Sets - Serious Adverse Events

Subcategory, n (%) [IR]	Induction (Weeks 0-12)	Maintenance (Weeks 12-52)	UC Treatment Regimen (Weeks 0-52)	All UC Mirikizumab	All Mirikizumab Exposures
	miri 300 mg IV Q4W N=958 PYE=221.8	miri 200 mg SC Q4W N=389 PYE=286	miri N=389 PYE=391.8	miri N=1349 PYE=2200.6	miri N=3591 PYE=7634.4
Participants with at least 1 MACE	0 (0) [0]	0 (0) [0]	0 (0) [0]	5 (0.4) [0.2]	26 (0.7) [0.3]
Cardiovascular death	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	2 (0.1) [0.3]
Nonfatal myocardial infarction	0 (0) [0]	0 (0) [0]	0 (0) [0]0	2 (0.1) [0.1]	16 (0.4) [0.2]
Nonfatal stroke	0 (0) [0]	0 (0) [0]	0 (0) [0]	3 (0.2) [0.1]	9 (0.3) [0.1]

Table 22 Exposure-Adjusted Incidence Rates of Adjudicated and Confirmed Cerebrocardiovascular Treatment-Emergent Adverse Events by Subcategory UC Induction Placebo-Controlled, UC Maintenance Mirikizumab Responder Placebo-Controlled, UC Treatment Regimen Integrated, All UC Mirikizumab Integrated, and All Mirikizumab Exposures Integrated Analysis Sets

Subcategory, n (%) [IR]	Induction (Weeks 0-12)	Maintenance (Weeks 12-52)	UC Treatment Regimen (Weeks 0-52)	All UC Mirikizumab	All Mirikizumab Exposures
	miri 300 mg IV Q4W N = 958 PYE = 221.8	miri 200 mg SC Q4W N = 389 PYE = 286	miri N = 389 PYE = 391.8	miri N = 1349 PYE = 2200.6	miri N = 3591 PYE = 7634.4
Participants with at least 1 CCV event	1 (0.1) [0.5]	0 (0) [0]	1 (0.3) [0.3]	11 (0.8) [0.5]	58 (1.6) [0.8]
Death	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	2 (0.1) [0.03]
Myocardial infarction	0 (0) [0]	0 (0) [0]	0 (0) [0]	2 (0.1) [0.1]	16 (0.4) [0.2]
Hospitalization for heart failure	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	3 (0.1) [0.04]
Hospitalization for hypertension	1 (0.1) [0.5]	0 (0) [0]	1 (0.3) [0.3]	1 (0.1) [0.05]	3 (0.1) [0.04]
Serious arrhythmia	0 (0) [0]	0 (0) [0]	0 (0) [0]	5 (0.4) [0.2]	24 (0.7) [0.3]
Resuscitated sudden death	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	1 (0.03) [0.01]
Coronary revascularization procedure	0 (0) [0]	0 (0) [0]	0 (0) [0]	2 (0.1) [0.1]	22 (0.6) [0.3]
Transient ischemic attack	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	5 (0.1) [0.1]
Stroke	0 (0) [0]	0 (0) [0]	0 (0) [0]	3 (0.2) [0.1]	9 (0.3) [0.1]
Peripheral arterial event	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	1 (0.03) [0.01]

Infusion Site Reactions

Participants in the UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Set only received SC administration of mirikizumab. Therefore, this dataset will not be included in the evaluation of infusion site reactions.

UC Induction Placebo-Controlled Analysis Set

Based on the Infusion site reaction HLT, the percentage of participants that reported at least 1 TE Infusion site reaction was 0.3% (n = 1) in placebo, and 0.4% (n = 4) in mirikizumab. In the placebo group, the reported TE Infusion site reaction (HLT) was infusion site paraesthesia. In the mirikizumab treatment group, the 4 reported TE Infusion site reactions (HLT) were infusion site erythema, infusion site pain infusion site paraesthesia, and infusion site pruritus. None of Infusion site reactions (HLT) were serious. No participants discontinued due to an Infusion site reaction (HLT).

UC Treatment Regimen, All UC Mirikizumab, and All Mirikizumab Exposures Integrated Analysis Sets

The frequencies of TE Infusion site reactions (HLT) in the UC Treatment Regimen, All UC Mirikizumab, and All Mirikizumab Exposures Integrated Analysis Sets were less than 1%. The differences in IRs of TE Infusion site reactions (HLT) between the Integrated Analysis Sets were small and not considered clinically meaningful. None of Infusion site reactions (HLT) were serious.

No participants with UC discontinued due to an Infusion site reaction (HLT). In the All Mirikizumab Exposures Integrated Analysis Set, the frequencies of discontinuations due to Infusion site reactions (HLT) was low and did not suggest an increase in the frequency of infusion site reaction-related events with increased duration of treatment.

Table 23 Exposure-Adjusted Incidence Rate of Infusion Site Reaction-Related Treatment-Emergent Adverse Events UC Induction Placebo-Controlled, UC Treatment Regimen Integrated, and All UC Mirikizumab Integrated Analysis Sets

Event, n (%) [IR]	Induction (Weeks 0-12)	UC Treatment Regimen (Weeks 0-52)	All UC Mirikizumab
	miri 300 mg IV Q4W N = 958 PYE = 221.8	miri N = 389 PYE = 100.4	miri N = 1364 PYE = 452.8
Participants with at least 1 TE infusion site reaction	4 (0.4) [1.8]	1 (0.3) [1.0]	8 (0.6) [1.8]
Infusion site erythema	1 (0.1 [0.5]	0 (0) [0]	2 (0.1) [0.4]
Infusion site pain	1 (0.1) [0.5]	0 (0) [0]	1 (0.1) [0.2]
Infusion site paraethesia	1 (0.1) [0.5]	1 (0.3) [1.0]	1 (0.1) [0.2]
Infusion site pruritus	1 (0.1) [0.5]	0 (0) [0]	1 (0.1) [0.2]
Infusion site reaction	0 (0) [0]	0 (0) [0]	1 (0.1) [0.2]
Infusion site swelling	0 (0) [0]	0 (0) [0]	1 (0.1) [0.2]
Infusion site warmth	0 (0) [0]	0 (0) [0]	1 (0.1) [0.2]

Injection Site Reactions

Participants in the UC Induction Placebo-Controlled Analysis Set only received IV administration of mirikizumab. Therefore, this dataset is not included in the evaluation of injection site reactions.

Treatment-Emergent Adverse Events

UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Set

The percentage of participants that reported at least 1 TE Injection site reaction (HLT)was 4.2% (n = 8) in placebo, and 8.7% (n = 34) in mirikizumab. In the placebo group, the most frequently reported TE Injection site reaction (HLT) was injection site pain (n = 6, 3.1%). In the mirikizumab treatment group, the most frequently reported TE Injection site reactions (HLT) were injection site pain (n = 17, 4.4%) injection site reaction (n = 10, 2.6%), and injection site erythema (n = 8, 2.1%). In the mirikizumab treatment group, Injection site reactions (HLT) were predominantly mild or moderate in severity.

UC Treatment Regimen Integrated Analysis Set

The IRs of TE Injection site reactions (HLT) in the UC Treatment Regimen, All UC Mirikizumab, and All Mirikizumab Exposures Integrated Analysis Sets were comparable to the Maintenance Analysis Set and did not suggest an increase in injection site reaction-related events with increased duration of treatment.

Table 24 Exposure-Adjusted Incidence Rate of Injection Site Reaction Related Adverse Events UC Maintenance Mirikizumab Responder Placebo-Controlled, UC Treatment Regimen Integrated, and All UC Mirikizumab Integrated Analysis Sets.

Event, n (%) [IR]	Maintenance (Weeks 12-52)	UC Treatment Regimen (Weeks 0-52)	All UC Mirikizumab
	miri 200 mg SC Q4W N = 389 PYE = 286	miri N = 389 PYE = 292.5	miri N = 1068 PYE = 1793.5
Participants with at least 1 injection site reaction (HLT)	34 (8.7) [12.8]	34 (8.7) [12.3]	92 (8.6) [5.6]
Injection site pain	17 (4.4) [6.2]	17 (4.4) [6.0]	44 (4.1) [2.5]
Injection site reaction	10 (2.6) [3.6]	10 (2.6) [3.5]	26 (2.4) [1.5]
Injection site erythema	8 (2.1) [2.8]	9 (2.3) [3.1]	25 (2.3) [1.4]
Injection site pruritus	2 (0.5) [0.7]	2 (0.5) [0.7]	5 (0.5) [0.3]
Injection site rash	1 (0.3) [0.4]	1 (0.3) [0.3]	4 (0.4) [0.2]
Injection site bruising	2 (0.5) [0.7]	2 (0.5) [0.7]	2 (0.2) [0.1]
Injection site dermatitis	1 (0.3) [0.4]	1 (0.3) [0.3]	1 (0.1) [0.1]
Injection site haematoma	1 (0.3) [0.3]	1 (0.3) [0.3]	2 (0.2) [0.1]
Injection site hypersensitivity	1 (0.3) [0.3]	1 (0.3) [0.3]	2 (0.2) [0.1]
Injection site induration	0 (0) [0]	0 (0) [0]	2 (0.2) [0.1]
Injection site swelling	0 (0) [0]	0 (0) [0]	2 (0.2) [0.1]
Injection site urticaria	1 (0.3) [0.4]	2 (0.5) [0.7]	2 (0.2) [0.1]
Injection site discolouration	0 (0) [0]	0 (0) [0]	1 (0.1) [0.1]
Injection site haemorrhage	0 (0) [0]	0 (0) [0]	1 (0.1) [0.1]
Injection site oedema	1 (0.3) [0.3]	1 (0.3) [0.3]	1 (0.1) [0.1]
Injection site paraesthesia	1 (0.3) [0.4]	1 (0.3) [0.3]	1 (0.1) [0.1]
Injection site warmth	0 (0) [0]	0 (0) [0]	1 (0.1) [0.1]

Based on the Injection site reaction HLT, no participant reported a serious Injection site reaction in the placebo group, no participants reported a reason for discontinuation due to a TE Injection site reaction.

In the mirikizumab treatment group, 1 (0.3%) participant discontinued due to a TE Injection site reaction (HLT) of injection site hypersensitivity.

UC Treatment Regimen, UC Mirikizumab Maintenance Responders, and All Mirikizumab Responders Integrated Analysis Sets.

No additional participants discontinued due to Injection site reactions (HLT) in the UC Treatment Regimen Integrated Analysis Set. One additional participant discontinued due to an event of injection site hypersensitivity in the All UC Mirikizumab Integrated Analysis Set (n = 2, 0.1%).

Two additional participants discontinued due to Injection site reactions (HLT) of injection site pain (n = 1, 0.0%) and injection site reaction (n = 1, 0.0%) in the All Mirikizumab Exposures Integrated Analysis Set.

Infusion and Injection Site Reactions by Antidrug Antibody Status.

In the UC Treatment Regimen Integrated Analysis Set, the frequency of participants with 1 or more Infusion site reactions (HLT) was similar between TE ADA negative (0.3%) and TE ADA positive participants (0%). The frequency of participants with 1 or more Injection site reactions (HLT) was similar between TE ADA negative (8.3%) and TE ADA positive participants (10.2%)

Treatment-Emergent Malignancies

The incidence rates (IR) of all malignancies among patients with UC range from 0.33 to 1.34 per 100PY, with some studies reporting UC to be associated with a significantly increased risk of malignancies (Karlén et al. 1999; Jussila et al. 2013; Jung et al. 2017; Burisch et al. 2022,), and other studies finding no significant association (Bernstein 2001a; Jess et al. 2013b; Biancone et al. 2016; van den Heuvel et al. 2016; So et al. 2017; Taborelli et al. 2020). The background incidence rates for selected relevant specific malignancies, associated with UC, were provided; colon, rectal, gastric, prostate, and non-melanoma skin cancer (NMSC).

The frequencies of TE malignancies were low and similar between the UC Induction and UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Sets and did not demonstrate a clinically meaningful difference between mirikizumab treatment and placebo.

In the *Neoplasms benign, malignant, and unspecified* SOC, a numerically higher frequency of TEAEs were reported with mirikizumab in the Study AMBG Extended Induction group (6 participants, 1.9%) compared with the UC Induction Placebo-Controlled Analysis Set (4 participants, 0.4%). The Extended Induction events included 1 event of gastric cancer in an Asian female with a family history of gastric and hepatic cancer and 5 different benign tumour types. Given the relatively short mirikizumab exposure preceding diagnosis, these benign and malignant neoplasms were likely pre-existing.

The IRs of TE malignancies in the UC Treatment Regimen Integrated Analysis Set and the All UC Mirikizumab Integrated Analysis Set, were comparable to the Induction and Maintenance Analysis Sets and do not suggest an increase in the frequency of malignancy related events with increased duration of treatment.

Table 25 Exposure Adjusted Incidence Rates of Malignancy Related Treatment-Emergent Adverse Events UC Induction Placebo-Controlled, UC Maintenance Mirikizumab Responder Placebo-Controlled, UC Treatment Regimen Integrated, and All UC Mirikizumab Integrated Analysis Sets

Event, n (%) [IR]	Induction (Weeks 0-12)		Maintenance (Weeks 12-52)		UC Treatment Regimen (Weeks 0-52)	All UC Mirikizumab
	placebo IV Q4W N = 321 PYE = 72.1	miri 300 mg IV Q4W N = 958 PYE = 221.8	placebo SC Q4W N = 192 PYE = 119.3	miri 200 mg SC Q4W N = 389 PYE = 286	miri N = 389 PYE = 391.8	miri N = 1442 PYE = 2250.9
Participants with at least 1 TE malignancy	0 (0) [0]	2 (0.2) [0.9]	1 (0.5) [0.8]	1 (0.3) [0.3]	1 (0.3) [0.3]	16 (1.1) [0.7]
Participants with at least 1 TE malignancy other than NMSC	0 (0) [0]	2 (0.2) [0.9]	0 (0) [0]	1 (0.3) [0.3]	1 (0.3) [0.3]	12 (0.8) [0.5]
Adenocarcinoma of colon	0 (0) [0]	2 (0.2) [0.9]	0 (0) [0]	0 (0) [0]	0 (0) [0]	3 (0.2) [0.1]
Rectal cancer	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	3 (0.2) [0.1]
Prostate cancer[a]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	1 (0.1) [0.1]
Gastric cancer	0 (0) [0]	0 (0) [0]	0 (0) [0]	1 (0.3) [0.3]	1 (0.3) [0.3]	1 (0.1) [0.04]
Carcinoid tumour of the GI tract	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	1 (0.1) [0.04]
Extranodal marginal zone B-cell lymphoma	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	1 (0.1) [0.04]
Kaposi's sarcoma	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	1 (0.1) [0.04]
Malignant melanoma	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	1 (0.1) [0.04]
Participants with at least 1 TE NMSC malignancy	0 (0) [0]	0 (0) [0]	1 (0.5) [0.8]	0 (0) [0]	0 (0) [0]	4 (0.3) [0.2]

Event, n (%) [IR]	Induction (Weeks 0-12)		Maintenance (Weeks 12-52)		UC Treatment Regimen (Weeks 0-52)	All UC Mirikizumab
	placebo IV Q4W N = 321 PYE = 72.1	miri 300 mg IV Q4W N = 958 PYE = 221.8	placebo SC Q4W N = 192 PYE = 119.3	miri 200 mg SC Q4W N = 389 PYE = 286	miri N = 389 PYE = 391.8	miri N = 1442 PYE = 2250.9
Squamous cell carcinoma of skin	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	3 (0.2) [0.1]
Basal cell carcinoma	0 (0) [0]	0 (0) [0]	1 (0.5) [0.8]	0 (0) [0]	0 (0) [0]	1 (0.1) [0.04]

2.6.8.3. Serious adverse event/deaths/other significant events

Deaths

Deaths reported during treatment and off-treatment

In the mirikizumab development programme, 17 deaths were reported including 3 reported after database lock. Out of the 17 deaths reported, 4 were reported off-treatment. Five deaths were reported in the mirikizumab UC clinical programme, 11 deaths were reported in the psoriasis clinical programme, and 1 death was reported in the CD clinical programme.

Deaths in the UC clinical programme

Five deaths were reported in the mirikizumab UC clinical programme, of these, 2 were reported in mirikizumab-treated participants during the follow-up period of Study AMAN (off-treatment; 1 disseminated intravascular coagulation, 1 sudden cardiac death)

1 COVID-19 death was reported in the placebo group during the maintenance period of Study AMBG

1 COVID-19 death was reported in a mirikizumab-treated participant after withdrawal from Study AMBG (off-treatment), and

1 COVID-19 bilateral pneumonia was reported in a mirikizumab-treated participant during Study AMAP.

Serious Adverse Events

UC Induction Placebo-Controlled Analysis Set

The percentage of participants with at least 1 SAE reported was 5.3% (n = 17) placebo, and 2.8% (n = 27) mirikizumab.

In both the placebo group and mirikizumab treatment groups, the most frequently reported SAE was colitis ulcerative:

3.1% (n = 10) placebo, and

0.8% (n = 8) mirikizumab.

UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Set

Overall, the frequency of SAEs was higher in the placebo group compared with the mirikizumab treatment group.

The percentage of participants with at least 1 SAE reported was 7.8% (n = 15) placebo, and 3.3% (n = 13) mirikizumab.

In the placebo group, the most frequently reported SAE was colitis ulcerative:

3.1% (n = 6) placebo, and 0 mirikizumab.

In the mirikizumab treatment group, all SAEs were single events reported for 1 participant (0.3%) each. One serious event of suicidal depression was reported, this event is discussed in the section below.

UC Treatment Regimen, All UC Mirikizumab, and All Mirikizumab Exposures Integrated Analysis Sets

In general, the types of SAEs reported in the All UC Mirikizumab were similar to events reported in the placebo-controlled analysis sets, except for 2 SAEs reported, Kaposi's sarcoma and ITP:

A patient who was a mirikizumab induction non-responder with delayed clinical response had a colonic biopsy obtained during the Visit 4/Week 12 endoscopy that exhibited histologic changes consistent with Kaposi's sarcoma. Last SC maintenance dose of mirikizumab prior to the diagnosis of Kaposi's sarcoma occurred on the study Day 84. Human immunodeficiency virus testing at induction baseline and at the time of Kaposi's sarcoma diagnosis was negative. No cutaneous lesions consistent with

Kaposi's sarcoma were identified during a dermatology consult. During the early termination visit on study Day 106, the participant withdrew consent and refused any post-treatment follow-up. The investigator was informed by the participant's family that the participant died of COVID-19, 67 days after withdrawing consent and 5 months and 21 days after last dose of study drug. As the participant withdrew consent and later died, no further follow-up was possible.

A patient (mirikizumab induction non-responder) with a history of ulcerative colitis since 2013 reported a SAE of immune thrombocytopenia on Study Day 14, approximately 14 days after his last dose of 300 mg mirikizumab IV. Weak positive binding of IgG to platelets was detected using flow cytometry, which was not enhanced by the addition of mirikizumab. These results suggested the presence of a platelet-reactive autoantibody in the participant's serum that is not dependent on mirikizumab. Additional testing for immunoreactivity of the participant's serum with a panel of platelet glycoproteins commonly associated with ITP were all negative. Although not definitive, given the above differential diagnosis, the laboratory results are overall most consistent with autoimmune ITP. The event was resolved 4 days after event onset and was assessed by the Investigator as related to the study drug. The participant discontinued from the study.

2.6.8.4. Laboratory findings

Haematology

Only laboratory haematology values that had a notable numerical difference between treatment groups are summarised.

Blood Monocytes – Low

Table 26 Shifts in Blood Monocytes UC Induction and UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Sets

	Induction (Weeks 0-12)		Maintenance (Weeks 12-52)	
	placebo IV Q4W	miri 300 mg IV Q4W	placebo SC Q4W	miri 200 mg SC Q4W
Mean changes from baseline (10^9/L)				
Baseline to minimum postbaseline	-0.044	-0.057	-0.106	-0.112
LSM difference	--	-0.028	--	-0.017
Baseline to last observation	-0.007	-0.051	0.036	-0.019
LSM difference	--	-0.052	--	-0.063
TE shifts, n/NAR (%)				
TE-low values	1/312 (0.3)	14/927 (1.5)	5/190 (2.6)	7/383 (1.8)
Participants with TE-low values and at least 1 low blood monocyte-related TEAE, n/NAR (%)				
Monocyte count decreased[a]	0/312 (0)	0/927 (0)	0/190 (0)	1/383 (0.3)

In the UC Induction and UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Sets, while there was a greater mean decrease from baseline to last observation in blood monocytes in the mirikizumab treatment group compared with the placebo group, the magnitude of these changes was small. Furthermore, TE-low blood monocytes did not consistently occur more frequently in the mirikizumab-treated participants and were not associated with low monocyte or infection TEAEs.

In the UC Induction Placebo-Controlled Analysis Set, among the 14 mirikizumab-treated participants with TE-low blood monocytes, there were no reported TEAEs associated with symptoms related to low blood monocytes. In the UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Set, among the 7 mirikizumab-treated participants with TE-low blood monocytes, 1 participant on concomitant azathioprine reported a mild TEAE of monocyte count decreased. Taken together, the small decrease in mean blood monocytes with mirikizumab treatment is not considered clinically adverse.

Blood Segmented Neutrophils – Low

Table 27 Shifts in Segmented Blood Neutrophils UC Induction and UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Sets

	Induction (Weeks 0-12)		Maintenance (Weeks 12-52)	
	placebo IV Q4W	miri 300 mg IV Q4W	placebo SC Q4W	miri 200 mg SC Q4W
Mean changes from baseline (10^9/L)				
Baseline to minimum postbaseline	-0.490	-0.997	-0.966	-1.428
LSM difference	--	-0.494	--	-0.383
Baseline to last observation	-0.092	-0.909	0.735	-0.234
LSM difference	--	-0.774	--	-0.910
TE shifts, n/NAR (%)				
TE-low values	15/304 (4.9)	78/917 (8.5)	27/178 (15.2)	54/355 (15.2)
Shift in CTCAE category, n/NAR (%)				
Any shift to a higher Grade	16/314 (5.1)	93/944 (9.9)	35/190 (18.4)	70/386 (18.1)
Shift to at least Grade 1	16/304 (5.3)	87/911 (9.5)	32/177 (18.1)	61/353 (17.3)
Shift to at least Grade 2	6/311 (1.9)	19/937 (2.0)	8/188 (4.3)	20/384 (5.2)
Shift to at least Grade 3	0/314 (0.0)	2/944 (0.2)	1/190 (0.5)	4/386 (1.0)
Shift to at least Grade 4	0/314 (0.0)	1/944 (0.1)	0/190 (0)	0/386 (0)
Participants with shift to any higher CTCAE grade and at least 1 low blood neutrophil-related TEAE, n/NAR (%)				
Neutropenia or Neutrophil count decreased[a]	1/314 (0.3)	7/944 (0.7)	1/190 (0.5)	1/386 (0.3)
Infections and infestations[b]	3/314 (1.0)	15/944 (1.6)	9/190 (4.7)	19/386 (4.9)

Induction dosing with mirikizumab resulted in a greater mean decrease in segmented neutrophil count and a higher frequency of TE-low segmented neutrophils in the mirikizumab treatment group. Although maintenance dosing with mirikizumab also demonstrated a greater mean decrease in neutrophils compared with placebo, the frequency of TE-low segmented neutrophils was similar between the mirikizumab treatment and placebo groups.

In the UC Induction Placebo-Controlled Analysis Set, shifts to a higher grade of neutropenia were reported more frequently in the mirikizumab-treated participants, with most shifts being from Grade 0 to 1. The frequency of shifts to Grade 2 or higher were similar between the mirikizumab treatment and placebo groups. In the UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Set, a similar proportion of mirikizumab and placebo participants had a shift to any higher grade of neutropenia.

In the UC Induction and UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Sets, infection-related TEAEs associated with shifts to any higher CTCAE grade occurred in a similar, small proportion of mirikizumab-treated and placebo participants.

In the UC Induction Placebo-Controlled Analysis Set, 1 mirikizumab-treated participant on concomitant azathioprine, who had a shift in neutrophil CTCAE grade from 0 to 1, was hospitalised with severe SAEs of klebsiella infection, colitis ulcerative, and, subsequently, listeria sepsis.

In the UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Set, 1 mirikizumab-treated participant reported an OI of oral candidiasis (not limited to the tongue) of mild severity.

The type and severity of infections with shifts to neutropenia CTCAE Grade 2 or higher were consistent with the overall participant population during induction and maintenance.

Although there were larger mean reductions in segmented neutrophils with induction and maintenance dosing with mirikizumab compared with placebo, there was no clinically meaningful difference between treatment groups in development of neutropenia, based on similar frequencies of shifts to higher CTCAE grades and low rates of infections reported when neutrophil counts decreased.

Blood Platelets – Low

Table 28 Shifts in Blood Platelets UC Induction and UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Sets

	Induction (Weeks 0-12)		Maintenance (Weeks 12-52)	
	placebo IV Q4W	miri 300 mg IV Q4W	placebo SC Q4W	miri 200 mg SC Q4W
Mean changes from baseline (10^9/L)				
Baseline to minimum postbaseline	-6.2	-32.9	-45.4	-51.3
LSM difference	--	-26.4	--	-10.2
Baseline to maximum postbaseline	11.6	-20.7	59.0	37.6
LSM difference	--	-31.8	--	-22.4
Baseline to last observation	-0.6	-36.7	17.5	-15.9
LSM difference	--	-35.0	--	-36.4
TE shifts, n/NAR (%)				
TE-low values	2/312 (0.6)	15/936 (1.6)	2/189 (1.1)	9/380 (2.4)
TE-high values	37/213 (17.4)	42/629 (6.7)	32/161 (19.9)	29/341 (8.5)
Participants with TE-low values and at least 1 low blood platelet-related TEAE, n/NAR (%)				
Platelet count decreased[a]	0/312 (0)	1/936 (0.1)	0/189 (0)	0/380 (0)
Lower gastrointestinal hemorrhage[a]	0/312 (0)	1/936 (0.1)	0/189 (0)	0/380 (0)

Findings were consistent in the UC Induction and UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Sets.

The mean decrease and the lower frequency of TE-high blood platelets with mirikizumab treatment is consistent with decreasing UC inflammation, also reflected by decreasing platelets (as an acute phase reactant).

In the UC Induction Placebo-Controlled Analysis Set, 1 mirikizumab-treated participant with TE-low blood platelets reported mild severity TEAE of platelet count decreased. The participant subsequently had an SAE of lower gastrointestinal haemorrhage 1 day following a study colonoscopy with biopsies. The TEAE of platelet count decreased was related to study drug by the investigator, and the SAE of lower gastrointestinal haemorrhage was related to protocol procedure by the investigator. The SAE of lower gastrointestinal haemorrhage resolved. In the UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Set, among mirikizumab-treated participants with TE-low blood platelets, no TEAEs associated with low blood platelets were reported.

Given that all but 1 of the mirikizumab-treated participants with TE-low blood platelets did not report platelet associated TEAEs, and the fact that a decrease in blood platelets is consistent with decreasing UC inflammation, the higher frequency of TE-low blood platelets was not considered clinically adverse.

Chemistry

Only laboratory chemistry values that had a notable numerical difference between treatment groups are summarised in this section.

Chemistry analytes related to hepatic safety

Serum chemistry analytes of ALT, AST, ALP, and TB, which are related to the hepatic safety adverse events of special interest, are presented and discussed above.

Blood Urea Nitrogen – High

Findings were consistent in the UC Induction and UC Maintenance Mirikizumab responder Placebo-Controlled Analysis Sets. Overall, the treatment group differences in mean change and TE-high blood urea nitrogen were small. In addition, no TEAEs were reported among mirikizumab-treated participants with TE-high blood urea nitrogen. As a result, these findings were not considered clinically adverse.

Creatine Kinase – High

Table 29 Shifts in Creatine Kinase UC Induction and UC Maintenance Mirikizumab Responder

Placebo-Controlled Analysis Set Induction

	Induction (Weeks 0-12)		Maintenance (Weeks 12-52)	
	placebo IV Q4W	miri 300 mg IV Q4W	placebo SC Q4W	miri 200 mg SC Q4W
Mean changes from baseline (U/L)				
Baseline to maximum postbaseline	-1.4	56.1	143.5	207.2
LSM difference	--	45.6	--	64.9
Baseline to last observation	-7.2	30.3	-11.6	6.7
LSM difference	--	23.6	--	12.2
TE shifts, n/NAR (%)				
TE-high values	11/295 (3.7)	70/894 (7.8)	41/177 (23.2)	71/369 (19.2)
Shift in CTCAE category, n/NAR (%)				
Any shift to a higher Grade	12/311 (3.9)	73/946 (7.7)	43/191 (22.5)	77/387 (19.9)
Shift to at least Grade 1	11/295 (3.7)	70/894 (7.8)	41/177 (23.2)	71/369 (19.2)
Shift to at least Grade 2	3/308 (1.0)	25/943 (2.7)	12/189 (6.4)	22/385 (5.7)
Shift to at least Grade 3	0/309 (0)	9/945 (1.0)	6/191 (3.1)	11/386 (2.9)
Shift to at least Grade 4	0/311 (0)	3/946 (0.3)	1/191 (0.5)	8/387 (2.1)
Participants with shifts to higher CTCAE grades and at least 1 high creatine kinase-related TEAE, n/NAR (%)				
Blood creatine phosphokinase increased[a]	2/311 (0.6)	4/946 (0.4)	4/191 (2.1)	9/387 (2.3)

In the UC Induction and UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Sets, while a small mean increase in serum CK was seen in mirikizumab-treated participants compared with the placebo group, shifts to TE-high CK were mostly to CTCAE Grade 1. Additionally, most CK elevations were transient and returned to baseline values without interruption of study treatment.

CK-related TEAEs associated with CTCAE grade shifts were few and were reported at a similar frequency in the mirikizumab treatment group compared with the placebo group. No cases of rhabdomyolysis or myopathy AEs were reported in either treatment group.

Further evaluation was done to determine the number of participants with concurrent CK shifts to CTCAE Grade 2 or higher and elevations of AST ≥3xULN. In the All UC Mirikizumab Integrated Analysis Set, 32 mirikizumab-treated participants had AST ≥3xULN, 10 (31.3%) of which had concurrent elevation of CK to CTCAE Grade 2 or higher. In the All Mirikizumab Exposures Integrated Analysis Set, 106 mirikizumab-treated participants had AST ≥3xULN, 27 (25.5%) of whom had concurrent elevation of CK to CTCAE Grade 2 or higher. These data support a muscle-related source of AST elevation over a liver-related cause for participants with concurrent CK and AST elevations.

Therefore, the observed transient small increases in mean CK in the mirikizumab treatment group for the UC Induction and UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Sets were not considered clinically adverse.

Serum Albumin – High

Table 30 Shifts in Serum Albumin UC Induction and UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Sets

	Induction (Weeks 0-12)		Maintenance (Weeks 12-52)	
	placebo IV Q4W	miri 300 mg IV Q4W	placebo SC Q4W	miri 200 mg SC Q4W
Mean changes from baseline (g/L)				
Baseline to maximum postbaseline	0.7	2.0	1.6	2.4
LsMean difference	--	1.3	--	0.7
Baseline to last observation	1.2	2.5	-1.2	0.4
LsMean difference	--	1.3	--	1.6
TE shifts, n/NAR (%)				
TE-high values	26/291 (8.9)	100/891 (11.2)	37/161 (23.0)	101/335 (30.1)
Participants with TE-high values and at least 1 high serum albumin-related TEAE, n/NAR (%)				
Dehydration[a]	0/291 (0)	1/891 (0.1)	0/161 (0)	0/335 (0)

Findings were consistent in the UC Induction and UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Sets.

A greater proportion of participants in the mirikizumab treatment group compared with placebo reported a TE-high serum albumin.

The higher increase in serum albumin in mirikizumab-treated participants compared with placebo participants was considered clinically meaningful as an indicator of response to treatment and not as an AE.

Sodium – High

Table 31 Shifts in Sodium UC Induction and UC Maintenance Mirikizumab Responder

Placebo-Controlled Analysis Sets

	Induction (Weeks 0-12)		Maintenance (Weeks 12-52)	
	placebo IV Q4W	miri 300 mg IV Q4W	placebo SC Q4W	miri 200 mg SC Q4W
Mean changes from baseline (mmol/L)				
Baseline to maximum postbaseline	-0.2	0.4	2.0	1.8
LSM difference	--	0.4	--	-0.0
Baseline to last observation	-0.1	0.2	-0.3	-0.6
LSM difference	--	0.2	--	-0.2
TE shifts, n/NAR (%)				
TE-high values	0/307 (0)	17/937 (1.8)	4/188 (2.1)	9/379 (2.4)
Participants with TE-high values and at least 1 high sodium-related TEAE, n/NAR (%)	0/307 (0)	0/937 (0)	0/188 (0)	0/379 (0)

Findings were consistent in the UC Induction and UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Sets.

Differences between treatment groups in mean changes from baseline and in proportion of participants with TE-high sodium were small.

In addition, no renal TEAEs were reported among mirikizumab-treated participants with TE-high sodium.

As a result, these findings were not considered clinically adverse.

Total Serum Protein – High

Table 32 Shifts in Total Serum Protein UC Induction and UC Maintenance Mirikizumab Responder

Placebo-Controlled Analysis Sets

	Induction (Weeks 0-12)		Maintenance (Weeks 12-52)	
	placebo IV Q4W	miri 300 mg IV Q4W	placebo SC Q4W	miri 200 mg SC Q4W
Mean changes from baseline (g/L)				
Baseline to maximum postbaseline	0.8	2.0	1.9	2.5
LSM difference	--	1.1	--	0.5
Baseline to last observation	1.4	2.4	-2.1	-0.6
LSM difference	--	0.9	--	1.4
TE shifts, n/NAR (%)				
TE-high values	9/304 (3.0)	46/920 (5.0)	6/181 (3.3)	19/373 (5.1)
Participants with TE-high values and at least 1 high total serum protein-related TEAE, n/NAR (%)				
Dehydration[a]	0/304 (0)	1/920 (0.1)	0/181 (0)	0/373 (0)

Findings were consistent in the UC Induction and UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Sets. Although, a greater mean increase in total serum protein and a greater proportion of participants was observed in the mirikizumab treatment group compared with placebo who developed a TE-high total protein serum level, differences were small, and there was 1 potentially associated AE of dehydration reported. Therefore, these changes were not considered to be clinically adverse.

2.6.8.5. Vital Signs, Physical Findings, and Other Observations Related to Safety

Blood Pressure

UC Induction and UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Sets

Systolic blood pressure

In the UC Induction and the UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Sets, there was a small mean increase in systolic BP from baseline (less than 2 mm Hg) with mirikizumab compared with placebo, which was not considered clinically meaningful.

Shifts to TE-high systolic BP were reported at a higher frequency in the mirikizumab treatment group compared with the placebo group. The majority of mirikizumab participants with TE-high systolic BP had fluctuations in BP over time with no distinct pattern, did not require antihypertensive treatment, and did not remain in the TE-high category at the end of the induction or maintenance treatment period.

Diastolic blood pressure

In the UC Induction and the UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Sets, mean change from baseline in diastolic BP was small (less than 2 mm Hg) in participants treated with mirikizumab and was not considered clinically meaningful. Shifts to TE-high diastolic BP were reported at a higher frequency in the mirikizumab treatment group compared with the placebo group. The majority of participants with TE-high diastolic BP had fluctuations in BP over time with no distinct pattern and did not require anti-hypertensive treatment. Approximately half did not remain in the TE-high category at the end of the induction treatment period.

Hypertension-related TEAEs associated with TE-high values of systolic blood pressure or diastolic blood pressure or both

In the UC Induction Placebo-Controlled Analysis Set, the percentage of participants with TE-high systolic or diastolic BP that reported a hypertension-related TEAE was 0 in placebo, and 6.2% (n = 5) in mirikizumab.

Most TEAEs were mild or moderate in severity, and no participants discontinued mirikizumab treatment due to a TEAE of hypertension. One mirikizumab-treated participant reported a moderate TEAE of hypertensive crisis in the induction treatment period. Participant with a prior medical history of tachyarrhythmia had a nonserious, moderate severity TEAE of hypertensive crisis, which resolved after 2 days without concomitant medication changes.

In the UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Set, the percentage of participants with TE-high systolic or diastolic BP that reported a hypertension-related TEAE was 2.4% (n = 1) in placebo, and 4.2% (n = 4) in mirikizumab.

Most TEAEs were mild or moderate in severity, and no participants discontinued mirikizumab treatment due to a TEAE of hypertension. The majority of participants were treated with anti-hypertensive therapy. One mirikizumab-treated participant reported a severe TEAE of hypertension during the maintenance treatment period. Participant with no relevant prior medical history or concomitant medications, had high normal BP of 137/87 at Study AMAN (induction) baseline and 122/89 at Study AMBG (maintenance) baseline. The participant reported a severe TEAE of hypertension starting on Day 200 of Study AMBG (or of the randomised maintenance period) in association with a maximal BP of 162/113, treated with amlodipine and candesartan, resulting in normalisation of BP.

UC Treatment Regimen, All UC Mirikizumab, and All Mirikizumab Exposures Integrated Analysis Sets

There were greater proportions of participants with TE-high BP in the All UC Mirikizumab Integrated Analysis Set compared with UC Treatment Regimen Integrated Analysis Set, and greater proportion in the All Mirikizumab Exposures Integrated Analysis Set compared with All UC Mirikizumab Integrated Analysis Set. The higher proportion of TEhigh BP likely reflects the higher opportunity for events of fluctuating BP due to the longer mean exposure to mirikizumab with increasing size and scope of the analysis sets.

Pulse

UC Induction Placebo-Controlled Analysis Set

A minimal mean decrease in pulse (less than 1 bpm) in the mirikizumab treatment group compared to the placebo group was observed, which was not considered a clinically meaningful difference between groups.

TE-low pulse was reported in no placebo participants and 0.1% of mirikizumab participants, and TE-high pulse was reported in 2.6% of placebo and 1.6% of mirikizumab participants with the majority of these reflecting fluctuations over time with normalisation towards the end of the treatment period.

Heart rate-related TEAEs associated with TE-low or TE-high pulse

The percentage of participants with TE-high pulse that reported an increased heart rate-related TEAE was 12.5% (n=1) in placebo, an 6.7% (n=1) in mirikizumab.

One mirikizumab-treated participant with a prior medical history of tachycardia had a non-serious, mild severity TEAE of supraventricular tachycardia with pulse of 183 bpm on the second dosing day of Study AMAN. The event was treated with sodium chloride and resolved the same day. Subsequent pulse measurements were within normal limits despite continued study treatment dosing.

None of the TE-low changes in pulse were associated with heart rate-related TEAEs.

UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Set

A minimal mean decrease in pulse (less than 1 bpm) in the mirikizumab treatment group compared to the placebo group was observed, which was not considered a clinically meaningful difference between groups,

TE-low pulse was reported in 1.1% of placebo participants and 0.8% of mirikizumab-treated participants, TE-high pulse was reported in 2.1% of placebo participants and 3.9% of mirikizumab-treated participants with the majority of these reflecting fluctuations over time with normalisation towards the end of the treatment period.

Heart rate-related TEAEs associated with TE-low or TE-high pulse

None of the TE-low or high changes in pulse were associated with heart rate-related TEAEs.

UC Treatment Regimen, All UC Mirikizumab, and All Mirikizumab Exposures Integrated Analysis Sets

The numerically higher frequency of TE-high pulse is not considered clinically meaningful and likely reflects the higher mean weeks of exposure in the All Mirikizumab Exposures Integrated Analysis Set compared with the All UC Mirikizumab Integrated Analysis Set.

Weight

UC Induction Placebo-Controlled Analysis Set

Mean increases from baseline in weight were small (less than 1 kg) across treatment groups. The mirikizumab treatment group demonstrated a small mean increase in weight compared with the placebo group.

Treatment-emergent adverse events

None of the TE-high weight changes were considered clinically adverse, as they were not associated with any relevant TEAEs other than 3 TEAEs of weight increased in mirikizumab-treated participants.

UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Set

Mean increases from baseline in weight were small (less than 2 kg) across treatment groups.

The mirikizumab treatment group demonstrated a small mean increase in weight compared with the placebo group.

The greater proportion of participants with TE-high weight values in the mirikizumab treatment group likely reflects an improvement in UC disease severity status in these participants.

2.6.8.6. Safety in special populations

Intrinsic and Extrinsic Factors

Intrinsic Factors

The frequencies of AEs were generally comparable across age, sex, race, region, and disease severity subgroups within the treatment groups. These results suggest there was no clinically meaningful interaction between mirikizumab treatment and intrinsic factors.

Extrinsic Factors

A greater frequency of participants who had prior biologic or tofacitinib exposure at baseline, reported TEAEs compared with the subgroup that never had prior biologic or tofacitinib exposure. Differences are primarily due to numerically higher frequencies of the events of iron deficiency anaemia, colitis ulcerative, headache, pyrexia, fatigue, and arthralgia reported in mirikizumab-treated participants with a history of prior exposure to biologics or tofacitinib. A numerically higher frequency of these events are also noted for placebo participants in the ever exposed group compared with the never exposed group. These differences may reflect a higher disease severity, more refractory population or the impact of previous therapies for those participants with previous exposures, regardless of treatment assignment in the UC Induction Placebo-Controlled Analysis Set. These data do not suggest a meaningful interaction specific to mirikizumab treatment.

Table 33 Frequencies of Treatment-Emergent Adverse Events by Prior Biologic or Tofacitinib Exposure at Baseline UC Induction Placebo-Controlled Analysis Set

Event, n (%)	Ever		Never	
	placebo IV Q4W N = 135	miri 300 mg IV Q4W N = 409	placebo IV Q4W N = 186	miri 300 mg IV Q4W N = 549
Participants with at least 1 TEAE	36 (26.7)	103 (25.2)	33 (17.7)	89 (16.2)
Nasopharyngitis	4 (3.0)	21 (5.1)	6 (3.2)	18 (3.3)
Upper respiratory tract infection	1 (0.7)	3 (0.7)	1 (0.5)	10 (1.8)
Oral herpes	0 (0.0)	6 (1.5)	2 (1.1)	4 (0.7)
Anaemia	7 (5.2)	12 (2.9)	12 (6.5)	20 (3.6)
Iron deficiency anaemia	5 (3.7)	7 (1.7)	2 (1.1)	3 (0.5)
Colitis ulcerative	16 (11.9)	10 (2.4)	8 (4.3)	7 (1.3)
Nausea	3 (2.2)	4 (1.0)	1 (0.5)	6 (1.1)
Headache	5 (3.7)	19 (4.6)	4 (2.2)	13 (2.4)
Pyrexia	3 (2.2)	9 (2.2)	0 (0.0)	5 (0.9)
Fatigue	1 (0.7)	8 (2.0)	1 (0.5)	4 (0.7)
Arthralgia	3 (2.2)	10 (2.4)	1 (0.5)	10 (1.8)
Pruritus	1 (0.7)	7 (1.7)	4 (2.2)	5 (0.9)
Hypertension	1 (0.7)	5 (1.2)	2 (1.1)	6 (1.1)

Use in Pregnancy and Lactation

Effects of mirikizumab on human fetal development are not known. Per Study AMAN Protocol (a) and Study AMBG Protocol (a), women of childbearing potential were required to test negative for pregnancy within 24 hours prior to mirikizumab exposure and had to either agree to remain abstinent or use 2 effective methods of contraception for the entirety of the study. Any pregnancy that occurred during study participation required permanent discontinuation. Pregnant participants and partner pregnancies were planned to be followed to completion, and outcomes are reported here.

Pregnancies During Mirikizumab Clinical Studies

Pregnancies during Phase 3 ulcerative colitis study participation

Pregnancies in female participants

As of 06 December 2021, five women became pregnant during a mirikizumab UC study. Of these 5 participants, 4 had a maternal exposure to mirikizumab during pregnancy and 1 had a maternal exposure before pregnancy.

Table 34 Pregnancies in Female Participants with UC Exposed to Mirikizumab

Outcome	No. of Event (n)	Percentage of Total Female Exposure (n/5)
Normal outcome	1	20%
Elective abortion	2	40%
Spontaneous abortion	1	20%
Unknown lost to follow-up	1	20%

Pregnancies in partners of male participants

As of 06 December 2021, three partners of male participants became pregnant during the male participants' UC study participation.

Table 35 Pregnancies in Partners of Male Participants with UC Exposed to Mirikizumab

Outcome	No. of Event (n)	Percentage of Total Male Exposure (n/3)
Normal outcome	1	33.3%
Spontaneous abortion	1	33.3%
Unknown lost to follow-up	1	33.3%

Pregnancies during any mirikizumab study participation

Pregnancies in female participants

As of 06 December 2021, a total of 28 women in the UC, CD, and psoriasis studies became pregnant during their mirikizumab study participation, including the participants with UC as described in this section.

Table 36 Pregnancies in Females Exposed to Mirikizumab

Outcome	No. of Event (n)	Percentage of Total Female Exposure (n/28)
Normal outcome	7	25%
Still in utero at data cutoff	7	25%
Elective abortion[a]	6	21%
Spontaneous abortion	3	11%
Premature birth	1	4%
Unknown as lost to follow-up[b]	4	14%

Pregnancies in partners of male participants

As of 06 December 2021, a total of 41 partners of male participants became pregnant during the male participants' mirikizumab study participation.

Table 37 Pregnancies in Partners of Male Participants Exposed to Mirikizumab All Mirikizumab Exposures Integrated Analysis Set

Outcome	No. of Event (n)	Percentage of Total Male Exposure (n/41)
Normal outcome	19	46%
Spontaneous abortion	7	17%
Still in utero at data cutoff	3	7%
Elective abortion	1	2%
Premature birth	1	2%
Congenital anomaly	1	2%
Unknown as lost to follow-up[a]	9	22%

Lactation During Mirikizumab Clinical Studies

No cases of mirikizumab use during breast-feeding in any of the clinical trials have been reported.

Elderly

Table 38 presents safety data by age ranges and categories as requested by CHMP. Given the small amount of exposure to mirikizumab represented by participants ≥65 years of age, caution in interpreting the frequencies of events is warranted. The intrinsic factor analyses for the placebo-controlled induction period of Study AMAN (presented in Section 2.7.4.5.1 of the Summary of Clinical Safety) and maintenance period of Study AMBG (presented in Lilly's Response to Question 164 in Section 5.29.1 of this document) do not demonstrate a clinically meaningful interaction between mirikizumab treatment and age. These results are further supported by the population PK analysis, where age was not found to be a clinically significant covariate.

Table 38 Overview of adverse events by age category All UC Mirikizumab integrated analysis set

Event Category	<65 Years (N=1335) n (%)	65-74 Years (N=96) n (%)	75-84 Years (N=11) n (%)	>=85 Years (N=0) n (%)
Total TEAEs	972 (72.8)	70 (72.9)	10 (90.9)	0
SAEs	107 (8.0)	12 (12.5)	4 (36.4)	0
Fatal	0	1 (1.0)	0	0
Hospitalization	102 (7.6)	11 (11.5)	4 (36.4)	0
Life-threatening	6 (0.4)	2 (2.1)	0	0
Disability	0	0	0	0
Other	14 (1.0)	2 (2.1)	0	0
AE leading to study drug discontinuation	65 (4.9)	4 (4.2)	0	0
Accidents and injuries (SMQ)	87 (6.5)	7 (7.3)	1 (9.1)	0
Infections and infestations (SOC)	501 (37.5)	29 (30.2)	4 (36.4)	0
Nervous system disorders (SOC)	206 (15.4)	9 (9.4)	2 (18.2)	0
Psychiatric disorders (SOC)	62 (4.6)	5 (5.2)	1 (9.1)	0
Cardiac disorders (SOC)	23 (1.7)	5 (5.2)	1 (9.1)	0
Vascular disorders (SOC)	66 (4.9)	11 (11.5)	2 (18.2)	0
Cerebrovascular disorders *a	1 (0.1)	2 (2.1)	0	0
Hypotension, falls, fractures *b	26 (1.9)	0	1 (9.1)	0
QOL decreased (PT)	0	0	0	0
Anticholinergic syndrome (SMQ)	102 (7.6)	4 (4.2)	1 (9.1)	0

Abbreviations: N = number of participants in the analysis set and age group; n = number of participants in the specified category; TEAE = treatment-emergent adverse event; AE = adverse event; PT = preferred term; SAE = serious adverse event; MACE = major adverse cardiovascular events, subset of cerebro-cardiovascular events; SMQ = standardized MedDRA query; SOC = system organ class; UC = Ulcerative Colitis.

Table 39 TEAEs that occurred in at least 3 participants ≥65 years of age and at an IR at least 1.5 times higher than the IR in participants <65 years of age. Most (15 of the 19) SOCs with at least 1 TEAE that met criteria had overall higher IRs for participants ≥65 years of age when compared to participants <65 years of age.

System Organ Class Preferred Term	<65 Years (N=3471, PYE=7158.0) n (%) PYR (IR; 95% CI)	65-74 Years (N=289, PYE=577.6) n (%) PYR (IR; 95% CI)	>=75 Years (N=38, PYE=65.6) n (%) PYR (IR; 95% CI)	>=65 Years (N=327, PYE=643.3) n (%) PYR (IR; 95% CI)
Patients with >=1 TEAE	2773 (79.9) 2131.1 (130.1; 125.3, 135.1)	244 (84.4) 168.7 (144.6; 127.0, 163.9)	31 (81.6) 24.2 (128.1; 87.0, 181.8)	275 (84.1) 192.9 (142.5; 126.2, 160.4)
Infections and infestations	1759 (50.7) 3997.3 (44.0; 42.0, 46.1)	140 (48.4) 336.2 (41.6; 35.0, 49.1)	19 (50.0) 39.0 (48.8; 29.4, 76.1)	159 (48.6) 375.1 (42.4; 36.1, 49.5)
Urinary tract infection	94 (2.7) 7010.7 (1.3; 1.1, 1.6)	15 (5.2) 558.4 (2.7; 1.5, 4.4)	2 (5.3) 65.2 (3.1; 0.4, 11.1)	17 (5.2) 623.6 (2.7; 1.6, 4.4)
Herpes zoster	38 (1.1) 7126.0 (0.5; 0.4, 0.7)	5 (1.7) 568.2 (0.9; 0.3, 2.1)	2 (5.3) 63.2 (3.2; 0.4, 11.4)	7 (2.1) 631.4 (1.1; 0.4, 2.3)

Abbreviations: miri = mirikizumab; N = number of patients in the analysis population; n = number of patients in the specified category; TEAE = treatment-emergent adverse event; IR = incidence rate per 100 patient-years; PYE = patient years of exposure; PYR = patient years at risk.

Many of the events with higher IRs in participants ≥65 years of age occurred at a low frequency and in few participants. Of the 66 PTs that occurred more frequently in participants ≥65 years, 49 occurred at an IR <1.0 in participants ≥65 years.

Some of the events with higher IRs in participants ≥65 years of age are not unexpected given the group's advanced age, such as cataracts (IR=0.2 in <65 and IR=1.5 in ≥65 years of age) and osteoarthritis (IR=0.6 in <65 and IR=1.6 in ≥65 years of age). Other events such as herpes zoster (IR=0.5 in <65 and IR=1.1 in ≥65 years of age) are identified as risks in both the elderly and in patients using immunomodulators.

Additional events, such as dermatitis contact (IR=0.6 in <65 and IR=1.4 in ≥65 years of age) and abdominal pain upper (IR=0.7 in <65 and IR=1.3 in ≥65 years of age) may be related to the underlying UC and its extraintestinal manifestation.

2.6.8.7. Immunological events

Immediate Hypersensitivity Events

UC Induction Placebo-Controlled Analysis Set

The percentage of participants that reported at least 1 TE immediate hypersensitivity event was 0.3% (n = 1) in placebo, and 1.0% (n = 10) in mirikizumab.

In the placebo group and mirikizumab treatment group, the most frequently reported TE immediate hypersensitivity event was infusion related hypersensitivity reaction. No participants reported anaphylaxis. None of the reported immediate hypersensitivity events were Serious. The percentage of participants that discontinued study treatment due to a TE immediate hypersensitivity event was low (0.3%) in the mirikizumab group.

UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Set

The percentage of participants that reported at least 1 TE immediate hypersensitivity event was 1.0% (n = 2) in placebo, and 1.8% (n = 7) in mirikizumab.

In the placebo group, the reported TE immediate hypersensitivity events were anaphylactic reaction (n = 1, 0.5%) and dermatitis allergic (n = 1, 0.5%). The anaphylactic reaction in the placebo participant was considered serious.

In the mirikizumab treatment group, the most frequently reported TE immediate hypersensitivity event was hypersensitivity (n = 3, 0.8%). No serious immediate hypersensitivity events were reported in mirikizumab-treated participants. In the placebo group, the reported reason for discontinuation due to a TE immediate hypersensitivity event was anaphylactic reaction (n = 1, 0.5%).

UC Treatment Regimen, All UC Mirikizumab, and All Mirikizumab Exposures Integrated Analysis Sets

The IRs of TE immediate hypersensitivity events in the UC Treatment Regimen, All UC Mirikizumab, and All Mirikizumab Exposures Integrated Analysis Sets were comparable to the Induction and Maintenance Analysis Sets and did not suggest an increase in immediate hypersensitivity events with increased duration of treatment. No serious immediate hypersensitivity events were reported in the UC Treatment Regimen and All UC Mirikizumab Integrated Analysis Sets.

In the All Mirikizumab Exposures Integrated Analysis Set, 2 (0.1%) events of anaphylactic reaction were reported. These events were from the CD Phase 2 study. During the maintenance period, 2 events of anaphylactic reaction were reported in the placebo/mirikizumab 1000 mg IV group with the lyophilised formulation. Both of the anaphylaxis events were reported as SAEs.

Both participants discontinued study treatment. After these events, mitigations were implemented to slow the rate of IV infusion. No subsequent anaphylactic reactions occurred. In the Phase 3 UC studies, the shelf-stable solution formulation was used for IV infusion with no anaphylactic reactions reported.

The number of discontinuations due to immediate hypersensitivity events in the UC Treatment Regimen, All UC Mirikizumab, and All Mirikizumab Exposures Integrated Analysis Sets was low and did not suggest an increase in immediate hypersensitivity-related events with increased duration of treatment.

Table 40 Exposure-Adjusted Incidence Rate of Immediate Hypersensitivity- Related TEAEs Occurring in at Least 3 Participants in the All UC Mirikizumab Integrated Analysis Set UC Induction Placebo-Controlled, UC Maintenance Mirikizumab Responder Placebo-Controlled, UC Treatment Regimen Integrated, and All UC Mirikizumab Integrated Analysis Sets

Event, n (%) [IR]	Induction (Weeks 0-12)	Maintenance (Weeks 12-52)	UC Treatment Regimen (Weeks 0-52)	All UC Mirikizumab
	miri 300 mg IV Q4W N = 958 PYE = 221.8	miri 200 mg SC Q4W N = 389 PYE = 286	miri N = 389 PYE = 391.8	miri N = 1442 PYE = 2250.9
Participants with at least 1 TE immediate hypersensitivity event	10 (1.0) [4.5]	7 (1.8) [2.5]	9 (2.3) [2.3]	32 (2.2) [1.4]
Infusion related reaction[a]	3 (0.3) [1.4]	--	1 (0.3) [0.3]	6 (0.4) [0.3]
Hypersensitivity	0 (0) [0]	3 (0.8) [1.1]	3 (0.8) [0.8]	4 (0.3) [0.2]
Infusion related hypersensitivity reaction[a]	4 (0.4) [1.8]	--	0 (0) [0]	4 (0.3) [0.2]
Rash	0 (0) [0]	2 (0.5) [0.7]	2 (0.5) [0.5]	3 (0.2) [0.1]

Non-Immediate Hypersensitivity Events

UC Induction Placebo-Controlled Analysis Set

The percentage of participants that reported at least 1 TE non-immediate hypersensitivity event was 2.2% (n = 7) in placebo, and 2.5% (n = 24) in mirikizumab.

In the placebo group and mirikizumab treatment group, the most frequently reported TE non-immediate hypersensitivity event was rash 0.6% (n = 2) in placebo, and 0.5% (n = 5) in mirikizumab.

None of the reported non-immediate hypersensitivity events were considered serious. No participants discontinued study treatment due to a non-immediate hypersensitivity event.

UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Set

The percentage of participants that reported at least 1 TE non-immediate hypersensitivity event was 2.6% (n = 5) in placebo, and 6.9% (n = 27) in mirikizumab.

In the mirikizumab treatment group, the most frequently reported TE non-immediate hypersensitivity event was rash (n = 13, 3.3%). The frequency of reports of rash notably increased in the mirikizumab treatment group during maintenance compared with induction. No rash was reported in the placebo group. Most events of rash were mild in severity. None resulted in study discontinuation. None of the reported non-immediate hypersensitivity events were considered serious.

Based on the non-immediate hypersensitivity event SMQ (narrow terms), the percentage of participants that discontinued study treatment due to a TE non-immediate hypersensitivity event was 0% (n = 0) in placebo, and 0.3% (n = 1) in mirikizumab. In the mirikizumab treatment group, the reported reason for discontinuation due to a TE non-immediate hypersensitivity event was injection site hypersensitivity (n = 1, 0.3%).

UC Treatment Regimen, All UC Mirikizumab, and All Mirikizumab Exposures Integrated Analysis Sets

The IRs for most TE non-immediate hypersensitivity events in the UC Treatment Regimen, All UC Mirikizumab, and All Mirikizumab Exposures Integrated Analysis Sets were comparable to the Induction and Maintenance Analysis Sets and did not suggest an increase in non-immediate hypersensitivity events with increased duration of treatment.

Compared to the UC Treatment Regimen Integrated Analysis Set, there were 2 events in the All UC Mirikizumab Integrated Analysis Set with higher IRs, that were, eczema and rhinitis allergic.

No events of eczema and rhinitis allergic were serious. The majority of participants reported events eczema and rhinitis allergic were of mild severity.

None of the participants discontinued from study treatment due to eczema or rhinitis allergic.

In the UC Treatment Regimen Integrated Analysis Set, no serious non-immediate hypersensitivity events were reported. In the All UC Mirikizumab Integrated Analysis Set, 1 serious non-immediate hypersensitivity event of rash was reported. In the All Mirikizumab Exposures Integrated Analysis Set, no additional serious non-immediate hypersensitivity events were reported.

The number of discontinuations due to non-immediate hypersensitivity events in the UC Treatment Regimen, All UC Mirikizumab, and All Mirikizumab Exposures Integrated Analysis Sets was low and did not suggest an increase in non-immediate hypersensitivity-related events with increased duration of treatment.

Table 41 Exposure-Adjusted Incidence Rate of Non-Immediate Hypersensitivity-Related TEAEs Occurring in at Least 3 Participants in the All UC Mirikizumab Integrated Analysis Set UC Induction Placebo-Controlled, UC Maintenance Mirikizumab Responder Placebo-Controlled, UC Treatment Regimen Integrated, and All UC Mirikizumab Integrated Analysis Sets.

Event	Induction (Weeks 0-12)	Maintenance (Weeks 12-52)	UC Treatment Regimen (Weeks 0-52)	All UC Mirikizumab
	miri 300 mg IV Q4W N = 958 PYE = 221.8	miri 200 mg SC Q4W N = 389 PYE = 286	miri N = 389 PYE = 391.8	miri N = 1442 PYE = 2250.9
Participants with at least 1 TE non-immediate hypersensitivity event, n (%) [IR]	24 (2.5) [11.0]	27 (6.9) [9.8]	34 (8.7) [9.1]	102 (7.1) [4.8]
Rash	5 (0.5) [2.3]	13 (3.3) [4.6]	13 (3.3) [3.4]	32 (2.2) [1.4]
Eczema	1 (0.1) [0.5]	1 (0.3) [0.4]	2 (0.5) [0.5]	15 (1.0) [0.7]
Conjunctivitis allergic	2 (0.2) [0.9]	1 (0.3) [0.3]	2 (0.5) [0.5]	7 (0.5) [0.3]
Rhinitis allergic	0 (0) [0]	0 (0) [0]	0 (0) [0]	7 (0.5) [0.3]
Dermatitis	1 (0.1) [0.5]	1 (0.3) [0.4]	2 (0.5) [0.5]	6 (0.4) [0.3]
Dermatitis contact	1 (0.1) [0.5]	2 (0.5) [0.7]	2 (0.5) [0.5]	6 (0.4) [0.3]
Urticaria	4 (0.4) [1.8]	1 (0.3) [0.3]	3 (0.8) [0.8]	6 (0.4) [0.3]
Rash pruritic	3 (0.3) [1.4]	1 (0.3) [0.4]	3 (0.8) [0.8]	5 (0.3) [0.2]
Hypersensitivity	0 (0) [0]	2 (0.5) [0.7]	2 (0.5) [0.5]	4 (0.3) [0.2]
Rash maculo-papular	1 (0.1) [0.5]	1 (0.3) [0.3]	1 (0.3) [0.3]	4 (0.3) [0.2]
Dermatitis acneiform	1 (0.1) [0.5]	0 (0) [0]	0 (0) [0]	3 (0.2) [0.1]
Dermatitis allergic	0 (0) [0]	0 (0) [0]	0 (0) [0]	3 (0.2) [0.1]

Abbreviations: IR = incidence rate; IV = intravenous; miri = mirikizumab; N = number of participants in the safety analysis set; n = number of participants in specified category; PYE = patient-years of exposure; Q4W = once every 4 weeks; SC = subcutaneous; TE = treatment-emergent; TEAE = treatment-emergent adverse event; UC = ulcerative colitis.

2.6.8.8. Safety related to drug-drug interactions and other interactions

Drug Interactions

One drug-drug interaction study of mirikizumab was completed in participants with moderate-to-severe psoriasis (Study AMBP).

The purpose of Study AMBP was to determine whether mirikizumab affects CYP activity in participants with psoriasis by using a "probe cocktail" approach, whereby the pharmacokinetics of CYP3A, CYP2C9, CYP2D6, CYP2C19, and CYP1A2 substrates midazolam, warfarin, dextromethorphan, omeprazole, and

caffeine, respectively, was evaluated before and after multiple mirikizumab doses were administered to participants with moderate-to-severe psoriasis.

The results concluded that multiple SC doses of mirikizumab are unlikely to change CYP activity in participants with moderate-to-severe psoriasis to a degree that would be expected to contribute to clinically meaningful changes in the exposure of CYP3A, CYP2C9, CYP2D6, CYP2C19, or CYP1A2 substrates.

Additionally, no deaths, SAEs, or AEs resulting in discontinuation of treatment were reported in Study AMBP.

2.6.8.9. Discontinuation due to adverse events

UC Induction Placebo-Controlled Analysis Set

The percentage of participants that discontinued study treatment due to an AE was numerically

higher in the placebo group compared with the mirikizumab treatment group: 7.2% (n = 23) placebo (of these, 11 were reported as serious) and 1.6% (n = 15) mirikizumab (of these, 8 were reported as serious).

Colitis ulcerative was the most frequently reported AE leading to discontinuation in both the placebo group and mirikizumab treatment group: 5.9% (n=19) placebo, and 0.5% (n=5) mirikizumab.

AEs that led to discontinuation more frequently in the mirikizumab-treated group compared with placebo were infusion-related hypersensitivity reaction 0% placebo, and 0.3% (n=3) mirikizumab, and lymphopenia (0% placebo, and 0.2% (n=2) mirikizumab).

Infusion-related hypersensitivity reaction leading to study treatment discontinuation

Of the reported infusion-related hypersensitivity reactions in mirikizumab-treated participants, none were serious, and all were mild or moderate in severity. Two events were reported after the second dose and 1 event was reported after the first dose.

Lymphopenia leading to study treatment discontinuation

Of the reported lymphopenia in mirikizumab-treated participants, 1 was reported as moderate and 1 was reported severe and both had concomitant corticosteroid use.

SAEs leading to study treatment discontinuation

Serious AEs that resulted in discontinuation of study treatment in the mirikizumab treatment group were

colitis ulcerative (n = 5)

deep vein thrombosis (n = 1) reported on Day 21

intestinal sepsis (n = 1) reported on Day 12 in a participant receiving concomitant

prednisone and azathioprine, and

spinal fracture (n = 1) reported on Day 81, 1 day after a fall.

Serious AEs that resulted in discontinuation of study treatment in the placebo group were

acute myocardial infarction (n = 1)

colitis ulcerative (n = 9), and

sinusitis (n = 1).

UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Set

The percentage of participants that discontinued study treatment due to an AE was 8.3% (n=16) placebo (of these, 9 were reported as serious);1.5% (n=6) mirikizumab (of these, 1 was reported as serious).

Colitis ulcerative was the most frequently reported AE leading to discontinuation in both the placebo group and mirikizumab treatment group.

5.7% (n = 11) placebo, and

0.5% (n = 2) mirikizumab.

SAEs leading to study treatment discontinuation

SAEs that resulted in discontinuation of study treatment in the mirikizumab treatment group

Were gastric cancer (n = 1) reported in participant with family history of gastric and hepatic cancer on Day 166.

SAEs that resulted in discontinuation of study treatment in the placebo group were

anaphylactic reaction (n = 1)

colitis ulcerative (n = 6)

COVID-19 (n = 1), and

presyncope (n=1).

UC Treatment Regimen, All UC Mirikizumab, and All Mirikizumab Exposures Integrated Analysis Sets

Colitis ulcerative remained the most frequently reported AE leading to discontinuation in the uncontrolled analysis sets. This observed finding may be due to the inclusion of participants with moderate or severely active UC who discontinued due to lack of efficacy.

The types of AEs leading to study treatment discontinuation, remained consistent throughout the uncontrolled analysis sets.

2.6.8.10. Post marketing experience

Mirikizumab has not yet obtained marketing authorisation. Therefore, no post-authorisation exposure data are available yet.

2.6.9. Discussion on clinical safety

This MAA concerns a new humanised IgG4 monoclonal antibody (mirikizumab) targeting the p19 subunit of IL-23 used for the treatment of patients with moderately-to-severely active UC.

The proposed recommended dose regimen for mirikizumab in this indication is intravenous administration of 300 mg at weeks 0, 4 and 8 followed by subcutaneous administration of 200 mg every 4 weeks (Q4W).

Safety pools

The main source of safety data provided in support of this application come from two pivotal studies (AMAN and AMBG) in patients with UC. AMAN (LUCENT-1) study was the placebo-controlled study which evaluated the safety of 300 mg of mirikizumab administrated intravenously every 4 weeks over a 12-week induction period. The safety data from this study are presented in the UC Induction Placebo-Controlled Analysis Set. A second placebo-controlled pivotal study (AMBG, LUCENT-2) investigated the maintenance treatment (from 12 to 52). During the maintenance period mirikizumab was given subcutaneously at the dose 200 mg every 4 weeks. The data from participants who were responders to mirikizumab in induction and continued their treatment in the maintenance period are presented in the UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Set.The safety data from these two pivotal studies were further analysed together in the UC Treatment Regimen Integrated Analysis Set.

The safety comparisons in the AMBG study made by the applicant are mainly within the mirikizumab Induction Responders group (patients re-randomised to either placebo or to mirikizumab). The applicant was requested to discuss and highlight differences when the mirikizumab treated patients are compared to placebo responders in the AMBG study. The applicant provided the requested discussion. In this comparison the following PTs were reported more frequently in the mirikizumab group: nasopharyngitis, arthralgia, injection site pain, injection site reaction, headache, gastroesophageal reflux disease, injection site erythema, fatigue. In relation to events of special interest injection site reactions and immediate and non-immediate hypersensitivity TEAEs were reported in higher frequencies in the mirikizumab responders as compared to in the placebo responders.

The data from two pivotal studies and additional uncontrolled data from Study AMBG (including AMAN non-responders who underwent open-label extended induction with mirikizumab and participants who received open label maintenance or loss of response rescue with mirikizumab) and the data from the AMAC and AMAP studies are included in the All UC Mirikizumab Integrated Analysis Set. The AMAC study was a phase 2 dose-ranging study which evaluated IV doses of mirikizumab in a range of 50 mg to 600 mg Q4W. AMAP was a long-term extension study in patients with UC who are receiving open-label mirikizumab 200 mg SC Q4W for up to 3 years. This study is currently ongoing. The applicant was requested to clarify the status of AMAP study (i.e a duration of exposure in this study) and provided the updated safety data from this study. As clarified by the applicant, in the updated safety database, 916 participants have been treated with mirikizumab in Study AMAP This is an increase of **12 participants** from the safety data contained in the mirikizumab UC initial submission.

The fifth analysis set (All Mirikizumab Exposures Integrated Analysis Set) included also patients who received mirikizumab for other indications such as psoriasis and CD. It is noted that the dose used for the treatment of UC is significantly higher as compared to doses investigated in the psoriasis development programme i.e 250 miri Q4W SC (induction) and 125 miri Q8W SC (maintenance) and therefore they are considered as supportive only in the context of this application.

Exposure

A total of 1442 subjects with moderately-to-severely active UC were exposed to mirikizumab across the Phase 2 and Phase 3 core UC studies (AMAN, AMBG, AMAC and AMAP), 725 of whom were exposed to iv mirikizumab for 12 weeks and 926 were exposed to mirikizumab for 1 year. 450 patients received

their treatment with mirikizumab for a period longer than 104 weeks. 3798 patients were exploded to mirikizumab across all studies investigating also other indications.

Adverse event (AE) profile

In the UC Induction and UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Sets, the percentage of participants with at least 1 TEAE was similar between the mirikizumab treatment groups and the placebo groups. TEAEs were reported in 46.1% in the placebo group and 44.5% in the mirikizumab group in the UC induction period and in 68.8 % in the placebo SC Q4W and 64.5% in the miri 200 mg SC Q4W group in the UC placebo-controlled maintenance period.

In the All Mirikizumab Exposures analysis set which includes patients with psoriasis and Crohn's disease the exposure adjusted IR of TEAEs was significantly lower (131.1) as compared to the exposure adjusted IR of TEAEs in patients with ulcerative colitis (i.e. IR of 261.0 in the Mirikizumab 300 mg IV group and IR of 160.1 the Mirikizumab 200 mg SC Q4W group).The reason for these differences could be related to the fact that the dose used in psoriasis studies was lower as compared to doses used for UC indication. The applicant was requested to discuss to what extent the safety data presented in the All Mirikizumab Exposures analysis set are relevant for the population of patients with UC. The applicant clarified that interpretation of the All Mirikizumab Exposures Integrated Analysis Set is limited by differences in exposure, background prevalence of various AEs, routes of administration, and dose between the different indications, making it difficult to make direct comparisons to the UC population. Therefore, the analyses of safety data from the All Mirikizumab Exposures Integrated Analysis Set should be considered as supplemental to any findings from the analyses of the UC cohorts and, in particular, results from the randomised, placebo-controlled cohorts of participants with UC.

For SAEs and discontinuation rates, the exposure adjusted IRs were comparable across analysis sets with the exception of the Mirikizumab treated patients in the UC induction period where the IR for SAEs and discontinuations was the highest.

Common TEAEs

SOCs for which TEAEs were reported by more than 10% of the participants in either treatment group were Infections and infestations and Gastrointestinal disorders in the UC induction period and Infections and infestations, Gastrointestinal disorders, General disorders and administration site conditions, Musculoskeletal and connective tissue disorders, and Skin and subcutaneous tissue disorders in the UC placebo-controlled maintenance period.

During the UC induction in the SOC Infections and infestations nasopharyngitis (3.1% for placebo, 4.1% for mirikizumab), URTI (0.6% for placebo, 1.4% for mirikizumab) and oral herpes (0.6 % for placebo and 1% for mirikizumab) were more frequently reported in the mirikizumab group. In the SOC Musculoskeletal and connective tissue disorders there was higher frequency of arthralgia (1.2 % versus 2.1% for placebo and mirikizumab, respectively), in the SOC Nervous system disorders there was higher frequency of headache (2.8 % versus 3.3% for placebo and mirikizumab, respectively). Pyrexia and Fatigue were also reported more frequently in the mirikizumab group (Pyrexia:0.9% versus 1.5%, Fatigue: 0.6% versus 1.3%). Hypertension also occurred with slightly higher frequency in patients receiving mirikizumab.

A number of PTs were reported with a higher frequency in the mirikizumab treatment group as compared to placebo during the UC placebo controlled maintenance period including nasopharyngitis (7.2%), arthralgia (6.7%), injection site pain (4,4%) headache (4.1%), abdominal pain (2.8%) fatigue (2.6%) hypertension, rash (3.6%), gastroesophageal reflux disease (2.6%), injection site reaction (2.6), injection site erythema (2.1%), pain in extremity (1.8%), cough (1.3%), influenza like illness

(1.3%), migraine (1.3%), oropharyngeal pain, urinary tract infection (1.3%) and vulvovaginal mycotic infection (1.3%), however differences as compared to placebo were small (around 3 to 0.6% difference).

The applicant performed additional analysis of clusters which included PTs that are essentially synonymous and refer to the same clinical concept.

The frequency rash cluster (rash, rash pruritic, rash macular, rash maculo-papular, and rash popular) was higher both in the induction and maintenance period. All cases reported were mild or moderate in severity and the frequency seemed to be higher in patients receiving therapy for longer term. The applicant listed rash as ADR in section 4.8 of the SmPC, which is supported.

The frequency of upper respiratory tract infection cluster (nasopharyngitis, upper respiratory tract infection, oropharyngeal pain, rhinitis, pharyngitis, sinusitis, tonsillitis, oropharyngeal discomfort, acute sinusitis, and viral URTI) was higher in the mirikizumab-treated participants. Taking into consideration the biologic plausibility for an association between mirikizumab and the occurrence of URTI (immunomodulatory mode of action of mirikizumab), the applicant listed URTI in section 4.8 of the SmPC, which is acceptable.

The frequency of Headache and Headache cluster was higher in patients receiving mirikizumab. All headache events were reported as mild or moderate. None were reported as serious or led to study treatment discontinuation. Headache is listed in section 4.8 of the SmPC.

Herpes zoster was the most frequently reported opportunistic infection in the All UC Mirikizumab and the All Mirikizumab Exposures Integrated Analysis Sets, the majority of which were mild to moderate in severity, with 1 participant reporting a severe event. There was a small imbalance in the frequency of opportunistic infections. In the UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Set, the frequency of opportunistic infections increased in the mirikizumab treatment group driven by cases of herpes zoster. Based on the immunomodulatory mode of action of mirikizumab, there is biologic plausibility for an association between the administration of mirikizumab and the occurrence of herpes zoster.

Arthralgia **-** higher frequency was observed in the induction period (1.2 % versus 2.1% for placebo and mirikizumab, respectively) and the maintenance period (3% versus 6.7% for placebo and mirikizumab, respectively). Further arthralgia is listed as ADR in the SmPC of other IL-23 inhibitors i.e. ustekinumab and guselkumab.

Arthralgia and herpes zoster infection were added to the list of ADRs in section 4.8 of the SmPC.

Fatigue - higher frequency was observed in the induction period (0.6% versus 1.3% for placebo and mirikizumab, respectively) and the maintenance period (0.7% versus 2.6 % for placebo and mirikizumab, respectively). In addition, for fatigue cluster the higher frequency as compared to placebo was observed in the maintenance period. Based on further clarification provided it was agreed with the applicant that the small imbalance in the frequency of reported fatigue mostly seen in the induction period no updates to the SmPC is necessary, especially taking into consideration that all events of fatigue were mild or moderate, and none were serious in either treatment group.

In All UC Mirikizumab Integrated Analysis Set the majority of common TEAEs were reported at a lower IR compared with the UC Treatment Regimen Integrated Analysis Set with exception of colitis ulcerative, COVID-19, and upper respiratory tract infection. On the other hand, for some common TEAEs such as Headache, Arthralgia, Anaemia, Upper respiratory tract infection, Pyrexia, Hypertension, Nausea, Back pain, Fatigue, Abdominal pain and Injection site pain the IR was higher in the UC Treatment Regimen Integrated Analysis Set as compared to the All UC Mirikizumab Integrated Analysis Set. The applicant was requested to comment on how to interpret these results. The applicant provided

an explanation regarding the higher IR of some AEs seen in the the UC Treatment Regimen Integrated Analysis Set as compared to the UC Mirikizumab Integrated Analysis Set. This clarification can be accepted.

As indicated by the applicant also in the All Mirikizumab Exposures Integrated Analysis Sets (which included patients treated for other indications), the majority of common TEAEs were reported at a lower IR compared with the UC Treatment Regimen Integrated Analysis Set. The applicant provided discussion in relation to TEAEs for which IR was higher in the All Mirikizumab Exposures Integrated Analysis Sets as compared to the UC Treatment Regimen Integrated Analysis Set. It was highlighted by the applicant that the numerical differences in IR were small, and the events were non-serious, expected in the general population, or reported at a low frequency overall.

Related TEAEs

During the induction period 35 patients (10.9%) in the placebo group and 99 patients (10.3%) in the treatment group reported related TEAEs. The most frequently related TEAEs were within SOC of Skin and subcutaneous tissue disorders followed by SOC of Infections and infestations. Pruritus, nasopharyngitis (6 patients), headache (13 patients), nausea (5 patients), leukopenia (5 patients) and arthralgia (5 patients) were most frequent PTs reported to be related the study treatment. For nasopharyngitis, headache, nausea and leukopenia the frequency was higher in the mirikizumab group as compared to the placebo group.

During the maintenance period, related TEAEs were reported in 32 patients (16.7%) in placebo group and in 65 patients (16.7%). Related TEAEs within the SOC of general disorders and administration site conditions were most frequently reported and included different types of injection site reactions. Related Infections and infestations were reported in 2 (1%) and 12 (3.1%) patients in the UC maintenance period in patients on placebo and Mirikizumab respectively. In relation to the types of infection reported they were viral infections (including Herpes simplex, Herpes zoster), fungal infections and URTI. The SmPC informs in 4.4 that opportunistic infections were reported in clinical trials.

In the UC Treatment Regimen, UC Miri Exposures and All Miri Exposures Integrated Analysis Sets related TEAEs were reported in 21.9, 23.0 and 26.8 % of patients respectively. Again, TEAEs within the SOC of General disorders and administration site conditions were most frequently reported followed by the Infections and infestations.

Severe TEAEs

The majority of reported TEAEs were mild or moderate. Severe TEAEs were reported in less than 9.5% in any treatment group.

During the UC induction period Severe TEAEs were reported in 23 (7.2%) of patients in the placebo group and 21 (2.2%) in the treatment group. During the induction period 5 cases of severe infections were reported such as pneumonia, cytomegalovirus colitis, intestinal sepsis, Dengue fever and Klebsiella infection. It can be agreed that there was no pattern in the type of severe TEAEs, as each PT was reported by 1 participant (with exception of anaemia reported by 2 patients). It is noted that one severe case of Fatigue was reported in this period.

During the maintenance period, severe TEAEs were reported in less than 9 % of patients in any treatment group. In patients receiving mirikizumab severe TEAEs were reported in 16 (4.1%) of patients. 3 severe infections were reported in the mirikizumab treated patients such as Nasopharyngitis, Herpes zoster, COVID-19 pneumonia. In the placebo-controlled maintenance period,

no pattern in the type of severe TEAEs can be identified. It is noted that one case of severe injection site pain and one case of hypertension was reported.

In the UC Treatment Regimen, All UC Mirikizumab, and All Mirikizumab Exposures Integrated Analysis Sets severe TEAEs were reported by 21 (5.4%), 104 (7.2%) and 331 (8.7%) patients, respectively. The applicant was requested to discuss and clarify if there was any pattern in the type of severe TEAEs reported in these sets. The applicant provided the requested discussion. When considering differences in population characteristics, sample size, exposure, and occurrence of single or infrequent severe events across the analysis sets, no clear pattern of severe TEAEs was observed by SOC or PT. In most cases, the frequencies and IRs of severe TEAEs were similar among the 3 analysis sets. Of the most frequently reported severe TEAEs, the PT of COVID-19 pneumonia.

Safety of extended induction dose

The extended induction cohort of Study AMBG was a non-randomised group of participants who did not achieve clinical response at the end of the 12-week induction and continued to receive the induction dose in the open-label extended induction period. There was 313 mirikizumab non-responders and 148 placebo non-responders. From the 313 mirikizumab-treated non-responders who entered Study AMBG, 277 (88.5%) completed 3 cycles of extended induction treatment for a total of 6 doses of mirikizumab 300 mg IV Q4W.

In the open-label extended induction period, the frequency of TEAEs reported for the placebo induction non-responders group was 29.1% (n=43) and for the mirikizumab induction non-responders group was 38.3% (n=120). Severe TEAEs were reported in 3.2% of patients in the mirikizumab induction non-responders group. SAE were reported in 5.4 % of mirikizumab induction non-responders.

<u>Study AMBG Extended Induction compared with UC Induction Placebo-Controlled Analysis Set</u>

For the analysis of safety of the extended induction dose, the data from mirikizumab-treated non-responders participating in the extended induction arm of Study AMBG (and therefore receiving up to 6 dose of 300 mg IV Q4W) were compared to the data from the mirikizumab-treated patients in the induction period (and therefore only receiving upto 3 doses of 300 mg IV Q4W).

This comparison showed that an additional 12 weeks of mirikizumab extended induction treatment was not associated with a meaningful increase in reporting of AEs in most SOCs. Only for three SOC (i.e Musculoskeletal and connective tissue disorders, Endocrine disorders and Neoplasms benign, malignant, and unspecified) the frequency of TEAEs was higher in the extended induction arm. For the SOC Musculoskeletal and connective tissue disorders this difference was mostly driven by PT arthralgia (listed in section 4.8). For the Neoplasms benign, malignant, and unspecified SOC there was a small difference in the frequency of malignancies reported (i.e 2 for the standard induction dose and 4 for the extended induction dose). However, taking into consideration types of malignancies reported (adenocarcinoma, rectal cancer and squamous cell carcinoma), increased risk for malignancies in these patients and relatively short exposure to the treatment, it is unlikely that there is an increased risk of malignancies with the extended induction dose. For the SOC Endocrine disorders a number of events was small, i.e. 3 cases.

It is noted that one case of Hy's Law was identified in the patient enrolled to the extended induction period (please see discussion below). Except the 1 participant meeting Hy's law criteria described below, no other mirikizumab-treated participants discontinued mirikizumab during the Extended Induction

period due to a hepatic TEAE.

Adverse events of special interest

Hepatic safety

Elevations in hepatic laboratory test in patients treated with mirikizumab were reported infrequently. Frequencies of liver enzymes ≥5x and ≥10x ULN were low.

In the UC Induction Placebo-Controlled Analysis Set the number of patients reporting at least one hepatic TEAE was small and similar between the treatment groups (1.6% in each treatment group).

In the UC placebo-controlled maintenance period again the frequency of patients reporting at least one hepatic TEAE were similar between the treatment groups (placebo responder, placebo SC-3.0%; mirikizumab responders, placebo SC-2.1% and mirikizumab responders 3.1%of patients).

In the All UC Mirikizumab Exposures Integrated Analysis Set, frequencies of TE elevations in ALT and AST ≥3xULN in mirikizumab-treated participants were low however higher (ALT = 2.0%, AST = 2.1%) than in participants in the UC Placebo Group (ALT = 1.1%, AST = 0.5%).

No hepatic SAEs were reported in the UC Induction and UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Set.

One patient experienced a serious adverse event of cholecystitis acute of moderate severity in the extension study i.e after 466 days after starting treatment with 300 miri Q4W IV (induction) and 76 days since the last dose of 200 miri Q4W SC.

In the UC development programme three patients discontinued their treatment with Mirikizumab due to hepatic adverse events. Two cases - one case of autoimmune hepatitis and one case of potential drug-induced liver injury without alternative aetiology or significant confounding risk factors - were the most concerning.

Autoimmune hepatitis

One mirikizumab-treated participant in the UC maintenance treatment period discontinued the study treatment due to a TEAE of autoimmune hepatitis which occurred 211 days after starting treatment with mirikizumab 300 mg Q4W IV in AMAN study. No relevant medical history was reported for this patient.

Cases of autoimmune hepatitis have been reported in patients receiving treatment with other biological therapies and the potential role of mirikizumab cannot be excluded. The investigator considered the AE of autoimmune hepatitis as not related to study drug, but the applicant considered this case as possibly related although it is more likely that it was a pre-existing AIH. Cases autoimmune hepatitis will be monitored post-marketing and if any cases reported will be presented in the PSUR.

Drug-induced liver injury

In total, 4 patients in the UC development programme fulfilled the criteria for DILI i.e. TB ≥2xULN and ALT or AST ≥3xULN (2 patients) and ALT or AST ≥10xULN (2 patients). For one case the applicant as well as 3 independent experts assessed the relationship to Mirikizumab as probable. For the remaining 3 cases this relationship was considered as unlikely.

For the patient, who discontinued the study treatment AST, ALT and serum total bilirubin elevations met the category of potential **drug-induced liver injury (meeting Hy's Law criteria).** This patient completed the AMAN study and entered into AMBG study as a mirikizumab non-responder and

continued receiving the higher iv dose of mirikizumab i.e 300 mg Q4W IV. In total, this patient received 5 doses of mirikizumab 300 mg Q4W IV (two last doses in the OL extended induction period).

No medical history or pre-existing conditions were reported for this patient and concomitant medications included prednisone only. The patient never consumed alcohol and never used tobacco. At screening the patient's hepatic enzymes were within normal limits. This patient first reported pruritus (noted as hepatic pruritus by the investigator) which was followed by changes in liver enzymes. ALT and AST peaked with ALT at 609 U/L (17.9x ULN), AST at 336 U/L (9.9x ULN). A total bilirubin reached 51 µmol/L (2.4x ULN) and ALP reached 187 U/L (1.8x ULN).

The investigator considered the AE of hepatic enzyme increased as related to study drug as no alternative aetiology or significant confounding risk factors were identified in this patient. The applicant considered this case as an idiosyncratic drug-induced liver injury.

In this patient liver enzymes normalised after the discontinuation of therapy (i.e. 56 days after the first elevation) without therapeutic intervention or hospitalisation.

In the psoriasis development programme further cases which fulfilled the criteria for DILI were reported.

An external committee, comprised of 3 independent external physicians trained in hepatology and with expertise in DILI, reviewed 6 cases with maximum ALT or AST ≥3xULN and TB ≥2xULN, 10 cases with ALT and/or AST ≥10xULN, and 8 cases of treatment discontinuations due to hepatic TEAEs. For three cases relationship to the study treatment was considered as probable or possible related.

This safety concern was extensively discussed with the applicant. It was noted that based on review of cases with a probable or possible association with mirikizumab treatment, elevations in hepatic enzymes improved or normalised with or without discontinuation of mirikizumab treatment, and none resulted in death, a serious outcome, or other sequelae. Further frequencies of elevations of ALT and AST reported in studies with mirikizumab were not higher as seen in studies for the products of the same class.

Based on the totality of the data the benefit/risk balance was considered as positive with the following risk mitigation measures:

A warning in section 4.4 was introduced with a recommendation for monthly liver monitoring during an induction followed by less frequently monitoring during the maintenance therapy. Further, 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.

Identification of elevations in ALT and AST as ADRs in Section 4.8 of the SmPC

Severe liver injury was added as an impotent potential risk in the RMP and additional pharmacovigilance activities were introduced, including use of spontaneous hepatic disorders follow-up form and inclusion of severe liver injury as an outcome of interest in the observational secondary database study to assess the long-term safety of mirikizumab.

Infections

Mirikizumab is an immunomodulatory drug and as such, may increase the risk of developing an infection or may exacerbate an existing infection. In geranial, the frequency of infections was higher in the mirikizumab treated patients as compared to those on placebo although the deference between the groups was small. During the induction period the percentage of participants that reported at least 1 TE infection was 14.0% (n = 45) in placebo, and 15.1% (n = 145) in the mirikizumab group. The most

frequently reported TE infection was nasopharyngitis, upper respiratory tract infection, oral herpes, rhinitis for which the frequency was higher in the mirikizumab group. Upper respiratory tract infections are listed in section 4.8 of the SmPC. The remaining types of infections no association with the mirikizumab treatment was determined.

During the placebo-controlled maintenance period the percentage of participants that reported at least 1 TE infection was 22.9% (n = 44) in placebo, and 23.9% (n = 93) in the mirikizumab group. Again nasopharyngitis was the most frequently reported followed by Covid 19 and upper respiratory tract infection.

Due to its mechanism of action mirikizumab may increase the risk of severe infection and the SmPC includes a contraindication in case of active tuberculosis and a warning that mirikizumab may increase the risk of severe infection and provides guidance in case of clinically important acute, chronic, or serious infection. In addition, serious infections are listed as an important potential risk for mirikizumab, and these events will be monitored in the post-authorisation setting via routine pharmacovigilance activities and as part of the objective of the additional post-authorisation pharmacovigilance study entitled "Observational Secondary Database Study to Assess the Long-Term Safety of Mirikizumab" that is a category 3 study in the RMP.

Opportunistic infections

The frequency of reported TE opportunistic infections was low however, they occurred more frequently in the mirikizumab treated patients. As discussed, the increased frequency of opportunistic infections in the mirikizumab treatment group was driven by cases of herpes zoster. Section 4.8 of the SmPC was updated in this regard. The remaining PTs were mostly represented by single events. During the induction period 1 oesophageal candidiasis, 2 cytomegalovirus colitis, 1 HZ, 1 intestinal tuberculosis were reported. During the placebo-controlled maintenance period, oral candidiasis and 4 HZ infections were reported. In the All UC Mirikizumab analysis set opportunistic infections were reported in 25 (1.7%) patients whereas in all Miri Exposures Integrated Analysis Set in 71 (1.9%) patients. Infections including opportunistic infections will be monitored in the post-authorisation setting via routine pharmacovigilance activities and as part of the objective of the additional post-authorisation pharmacovigilance study (as discussed above).

Serious infections

Serious infections were reported infrequently i.e less than 2.3% in any treatment group. Pneumonia was the most frequently reported. It is noted that serious infections are included in the RMP as Important potential risks, which is acceptable. Opportunistic infections and serious infections will be monitored in the planned by the applicant the observational secondary database study, which is supported.

Infusion and injection site reactions

Infusion site reactions

Infusion site reactions were reported in 8 patients (0.6%) receiving mirikizumab iv. Infusion site erythema, infusion site pain, infusion site paraesthesia, infusion site pruritus, Infusion site swelling, infusion site bruising, infusion site bruising, infusion site extravasation, infusion site hypoaesthesia, infusion site urticarial were reported. None of Infusion site reactions were serious. No participants discontinued due to an infusion site reaction. Infusion-related hypersensitivity infusion site reactions are listed in section 4.8 of the SmPC.

Injection site reactions (SC)

Injection site reactions were reported in 8.7% of UC patients. Inactions site pain was the most frequently reported. No serious Injection site reactions were reported. One patient discontinued due to a TE Injection site reaction. Injection site reaction cluster are listed in the SmPC which is acceptable. The frequency of participants with 1 or more Injection site reactions (HLT) was similar between TE ADA negative (8.3%) and TE ADA positive participants (10.2%).

Malignancy

Malignancies were reported in 16 (1.1%) of patients exposed to mirikizumab in the UC development programme. Adenocarcinoma of colon and rectal cancer was the most frequently reported (3 patient each). None were considered related to mirikizumab by the investigators. In evaluating the frequency of malignancies by 12-week intervals, there was no increase in the frequency of malignancy events in the All UC Mirikizumab Integrated Analysis Set with increasing duration of mirikizumab exposure

There is no clear evidence of an increased risk for developing malignancies following treatment with mirikizumab based on results of the clinical trials presented so far in this application. As there is an established increased risk for cancer development in UC and there is a theoretical possibility of decreased immune surveillance against malignancies with alteration of immune pathways with mirikizumab treatment, malignancy was added Important Potential Risk in the RMP. In addition, rare events and events with longer latency, which includes malignancies will be investigated in the planned post-authorisation safety study entitled "Observational Secondary Database Study to Assess the Long-Term Safety of Mirikizumab."

Cerebrocardiovascular Events

In total, 28 cases of Adjudicated Major Adverse Cardiovascular Events (MACE) were reported in mirikizumab-treated participants in the All Mirikizumab Exposures Integrated Analysis Set which included not only patients with UC but also those treated for other indications such as psoriasis and CD.

Only 6 MACEs were from patients with moderately to severely active UC and all of them were reported in the extended maintenance or long-term extension periods of studies.

The remaining 22 cases were from the psoriasis development programme and again most of them (17 out of 22) were reported in the maintenance or long-term extension studies.

In the placebo-controlled period of the mirikizumab psoriasis development programme, a numerical imbalance for MACE (placebo = 0; mirikizumab = 5; 0.4% [1.2 IR]) was observed. However, this numerical imbalance in participants with psoriasis needs to be interpreted in the context of o randomisation differences between placebo- and mirikizumab-treated participants (6:1) and subsequently a significant imbalance in the number of patients enrolled to each arm.

The IRs for MACE observed in the All UC Mirikizumab Integrated Analysis Set (IR=0.2) and the All Mirikizumab Exposures Integrated Analysis Set (IR=0.3 IR) were not higher as compared to the background rate for MACE as reported in the literature.

The majority of cases (22 out of 28) of MACEs were not considered related to the study treatment by investigators. In 6 patients MACEs were assessed by investigators as possibly related to mirikizumab however, all these patients had risk factors for such evens.

In conclusion, a causal relationship of MACE with mirikizumab treatment was not determined based on the data presented so far.

Nevertheless, taking into consideration small imbalances of MACEs in psoriasis studies these cases will be monitored post-marketing including in the observational secondary database study planned by the

applicant. Further, in line with other IL23 inhibitors major adverse cardiovascular events (MACE) was included as an important potential risk to the RMP.

17 patients in the psoriasis studies reported 19 AEs of cardiac arrhythmias (including 5 severe events). The IR of TE serious arrhythmia events in the All UC Mirikizumab (IR=0.2) and All Mirikizumab Exposures Integrated Analysis Sets (IR=0.3) was not higher than seen in general population.

Of the 22 UC and psoriasis participants in the mirikizumab development programme who reported serious arrhythmias, all had risk factors including age older than 50 years, increased BMI, and preexisting and/or medical history of CV disease.

Depression and Suicide

Both in the UC induction and placebo-controlled maintenance period a lower percentage of participants in the mirikizumab treatment group reported any worsening of depression or worsening from No or Mild depression to Moderate, Severe, or Very Severe compared with the placebo group. The percentage of participants that reported at least 1 depression event similar between the treatment groups. Depression was reported in 0.6% (n = 2) in placebo, and 0.4% (n = 4) in mirikizumab during the induction period and in 0% in placebo, and 1.0% (n = 4) in mirikizumab during the maintenance placebo-controlled period. 2 patients (one with UC and one with psoriasis) reported TE suicide and self-injury event. Both cases were considered as not related to mirikizumab and both patients had history of depression.

Hypersensitivity

Immediate hypersensitivity events were reported in UC development programme including Infusion related reaction (6 patients), infusion related hypersensitivity reaction (4 patients), Hypersensitivity (4 patients) and rash (3 patients). No anaphylactic reactions were reported in the mirikizumab treated patients.

All Mirikizumab Exposures Integrated Analysis Set, 2 (0.1%) events of anaphylactic reaction were reported in the CD Phase 2 study. During the maintenance period, 2 events of anaphylactic reaction were reported in the placebo/mirikizumab 1000 mg IV group with the lyophilised formulation. After these events, mitigations were implemented to slow the rate of IV infusion. No subsequent anaphylactic reactions occurred. In the Phase 3 UC studies, the shelf-stable solution formulation was used for IV infusion with no anaphylactic reactions reported. In the proposed SmPC, it is stated that 300mg should be administered over at least 30 minutes.

Immunogenicity

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. Using all narrow and broad search terms in the UC Treatment Regimen Integrated Analysis Set, the frequency of hypersensitivity reactions was similar between TE ADA negative and TE ADA positive patients (15.2% and 15.9%, respectively). The frequency of patients with at least 1 infusion site reaction was similar between TE ADA negative and TE ADA positive patients (0.3% and 0%, respectively). The frequency of patients with at least 1 injection site reaction high-level term (HLT) TEAE was slightly higher in the TE ADA positive patients (8.3% for TE ADA negative patients and 10.2% for ADA positive patients respectively).

Serious adverse events and deaths

Deaths

In the mirikizumab development programme, 17 deaths were reported including 3 reported after database lock. Out of the 17 deaths reported, 4 were reported off-treatment. Five deaths were

reported in the mirikizumab UC clinical programme, 11 deaths were reported in the psoriasis clinical programme, and 1 death was reported in the CD clinical programme.

It is noted that 7 out of 14 deaths were associated with Covid -19 infection (3 in the UC development programme and 4 in the psoriasis development programme). Patients who died due to Covid -19 infections had many comorbidities such as hypertension, morbid obesity, type 1 diabetes mellitus however they were relatively young with mean age of this group 57 years of age. Investigators considered that these Covid -19 related deaths were unrelated to the study treatment or protocol procedures.

The treatment with Mirikizumab could promote development of serious infections and serious infections are listed in the RMP as important potential risks, therefore some role of mirikizumab in this context cannot be excluded. In the SmPC is included the following statement: "Mirikizumab may increase the risk of infection. Treatment with mirikizumab should not be initiated in patients with a clinically important active infection until the infection resolves or is adequately treated". The applicant was requested to discuss imbalances in deaths reported in patients with Covid-19 infections and the potential contributing role of mirikizumab. The applicant provided the requested discussion. It is noted that patients who died due to Covid-19 infections had risk factors for death.

Two deaths in the UC development programme were not Covid–19 related.

Death in one AMAN patient seems to be secondary to acute severe ulcerative colitis in a patient who had been unresponsive to a number of medical interventions in the past. This patient required subtotal colectomy but unfortunately was already a high-risk candidate for this due to her medical comorbidities. Disseminated intravascular coagulation, systemic candida and cytomegalovirus colitis reported in this patient were not considered related to the study treatment by the investigated. The second non-Covid-19 death occurred 117 days after receiving his last dose of 300 mg mirikizumab IV, following a proctocolectomy and ileostomy for UC and adenocarcinoma of the rectum.

There were two cardiovascular deaths in the psoriasis development programme, one due to intracranial haemorrhage (37 days since the last dose of 125 miri Q8W SC) and one due to acute myocardial infarction (98 days since the last dose of 250 miri Q4W SC). Both patients had a history of hypertension. In addition, one patient aged 40 experienced sudden death (59 days since the last dose of 125 miri Q8W SC). Finally, three deaths in the psoriasis development programme were malignancy related.

Serious adverse events

In the UC Induction and UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Set, a numerically higher percentage of participants in the placebo group reported at least 1 SAE compared to the mirikizumab treatment group.

During the induction period the percentage of participants with at least 1 SAE reported was 5.3% (n = 17) in the placebo group and in the 2.8% (n = 27) mirikizumab group. In both the placebo group and mirikizumab treatment groups, the most frequently reported SAE was colitis ulcerative. It can be agreed that there was no pattern in the type of SAEs reported, as each PT was reported by 1 participant only (with exception of colitis ulcerative reported in 8 patients and 2 patients with pneumonia).

During the placebo-controlled maintenance period the percentage of participants with at least 1 SAE reported was 7.8% (n = 15) in the placebo group and 3.3% (n = 13) in the mirikizumab group. Again, there was no pattern in the type of SAEs, as each PT was reported by 1 participant only.

In the UC Treatment Regimen, All UC Mirikizumab, and All Mirikizumab Exposures Integrated Analysis Sets SAEs were reported by 18 (4.6%), 123 (8.5%) and 385 (10.1%) patients respectively. Colitis

ulcerative, COVID-19 pneumonia, Pneumonia, Acute myocardial infarction and appendicitis were most frequently reported.

Laboratory findings

Haematology

Higher frequencies for TE-decreased monocytes, neutrophils, and platelets in the mirikizumab treatment group as compared to the placebo group were observed the UC Induction Placebo-Controlled Analysis Set however, the number of affected patients was low in any treatment group (0.3% versus 1.5% for monocytes, 4.9% versus 8.5% for neutrophils and 0.6% versus 1.6% for platelets).

For monocytes and neutrophils in the UC Maintenance Mirikizumab Responder Placebo-Controlled Analysis Set the frequency of patients with low values was not higher in the mirikizumab treatment group

whereas for platelets again TE-low values were more frequently reported in the mirikizumab treated patients.

The analyses based on the change from baseline showed a greater decrease in blood monocyte neutrophils, and platelets in mirikizumab treated participants than in the placebo group but the mean decrease in cell counts from baseline were small and not considered to be of clinical significance.

Some patients were taking concomitant therapies (including corticosteroid, azathioprine and sulfasalazine) which could affect cell counts in these patients.

There is no clear biologic plausibility for an association between decreased monocytes or decreased platelets and mirikizumab treatment. Therefore, taking also into consideration a small number of cases reported, no update to the SmPC was required.

Although there is biologic plausibility for low neutrophils in participants treated with mirikizumab, also for neutrophils update to the product information was not considered necessary.

This was based on the fact that the number of cases was small and there was lack of consistent findings in the induction and maintenance periods (during maintenance no differences between the treatment group were seen). Further there was no difference in the frequencies and types of infection-related TEAEs in participants with shifts to a higher CTCAE grade between the placebo and mirikizumab treatment groups.

The applicant agreed to monitor changes in monocytes, as well as neutrophils and platelets, in the ongoing clinical trials and through routine postmarketing pharmacovigilance activities. Further, cases of decreased neutrophils should be presented in the PSUR as a topic of special interest.

Chemistry

Cases of elevated liver enzymes were reported in subject participating in the studies with mirikizumab and these elevations occurred more frequently in the mirikizumab treated subjects as compared to those on placebo. In addition, cases of potential hepatocellular and cholestatic DILI were reported (for further discussion in relation to hepatic safety please see above).

In relation to other laboratory chemistry parameters numerical differences between treatment groups were noted for blood urea nitrogen, creatinine kinase, serum albumin sodium, and total serum protein although these changes were considered of lower clinical significance.

The increase in serum CK was seen in mirikizumab-treated participants compared with the placebo group. The majority of patients had Grade 1 increase however Grade 4 increases were also reported

(in 11 mirikizumab-treated patients and only one patient on placebo). 30 % of patients with an increase in serum CK had also concurrent elevation of AST. No cases of rhabdomyolysis or myopathy were reported.

In relation to the reported changes in serum CK discussion was requested and few mirikizumab-treated participants reported TEAEs of increased CK in association with a shift to a higher CTCAE grade (0.4%), and those that were reported were not serious. TEAEs that may be associated with a shift to a higher CTCAE grade for CK were reported at a higher frequency in the placebo group (0.6%) than in the mirikizumab treatment group (0.5%). Additionally, most elevations were transient and returned to baseline at next assessment while continuing mirikizumab treatment, were associated with other medications, physical activity, or AEs that could result in an increased risk for serum CK elevations, and time-to-onset was variable. High serum CK does not demonstrate any unique time course or any new or unique risk factors that could be identified. There were no CK elevations associated with infusion reactions, and no temporal relationship with injection site reactions was identified. Based on the justification provided by the applicant CHMP agreed that no SmPC update is required.

Vital signs

A higher frequency of TE-high systolic and diastolic BP was observed among mirikizumab-treated participants compared to those who received placebo: however, most of these events were non-serious, had no clinical sequelae, did not lead to study discontinuation, and were assessed as not related to mirikizumab by the study investigators.

In relation to the mean and median systolic and diastolic BP, these were higher in the mirikizumab-treated participants compared to those who received placebo: however, the difference between the groups was small, i.e. less than 2 mmHg which is considered as clinically insignificant difference.

Therefore, no update to the SmPC was considered necessary.

Safety in subpopulations

The applicant analysed the safety of mirikizumab depending on the intrinsic (age, sex, race, region, and disease severity) and extrinsic factors (prior biologic or tofacitinib exposure at baseline).

Some differences were noted. TEAEs were reported more frequently in Female patients (26.2%) as compared to male patients (16.2%). In addition, Infections and infestations were more frequently reported in female participants.

No differences in the frequency TEAEs were reported in age groups. TEAEs were reported 20.1% of patients aged 65 or less as compared to 19.5% of patients >65 years of age.

Use in pregnancy

There were no adverse effects on the embryos, foetuses, and off springs demonstrated in non-clinical studies using pregnant monkeys. Pregnant or lactating women were excluded from the development programme. There were 28 pregnancies from maternal exposure and 41 pregnancies from paternal exposure reported. No cases of mirikizumab use during breast-feeding were reported Therefore, the available data are insufficient to conclude on the safety of mirikizumab use in pregnancy or lactation and the SmPC wording is reflecting this. Safety of mirikizumab in pregnant women and lactating women is included as missing information in the RMP which is supported. It needs to be noted that Women of childbearing potential are expected to comprise a significant proportion of the target UC population.

Use in patients with severe hepatic impairment and severe renal impairment

Specific clinical pharmacology studies to evaluate the effects of renal impairment and hepatic impairment on the PK of mirikizumab were not conducted which was considered acceptable my the CHMP.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.10. Conclusions on the clinical safety

Adequate risk mitigation has been implemented on the main safety concerns. Long term safety in particular on MACE and DILI will be further characterised post authorisation by means of an observational secondary database study as described in the RMP (category 3).

2.7. Risk Management Plan

2.7.1. Safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	• Serious infections • Severe liver injury • Malignancies • MACE
Missing information	• Safety of mirikizumab in pregnant women and lactating women

Abbreviation: MACE = major adverse cardiac event.

2.7.2. Pharmacovigilance plan

Table Part III.3.1: On-going and planned additional pharmacovigilance activities

Study (study short name, and title) **Status** (planned/ongoing)	**Summary of objectives**	**Safety concerns addressed** (list)	**Milestones** (required by regulators)	**Due dates** (in DD/Mon/YYYY format)*
Category 1 - Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities that are specific obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
Observational Secondary Database Cohort Study on Mirikizumab Exposure and Pregnancy Planned	• To monitor the use of mirikizumab among women of childbearing age. • To determine the incidence of pregnancy- and foetal/infant outcomes among pregnant women with ulcerative colitis who are exposed to mirikizumab during pregnancy. • If sufficient sample size allows, to compare the incidence of pregnancy and foetal/infant outcomes of women with ulcerative colitis who are exposed to mirikizumab during pregnancy to women with ulcerative colitis who are not	Missing information: Use in pregnancy.	Start of data collection Study progress report Interim report	Within 2 years of first regulatory approval To be submitted with the PSUR (after the start of data collection) Approximately 4 years after start of data collection
			Final report	31 Dec 2031

Study (study short name, and title) **Status** (planned/ongoing)	**Summary of objectives**	**Safety concerns addressed** (list)	**Milestones** (required by regulators)	**Due dates** (in DD/Mon/YYYY format)*
	exposed to mirikizumab and/or who are exposed to other medications indicated for the treatment of ulcerative colitis during pregnancy.			
Observational Secondary Database Study to Assess the Long-Term Safety of Mirikizumab Planned	• To examine the incidence of severe liver injury, serious infections including opportunistic infections, malignancies excluding non-melanoma skin cancer and MACE among patients with ulcerative colitis who are exposed to mirikizumab compared to patients with ulcerative colitis who are not exposed to mirikizumab and/or who are exposed to other medications indicated for the treatment of ulcerative colitis, in real world clinical practice in the US.	Important potential risks: Severe liver injury, serious infections, malignancy, and MACE.	Start of data collection Study progress report Interim report	Within 2 years of first regulatory approval To be submitted with the PSUR (after the start of data collection) Approximately 7 years after the start of data collection
			Final report	31 Dec 2037

Abbreviations: MACE = major adverse cardiovascular event; PSUR = periodic safety update report.

2.7.3. Risk minimisation measures

2.7.3.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	**Routine risk minimisation activities**
Severe Liver Injury	Routine risk communication: • SmPC Sections 4.4 and 4.8 • PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.4 advises: • Elevations of aminotransferases have been reported in patients receiving mirikizumab. Evaluate liver enzymes as clinically indicated. If increases in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) are observed and drug-associated liver injury is suspected, discontinue mirikizumab until this diagnosis is excluded. SmPC Section 4.8 indicates: • Over all mirikizumab treatment periods in the ulcerative colitis clinical development programme (including the placebo controlled and open-label induction and maintenance periods), there have been elevations of ALT to ☐3x upper limit of normal (ULN) (2.0%), ☐5xULN (0.7%) and ☐10xULN (0.2%) and AST to ☐3xULN (2.1%), ☐5xULN (1.1%), and ☐10xULN (0.1%) in patients receiving mirikizumab (see Section 4.4). These elevations have been noted with and without concomitant elevations in total bilirubin. PL Section 2 advises • Your doctor may check blood tests to help tell if your liver is functioning normally. If blood tests are abnormal, your doctor might interrupt therapy with mirikizumab and do additional tests on your liver to determine the cause. Pack size: Not applicable Legal status: Not applicable

Safety of mirikizumab in pregnant women and lactating women	Routine risk communication: • SmPC Section 4.6 • PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.6 provides guidance: • Women of childbearing potential should use an effective method of contraception during treatment and for at least 10 weeks after treatment. • 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 mirikizumab during pregnancy. • 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. Afterwards, mirikizumab could be used during breast-feeding if clinically needed. PL Section 2 advises: • If you are pregnant, think you may be pregnant, or are planning to have a baby, ask your doctor for advice before using this medicine. It is preferable to avoid the use of mirikizumab in pregnancy. The effects of mirikizumab in pregnant women are not known. If you are a woman of childbearing potential, you are advised to avoid becoming pregnant and should use adequate contraception while using mirikizumab and for at least 10 weeks after the last mirikizumab dose. • If you are breast feeding or are planning to breast-feed, talk to your doctor before using this medicine. Pack size: Not applicable. Legal status: Not applicable.

Long-term safety of mirikizumab for events with a low frequency and/or long latency, including MACE and malignancy	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Pack size: Not applicable Legal status: Not applicable

2.7.4. Conclusion

The CHMP considers that the risk management plan version 0.3 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.3 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons: considering that Omvoh 300 mg concentrate for solution for infusion is to be diluted and administered by a qualified healthcare professional, and taken into account the proven space constraints, the QRD Group agreed to apply the minimum particulars to the 15-mL vial.

2.9.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Omvoh (mirikizumab) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

UC is a chronic disease of unknown aetiology that is characterised by inflammation of the colon and rectum. Symptoms include diarrhoea, rectal bleeding, abdominal pain, and bowel movement urgency. UC has a relapsing-remitting course, meaning that many patients have intermittent disease flares that are interspersed with periods of remission. It has a reported prevalence of 2.4 to 505 per 100,000 persons in Europe.

The most severe intestinal manifestations of UC which are life threatening and can be fatal are toxic megacolon and perforation. Extraintestinal complications include arthritis (peripheral or axial involvement), dermatological conditions (erythema nodosum, aphthous stomatitis, and pyoderma gangrenosum), inflammation of the eye (uveitis), and liver dysfunction (primary sclerosing cholangitis)

Treatment goals in UC include induction of remission (typically within a 6 to 12-week time frame) and maintenance of remission in the longer term (assessed over 52 weeks of continuous treatment in clinical trials). In both clinical practice and in clinical trials, clinical response and clinical remission are assessed by a combination of endoscopy (improvement in the endoscopic appearance of the mucosa and healing of ulcers) and patient-reported outcomes, including a reduction in stool frequency (SF) and a resolution of RB (Levesque et al. 2015). Control of intestinal inflammation in UC is also associated with a reduction in the risk of hospitalisation, colectomy, and in the longer term, UC associated dysplasia and colorectal cancer.

The applicant initially applied for the following indication: *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 or a Janus kinase (JAK) inhibitor, or have medical contraindications to such therapies (see section 5.1).*

3.1.2. Available therapies and unmet medical need

Medications used for the treatment of UC include 5-aminosalicylic acid (5-ASA)–containing medications (sulfasalazine, mesalazine, balsalazide, olsalazine), corticosteroids, immunomodulators such as AZA and 6-MP, and biologic medications. A significant proportion of patients with moderately to severely active UC may have an inadequate response to medicines such as 5-ASAs or corticosteroids, be unable to maintain a clinical response to 5-ASAs or AZA or are unable to discontinue corticosteroids without a relapse in disease activity (reviewed in Dignass et al. 2012). Many of these patients require additional

treatment with the next line of therapy, which could include medical treatment with a biologic medication or surgical treatment with a colectomy.

Biologics, including antitumour necrosis factor (TNF) antibodies (infliximab, adalimumab, golimumab) and vedolizumab, an anti-α4β7 integrin antibody, are indicated for the treatment of UC in patients who fail to respond to, have an inadequate response to, or are intolerant to other medications used in the treatment of UC medications, and as a first-line treatment for UC in selected patients. However, in the pivotal ACT1 and ACT2 studies of infliximab therapy in patients with moderately to severely active UC and in the pivotal PURSUIT studies of golimumab in the same patient population, only approximately 50% to 65% of the patients achieved clinical response (as defined by complete Mayo score) at the induction time point (Weeks 6 to 8), with approximately 50% of the patients maintaining clinical response to Week 54 (Rutgeerts et al. 2005; Sandborn et al. 2014a, 2014b). In the pivotal ULTRA studies of adalimumab in the same patient population, 16.5% of patients achieved clinical remission at Week 8 (Sandborn et al. 2012a). Similarly, in the pivotal GEMINI 1 study of vedolizumab in patients with moderately to severely active disease, 47% achieved a clinical response at Week 6 and up to 45% of these patients were in clinical remission at Week 52 (Feagan et al. 2013).

While the recent approvals of multiple therapies including JAK inhibitors for UC are encouraging, clinical trial remission rates for both induction and maintenance treatment in UC remain limited. Therefore, there is a continued need for new therapies in UC.

3.1.3. Main clinical studies

The pivotal induction study

(Study 16T-MC-AMAN) was a phase 3, randomised, double-blind, parallel-group, placebo-controlled, multicentre studies designed to evaluate the efficacy and safety of Mirikizumab 300mg IV versus placebo for up to 12 weeks. The study population included patients with moderately to severely active ulcerative colitis (UC) who had an inadequate response to, loss of response to, or are intolerant to conventional (nonbiologic) therapy for UC (conventional-failed), and those who had an inadequate response to, loss of response to, or are intolerant to biologic therapy for UC (biologic-failed).

Patients were randomised 3:1 to receive blinded intravenous (IV) administration of 300 mg mirikizumab or placebo every 4 weeks (Q4W) and were stratified on biologic-failed status (yes/no), baseline corticosteroid use (yes/no), baseline disease activity (modified Mayo score [MMS]: [4-6] or [7-9]), and geographic region (North America/Europe/Other).

There was no rescue arm in Study AMAN. However, patients who completed Study AMAN through Week 12 (with an acceptable safety profile) who did not achieve a clinical response to mirikizumab at Week 12 could be eligible to receive an induction dose of mirikizumab in maintenance Study AMBG. At the end of Week 12 of the induction period, patients could either: enter Study I6T-MC-AMBG (maintenance study) or discontinue study treatment and complete the post-treatment follow-up period.

The primary endpoint of Study AMAN was the proportion of patients in clinical remission at Week 12. Clinical remission per modified mayo score, was defined as SF subscore = 0, or SF subscore = 1 with a ≥1-point decrease from baseline, RB subscore = 0, and ES = 0 or 1 (excluding friability).

The pivotal maintenance study

(Study I6T-MC-AMBG) was a Phase 3, multicentre, randomised, double-blind, parallel-arm, placebo-controlled maintenance study evaluating the efficacy and safety of 200 mg mirikizumab Q4W SC at Week 40 (52 weeks of continuous therapy) in patients with moderately to severely active ulcerative colitis.

The study population included patients with moderately to severely active ulcerative colitis (UC) who completed Study AMAN. Treatment depended on the patients' response and what treatment they were receiving in study AMAN. Patients who achieved clinical response with blinded mirikizumab treatment during Study AMAN were randomised 2:1 to blinded 200 mg mirikizumab Q4W SC or blinded placebo (randomised withdrawal). Patients who responded to blinded placebo in their induction study remained on blinded placebo in Study AMBG. Open-label rescue therapy with 300 mg mirikizumab Q4W intravenously (IV) was administered for 3 doses if these patients lost response.

Patients who did not achieve clinical response with either blinded mirikizumab or blinded placebo during Study AMAN received open-label extended induction therapy with 300 mg mirikizumab Q4W IV administered for 3 doses. Patients who achieved delayed clinical response (defined using induction study baseline) received open-label 200 mg mirikizumab Q4W SC. Induction study non responders who did not achieve clinical response at Week 12 of Study AMBG were discontinued.

Clinical response was based on modified mayo score (MMS) and defined as a decrease from baseline in the MMS of ≥ 2 points and ≥ 30% from baseline and a decrease in rectal bleeding score (RBS) ≥ 1 or an RBS of 0 or 1. The primary analysis for the main result were conducted in a subgroup of these patients who were randomised 2:1 to blinded 200 mg mirikizumab Q4W SC or blinded placebo.

The primary endpoint of Study AMBG is the proportion of patients in clinical remission at Week 40 among patients induced into clinical response at Week 12 in Study AMAN.

3.2. Favourable effects

Induction study AMAN: The primary endpoint clinical remission MMS at week 12 was achieved in 24.2% (n=201) of patients receiving mirikizumab 300 mg IV compared to 13.3 % (n=39) patients on placebo. The risk difference was 11.1 % (3.2, 19.1) this was statistically significant p =0.00006. All ranked secondary endpoints were statistically significantly better compared to placebo.

These included:

- Endoscopic remission: Mirikizumab 36.3% (n 315) compared to placebo 21.1 % (n 62). Risk difference was 15.4% (6.3-24.5) and was statistically significant p < 0.00001.
- Clinical response: Mirikizumab achieved a clinical response of 63.5% (n 551) compared to placebo 42.2 % (n 124). The risk difference of 21.4 % (10.8, 32.0) p < 0.0001
- Symptomatic remission at week 4: Mirikizumab 21.8% (n 189) versus placebo 12.9% (n 38) risk difference 9.2% (1.4. 16.9) p < 0.00064
- Symptomatic remission at week 12: Mirikizumab 45.5 % (n 395) versus placebo 27.9% (n 82) risk difference 17.5 % (7.5, 27.6) p < 0.00001.
- Clinical response by biologic failed patients at week 12: In the subgroup that had failed at least 1 biologic or Tofacitinib treatment. Clinical response was achieved in 54.6% of patients compared to 29.7% of patients on placebo risk difference was 24.9% (15.2, 34.6) P < 0.001. In the more than 1 biologic or tofacitinib failed subgroup 45.3 % of patients achieved a clinical response with mirizukizumab versus 20.8% of patients on placebo risk difference was 24.5% (11.4, 37.7) P = 0.001.
- Histologic- Endoscopic Mucosal Improvement ay week 12: A significantly greater percentage of patients achieved histologic-endoscopic mucosal improvement at Week 12 in the mirikizumab-treatment group compared to the placebo group. Patients on mirikizumab achieved a response in 27.1% of patients (n 235) compared to 13.9% on placebo (n 41). The risk difference was 13.4 % (5.5, 21.4) p < 0.00001.
- Bowel Movement Urgency NRS Change from Baseline: Patients in the mirikizumab-treatment group experienced a significantly greater reduction in Bowel Movement Urgency NRS at Week

12 compared to the placebo group. Mirikizumab LSM change form baseline -2.59 (-2.9, -2.3) compared ti placebo -1.63 (-2.1, -1.2) difference of -0.95 (-1.5, -0.4) p < 0.00001.

Maintenenace study AMBG: The primary objective of the study was met. Among mirikizumab induction responders, mirikizumab was superior to placebo in achieving clinical remission at Week 40 (Week 52 of continuous therapy) in the mITT population. Patients on mirikizumab 49.9% (n 182) compared to placebo 25.1% (n45) risk difference 23.2% (15.2, 31.2) p < 0.001. All ranked secondary endpoints were statistically significantly better compared to placebo:

- Alternate Clinical remission: Mirikizumab 51.8% (n 189) compared to placebo 26.3% (n 47). Risk difference 24.1% (16.0, 32.2) P < 0.001
- Endoscopic Remission at Week 40: Mirikizumab 58.6% (n 214) versus 29.1% (52) risk difference 28.5% (20.2, 36.8) p < 0.001.
- Maintenance of clinical remission Rates at Week 40: Mirikizumab 63.6% (n 91) compared to placebo 26.9% (n 24) risk difference 24.8% (10.4, 39.2) p < 0.001
- Corticosteroid-free remission without surgery at Week 40. This was achieved in 44.9% of patients on Mirkizumab (n 164) compared to placebo 21.8% (n 39). The risk difference 21.3% (13.5, 29.1) p < 0.001.
- Histologic-Endoscopic Mucosal Remission at Week 40: This was achieved in 43.3% of patients on Mirkizumab (n 158) compared to placebo 21.8% (n 39). The risk difference 19.9% (12.1, 27.6) p < 0.001.
- Bowel Movement Urgency NRS Improvement (Change from Induction Baseline) at Week 40 LSM change from baseline Mirkizumab -3.80 (0.139) compared to placebo -2.74 (0.202) LSM difference -1.06 (-1.51, -0.61) p < 0.001.

Subgroup analysis by demographic and baseline disease characteristics were conducted for the primary and all major secondary endpoints in Study AMAN and Study AMBG. These demonstrated a consistent effect across all of the subgroups in favour of mirkizumab treatment. Additionally, favourable effects were demonstrated on patients' quality of life with treatment through validated scoring systems. These effects along with the improvements in endpoints above were also supported by demonstration of improvement on inflammatory biomarkers with mirikizumab treatment.

3.3. Uncertainties and limitations about favourable effects

For the **Induction treatment** there seemed to be a lower response in patients on baseline steroids versus those that were not, as well as in patients who failed biological treatment, or JAK inhibitors at baseline. The effects seem limited and may take patients a longer time i.e. an additional 12 weeks-3 doses for patients to achieve a clinical remission, or an adequate clinical response. Patients were excluded if they had received or failed 3, or more biologic therapies, therefore in these patients, which represent a more difficult to treat population the efficacy is not certain.

The inclusion criteria enrolled patients with a modified Mayo score (MMS) of 4 to 9 with an endoscopic subscore (ES) ≥2, therefore patients beyond this were not included. A description of this details in 5.1 of the SmPC is included to inform the prescriber which is acceptable to the CHMP. Also, patients with UC proctitis (disease limited to the rectum, that is, distal to the recto-sigmoid junction, which lies approximately 10-15 cm from anal margin) were excluded it is therefore unclear whether mirikizumab would be effective in this population, however these patients are usually treated with localised therapies such as steroid enemas and antibiotics.

For the **maintenance phase** study, 19 patients who were in remission lost response when they were treated with 200 mg sc Q4W, it is unclear whether patients at risk of loss of response can be identified.

Also, as the duration of the follow up in the maintenance phase was 44 weeks or shorter in case of a second induction course additional patients may lose response over a longer duration and require rescue treatment with 300mg iv.

3.4. Unfavourable effects

In the All UC Mirikizumab Exposures Integrated Analysis Set, frequencies of TE elevations in ALT and AST ≥3xULN in mirikizumab-treated participants were low however higher (ALT = 2.0%, AST = 2.1%) than in participants in the UC Placebo Group (ALT = 1.1%, AST = 0.5%). The difference in the frequency of elevated liver enzymes was also seen in studies in other indications.

In the All Mirikizumab Exposures Integrated Analysis Set mirikizumab treatment group, there were slightly higher frequencies of TE elevations in ALT and AST ≥3xULN (ALT = 3.0%, AST = 2.8%) compared with the All Placebo Group (ALT = 1.3%, AST = 0.6%). AST and ALT elevation are defined in 4.8 of the SmPC. The risk is described under selected adverse reactions in the SmPC and a warning statement on regular monitoring of liver enzymes and bilirubin was added to 4.4 of the SmPC for the attention of the prescriber.

In general, the frequency of infections was higher in the mirikizumab treated patients as compared to those on placebo although the deference between the groups was small. During the induction period the percentage of participants that reported at least 1 TE infection was 14.0% (n = 45) in placebo, and 15.1% (n = 145) in the mirikizumab group. During the placebo-controlled maintenance period the percentage of participants that reported at least 1 TE infection was 22.9% (n = 44) in placebo, and 23.9% (n = 93) in the mirikizumab group. Due to its mechanism of action mirikizumab may increase the risk of severe infection and the SmPC includes a contraindication in case of active tuberculosis and a warning that mirikizumab may increase the risk of severe infection and provides guidance in case of clinically important acute, chronic, or serious infection. In addition, serious infections are listed as an important potential risk for mirikizumab, and these events will be monitored in the post-authorisation setting via routine pharmacovigilance activities and as part of the objective of the additional post-authorisation pharmacovigilance study entitled "Observational Secondary Database Study to Assess the Long-Term Safety of Mirikizumab" that is a category 3 study in the RMP.

Opportunistic infections were infrequently reported. All UC Mirikizumab analysis set opportunistic infections were reported in 25 (1.7%) patients', whereas in all Miri Exposures Integrated Analysis Set in 71 (1.9%) patients. Serious infections were reported infrequently i.e less than 2.3% in any treatment group. Pneumonia was the most frequently reported.

Infusion site reactions were reported in 8 patients (0.6%) of patients receiving mirikizumab iv. Injection site reactions were reported in 8.7% of UC patients. Inactions site pain was the most frequently reported. No serious Injection site reaction were reported. One patient discontinued due to a TE Injection site reaction. Injection site reaction cluster are listed in the SmPC which is acceptable. The frequency of participants with 1 or more Injection site reactions (HLT) was similar between TE ADA negative (8.3%) and TE ADA positive participants (10.2%). Injections and infusion site reactions are included in section 4.8 of the SmPC.

Immediate hypersensitivity events were reported in UC development programme including Infusion related reaction (6 patients), infusion related hypersensitivity reaction (4 patients), Hypersensitivity (4 patients) and rash (3 patients). No anaphylactic reactions were reported in the mirikizumab treated patients. Infusion-related hypersensitivity reactions are listed in 4.8 of the SmPC and hypersensitivity to the active substance of to any of the excipients is a contraindication and adequate precautionary statements are included in 4.4. of the SmPC.

For arthralgia a higher frequency was observed in the UC induction period (1.2 % versus 2.1% for placebo and mirikizumab, respectively) and the UC maintenance period (3% versus 6.7% for placebo and mirikizumab, respectively). Further arthralgia is listed as ADR in the SmPC of other IL-23 inhibitors i.e. ustekinumab and guselkumab. Arthralgia was added to the list of ADR in section 4.8 of the SmPC.

The frequency of Headache and Headache cluster was higher in patients receiving mirikizumab. All headache events were reported as mild or moderate. None were reported as serious or led to study treatment discontinuation. Headache is listed in section 4.8 of the SmPC.

3.5. Uncertainties and limitations about unfavourable effects

On hepatic safety 3 cases which fulfil the criteria for DILI were classified as probably or possibly related to treatment with mirikizumab. One case meeting Hy's Law criteria was particularly concerning as no alternative aetiology or significant confounding risk factors were identified in this patient. Further, there was small imbalance in the percentage of patients with increased liver enzymes between the treatment groups.

Based on review of cases with a probable or possible association with mirikizumab treatment, elevations in hepatic enzymes improved or normalised with or without discontinuation of mirikizumab treatment, and none resulted in death, a serious outcome, or other sequelae. Further frequencies of elevations of ALT and AST reported in studies with mirikizumab were not higher as seen in studies for the products of the same class.

To balance the risk a warning was introduced in section 4.4 with a recommendation for monthly liver monitoring during induction followed by less frequent monitoring during the maintenance therapy. Further, 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. Furthermore, cases of elevations in ALT and AST are described in Section 4.8 of the SmPC.

Further, to characterise the risk further post marketing severe liver injury was added as an impotent potential risk in the RMP and additional pharmacovigilance activities were introduced, including the use of a spontaneous hepatic disorders follow-up form and inclusion of severe liver injury as an outcome of interest in the observational secondary database study to assess the long-term safety of mirikizumab.

Cardiovascular safety

In total, 28 cases of Adjudicated Major Adverse Cardiovascular Events (MACE) were reported in mirikizumab-treated participants in the All Mirikizumab Exposures Integrated Analysis Set which included not only patients with UC but also those treated for other indications such as psoriasis and CD.

In the placebo-controlled period of the mirikizumab psoriasis development programme, a numerical imbalance for MACE (placebo = 0; mirikizumab = 5; 0.4% [1.2 IR]) was observed. However, this numerical imbalance in participants with psoriasis needs to be interpreted in the context of o randomisation differences between placebo- and mirikizumab-treated participants (6:1) and subsequently a significant imbalance in the number of patients enrolled to each arm.

Although a causal relationship of MACE with mirikizumab treatment was not determined based on the data presented so far, taking into consideration small imbalances of MACEs in psoriasis studies these cases will be monitored post-marketing including in the observational secondary database study

planned by the applicant. Further, in line with other IL-23 inhibitors major adverse cardiovascular events (MACE) was included as an important potential risk to the RMP.

Malignancy

There is no clear evidence of an increased risk for developing malignancies following treatment with mirikizumab based on results of the clinical trials presented so far in this application. As there is an established increased risk for cancer development in UC and there is a theoretical possibility of decreased immune surveillance against malignancies with alteration of immune pathways with mirikizumab treatment, malignancy was added Important Potential Risk in the RMP.

Infections

Mirikizumab is an immunomodulatory drug and as such, may increase the risk of developing an infection or may exacerbate an existing infection. In studies performed by the applicant the frequency of infections was higher in the mirikizumab treated patients as compared to those on placebo although the deference between the groups was small. Serious infections were reported infrequently i.e. less than 2.3% in any treatment group. Pneumonia was the most frequently reported. A warning highlighting a potential for an increased risk for infection was added to section 4.4 of the SmPC. In addition, this risk will be further monitored and characterised post marketing i.e opportunistic infections and serious infections will be monitored by the applicant in the planned observational secondary database study as described in the RMP. Serious infections are included in the RMP as an Important potential risk.

Laboratory abnormalities

In relation to haematology laboratory values in the UC induction period as well as in the UC maintenance placebo-controlled period a greater mean decrease in blood monocytes, segmented blood neutrophils and blood platelets was noted in the mirikizumab treatment group as compared to the placebo group. There is no clear biologic plausibility for an association between decreased monocytes or decreased platelets and mirikizumab treatment. Therefore, taking also into consideration the small number of cases reported, no update to the SmPC was required.

Although there is biologic plausibility for low neutrophils in participants treated with mirikizumab, also for neutrophils update to the product information was not considered necessary. This was based on the fact that the number of cases was small and there was lack of consistent findings in the induction and maintenance periods (during maintenance no differences between the treatment group were seen). Changes in monocytes, neutrophils and platelets will be monitored post -marketing in the ongoing clinical trials and through routine post-marketing pharmacovigilance activities.

3.6. Effects Table

Effects Table for Mirikizumab in 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

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Clinical remission per MMS at week 12.	Proportion of patients with SF =0 or SF =1 with a ≥1 point decrease from baseline, RBS)=0, and ES=0 or 1 without friability	N (%)	Mirikizumab 300mg 210/868 (24.2%)	Placebo 39/294 (13.3%)	Risk difference (98.875% CI) 11.1 % (3.2, 19.1) P<0.001	Study I6T-MC AMAN
Alternate clinical remission per MMS at week 12.	Proportion of patients with SF =0 or SF =1 decrease from baseline, RBS)=0, and ES=0 or 1 without friability	N (%)	Mirikizumab 300mg 222/868 (25.6%)	Placebo 43/294 (14.6%)	Risk difference (98.875% CI) 11.1% (3.0, 19.3) P 0.0007	Study I6T-MC AMAN
Clinical response at week 12	A decrease in the Modified Mayo score ≥ 2 points and ≥ 30% from baseline, and a decrease in RBS ≥ 1 from baseline or an absolute RBS of 0 or 1.	N (%)	Mirikizumab 300mg 551/868 (63.5%)	Placebo 124/294 (42.2%)	Risk difference (98.875% CI) 21.4% (10.8, 32.0) P<0.0001	Study I6T-MC AMAN
Endoscopic improvement at week 12	ES=0 or 1 (excluding friability)	N (%)	Mirikizumab 300mg 315/868 (36.3%)	Placebo 62/294 (21.1%)	Risk difference (98.875% CI) 15.4 (6.3. 24.5) P<0.00001	Study I6T-MC AMAN
Symptomatic remission at week 4 Symptomatic remission at week 12	Proportion of patients with SF =0 or SF =1 with a ≥ 1 point decrease from baseline and RB=0.	N (%)	Mirikizumab 300mg 189/868 (21.8%) 395/868 (45.5%)	Placebo 38/294 (12.9%) 82/294 (27.9)	Risk difference (98.875% CI) 9.2 (1.4, 16.9) P 0.00064 17.5 (7.5, 27.6) P < 0.00001	Study I6T-MC AMAN
Clinical response per Modified Mayo Score at Week 12 in patients who failed biologic or JAKi therapy for UC	A decrease in partial MMS ≥ 1 points and ≥ 30% from baseline, and a decrease in RBS≥ 1 from baseline or an absolute RBS of 0 or 1		Mirikizumab 300mg 197/361 (54.5%)	Placebo 35/118 (29.7%)	Risk difference (98.875% CI) 25.0 (9.0, 41.1) P<0.00001	Study I6T-MC AMAN

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Bowel urgency severity at week 12	The change from baseline in the urgency numeric rating scale score.	LSM change from baseline	Mirikizumab 300mg -2.59 (0.083)	Placebo -1.63 (0.141)	LSM difference (99.875% CI) -0.95 (-1.47, -0.44) P<0.00001	Study I6T-MC AMAN
Histo-endoscopic improvement at week 12	Histologic improvement Geboes scoring system with neutrophil infiltration in 5% of crypts, no crypt destruction, nor erosions, ulceration or granulation tissue Endoscopic improvement ES0 or 1 (excluding friability)	N (%)	Mirikizumab 300mg 235/868 (27.1%)	Placebo 41/294 (13.9%)	Risk difference (98.875% CI) 13.4 (5.5, 21.4) P<0.00001	Study I6T-MC AMAN
Clinical remission at Week 40 among subjects who have achieved clinical response at the end of the induction treatment	Proportion of patients with SF =0 or SF =1 with a ≥1 point decrease from baseline, RBS)=0, and ES=0 or 1 without friability	N (%)	Mirikizumab 200mg 182/365 (49.9%)	Placebo 45/179 (25.1%)	Risk difference (95% CI) 23.2 (15.2, 31.2) P<0.001	**Study I6T-MC-AMBG**
Alternate Clinical remission at week 40 among subjects who have achieved clinical response at the end of the induction treatment	Proportion of patients with SF =0 or SF =1 decrease from baseline, RBS)=0, and ES=0 or 1 without friability	N (%)	Mirikizumab 200mg 189/365 (51.8%)	Placebo 47/179 (26.3%)	Risk difference (95% CI) 24.1 (16.0, 32.2) P<0.001	**Study I6T-MC-AMBG**
Clinical remission at Week 40 among subjects who have achieved clinical remission at the end of the induction treatment	Proportion of patients with SF =0 or SF =1 with a ≥1 point decrease from baseline, RBS)=0, and ES=0 or 1 without friability	N (%)	Mirikizumab 200mg 91/143 (63.6%)	Placebo 24/65 (36.9%)	Risk difference (95% CI) 24.8 (10.4, 39.2) P<0.001	**Study I6T-MC-AMBG**

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Endoscopic improvement at week 40 in patients induced into clinical response at the end of induction	ES=0 or 1 (excluding friability)	N (%)	Mirikizumab 200mg 214/365 (58.6%)	Placebo 52/179 (29.1)	Risk difference (95% CI) 28.5 (20.2, 36.8) P<0.001	**Study I6T-MC-AMBG**
Corticosteroid free remission at week 40 in patients induced into clinical response at the end of induction	Clinical remission at week 40, symptomatic remission at week 28 and no corticosteroid use for at least 12 weeks prior to week 40	N (%)	Mirikizumab 200mg 164/365 (44.9%)	Placebo 39/179 (21.8%)	Risk difference (95% CI) 21.3 (13.5, 29.1) P<0.001	**Study I6T-MC-AMBG**
Histo-endoscopic improvement at week 40 in patients induced into clinical response at the end of induction	Histological remission, resolution of mucosal neutrophils using Geboes scoring system. with subscores of 0 for grades, and ES =0 or 1	N (%)	Mirikizumab 200mg 158/365 (43.3%)	Placebo 39/179 (21.8%)	Risk difference (95% CI) 19.9 (12.1, 27.6) P<0.001	**Study I6T-MC-AMBG**
Unfavourable Effects						
TEAEs Induction period		N (%)	miri 300 mg IV Q4W 426 (44.5%)	placebo IV Q4W 148 (46.1%)		Study I6T-MC AMAN
TEAEs Blinded maintenance period		N (%)	miri 200 mg SC Q4W 251 (64.5%)	Miri Induction Responder Placebo SC Q4W 132 (68.8%) Placebo Induction Responde Placebo SC Q4W 82 (60.7%)		**Study I6T-MC-AMBG**
SAEs Induction period		N (%)	miri 300 mg IV Q4W 27 (2.8%)	placebo IV Q4W 17 (5.3%)		Study I6T-MC AMAN

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
SAEs Blinded maintenance period		N (%)	miri 200 mg SC Q4W 13 (3.3%)	Miri Induction Responder Placebo SC Q4W 15 (7.8%) Placebo Induction Responde Placebo SC Q4W 7 (5.2%)		**Study I6T-MC-AMBG**
Infections Induction period		N (%)	miri 300 mg IV Q4W 145 (15.1%)	placebo IV Q4W 45 (14%)		Study I6T-MC AMAN
Infections Blinded maintenance period		N (%)	miri 200 mg SC Q4W 93 (23.9%)	Miri Induction Responder Placebo SC Q4W 44 (22.9%) Placebo Induction Responde Placebo SC Q4W 30 (22.2%)		**Study I6T-MC-AMBG**
Hepatic disorders TEAEs (narrow terms) Induction period		N (%)	miri 300 mg IV Q4W 15 (1.6%)	placebo IV Q4W 5 (1.6%)		Study I6T-MC AMAN
Hepatic disorders TEAEs (narrow terms) Blinded maintenance period		N (%)	miri 200 mg SC Q4W 12 (3.1%)	Miri Induction Responder Placebo SC Q4W 4 (2.1%) Placebo Induction Responde Placebo SC Q4W 4 (3.0%)	Major safety concerns were identified for mirikizumab in relation to hepatic safety, as 3 cases which fulfill criteria for DILI were classified as probably or possibly related to treatment with mirikizumab (including patients with psoriasis)	**Study I6T-MC-AMBG**

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
MACE Induction period		N (%)	miri 300 mg IV Q4W 0	placebo IV Q4W 0	There are concerns in relation to cardiovascular safety in patients treated with mirikizumab but mostly based on the safety data in the psoriasis development programme There was imbalance in the incidence rate of TE MACE as compared to placebo.	Study I6T-MC AMAN
MACE Blinded maintenance period		N (%)	miri 200 mg SC Q4W 0	Miri Induction Responder Placebo SC Q4W 1(0.5%) Placebo Induction Responde Placebo SC Q4W 0	There are concerns in relation to cardiovascular safety in patients treated with mirikizumab but mostly based on the safety data in the psoriasis development programme There was imbalance in the incidence rate of TE MACE as compared to placebo.	**Study I6T-MC-AMBG**

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Efficacy

The pivotal induction study demonstrated a clinically relevant and statistically significant superiority of mirikizumab 300mg iv Q4W compared to placebo in inducing remission in patients with moderate to severe ulcerative colitis. Also, a larger majority of patients achieved a clinically relevant response at week 12 compared to placebo. Statistically significant results were demonstrated in favour of treatment with mirikizumab for all of the secondary endpoints.

A heterogeneous population was recruited and while a more significant effect was seen in biological naïve patients, the effects seen in more heavily treated patients was considered to be clinically relevant. A key secondary endpoint was to examine the effects in patients who had previously failed biological or JAK inhibitor treatment and again a consistent beneficial effect was seen with mirikizumab treatment. Symptomatic remission was achieved as early as 4 weeks following treatment and increased at 12 weeks treatment. When assessing endoscopic and histologic effects, superiority was also seen with mirikizumab treatment. An approximate 2-fold higher response was seen in both histological and endoscopic improvement with treatment at 12 weeks compared to placebo.

In the maintenance study, a lower dose of mirikizumab, 200 mg SC Q4W, was investigated. The overall results again were in favour of mirikizumab treatment compared to placebo for the primary and all key secondary endpoints. The applicant also demonstrated more than 2-fold higher response rate in favour of mirikizumab in endoscopic improvement, corticosteroid free remission and histological and endoscopic response at week 40, which are all considered clinically relevant.

Overall, the treatment effect is considered to be clinically relevant and in line with other approved products with the same indication, although it is acknowledged that a formal comparison between products is not possible.

For part of the intended indication the applicant had initially sought a claim in patients who had failed, or were intolerant to Janus kinase inhibitors, however, it seems that the only member of this class of medications investigated was tofacitinib. The number of patients who had failed tofacitinib alone at baseline was rather low (6 placebo, 34 mirikizumab). This was therefore raised as a concern, and the applicant has acknowledged this and removed the relevant text from the indication. The applicant has also removed a reference to section 5.1 as requested by the CHMP.

In addition, the applicant was seeking to include "(…), or, have medical contraindications to such therapies" in the indication statement. The applicant was asked to delete this text as any such statement is considered inappropriate in this section of the SmPC, and the applicant has done so.

The indication now sought by the applicant is:

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 ~~or a Janus kinase (JAK) inhibitor, or have medical contraindications to such therapies (see section 5.1).~~

This updated indication claim is consistent with the development programme and the results provided and therefore acceptable.

Safety

A Case of Hy's Law was identified in a patient enrolled to the OL extended induction period and receiving the highest dose of mirikizumab (i.e 5 doses of mirikizumab 300 mg Q4W IV). As indicated by the applicant, the elevation in liver enzymes for this participant is most likely due to an idiosyncratic drug-induced liver injury.

The following risk mitigation measures were implemented and are considered to mitigate and further characterise sufficiently this important potential risk:

A warning in section 4.4 was introduced with a recommendation for monthly liver monitoring during an induction followed by less frequent monitoring during the maintenance therapy. Severe liver injury was added as an impotent potential risk in the RMP and additional pharmacovigilance activities were introduced, including the use of spontaneous hepatic disorders follow-up form and inclusion of severe liver injury as an outcome of interest in the observational secondary database study to assess the long-term safety of mirikizumab.

3.7.2. Balance of benefits and risks

The benefit risk for mirikizumab 300mg iv Q4W and 200 mg sc Q4W for treatment of UC is considered positive.

3.8. Conclusions

The overall benefit/risk balance of Omvoh is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Omvoh is favourable in the following indication(s):

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

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that mirikizumab is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.