12 December 2024
EMA/16371/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Omvoh

International non-proprietary name: Mirikizumab

Procedure No. EMEA/H/C/005122/X/0006/G

Note

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

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List of abbreviations

6-MP	6-mercaptopurine
ADA	antidrug antibody
ADR	adverse drug reaction
AE	adverse event
AI	Autoinjector
ALT	Alanine aminotransferase
AMAG	Phase 2 Study I6T-MC-AMAG
AMAM	Phase 3 Registration Study I6T-MC-AMAM
AMAX	Phase 3 Long-Term Extension Study I6T-MC-AMAX
AMAY	Phase 3 Pediatric Study I6T-MC-AMAY
AMAZ	Phase 3 Pediatric Long-Term Extension Study I6T-MC-AMAZ
AMBT	Phase 1 Study I6T-MC-AMBT
AMBX	Phase 1 Study I6T-MC-AMBX
AMBY	Phase 1 Study I6T-MC-AMBY
AP	abdominal pain
AST	aspartate aminotransferase
AZA	azathioprine
BE	bioequivalence
CD	Crohn’s disease
CDAI	Crohn’s Disease Activity Index
COVID-19	coronavirus disease 2019
CRP	C-reactive protein
CSR	clinical study report
CV	coefficient of variation
EAIR	exposure-adjusted incidence rate
ECCO	European Crohn’s and Colitis Organisation
EQ-5D-5L	European Quality of Life 5-Dimension 5 Level
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy – Fatigue Scale
HLT	high-level term
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
IL	interleukin

IR	incidence rate
IV	intravenous
JAK	Janus kinase
MACE	major adverse cardiac event
MTX	methotrexate
NRS	numeric rating scale
PAS	primary analysis set
PK	pharmacokinetics
PRO2	Patient-Reported Outcome 2; 2 of the patient-reported items of the CDAI (SF and AP) using the original CDAI multiplication factors for weighting SF and AP items
PT	preferred term
PYE	patient-years of exposure
Q4W	every 4 weeks
SAE	serious adverse event
SC	subcutaneous
SCE	summary of clinical efficacy
SCP	summary of clinical pharmacology
SCS	summary of clinical safety
SF	stool frequency
SF-36	Medical Outcomes Study 36-item Short-Form health survey
TE	treatment-emergent
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
UC	ulcerative colitis
ULN	upper limit of normal
URTI	upper respiratory tract infection
WPAI	Work Productivity and Activity Impairment Questionnaire

1. Background information on the procedure

1.1. Submission of the dossier

Eli Lilly Nederland B.V. submitted on 26 April 2024 a group of variation(s) consisting of an extension of the marketing authorisation and the following variation(s):

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II
B.II.a.3.b.5	B.II.a.3.b.5 - Changes in the composition (excipients) of the finished product - Other excipients - Change that is supported by a bioequivalence study	II
B.II.b.4.a	B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size	IB
B.I.a.2.c	B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol	II
B.I.a.2.z	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	IB
A.5.b	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	IA

Extension application to add a new strength of 200 mg grouped with an extension of indication (C.I.6) to include treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic treatment, for Omvoh, based mainly on final results from study I6T-MC-AMAM; this is a phase 3, multicenter, randomized, double-blind, placebo- and active-controlled, treat-through study to evaluate the efficacy and safety of mirikizumab in patients with moderately to severely active Crohn's disease. As a consequence, sections 1, 2, 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2, 5.3, 6.1, 6.5, 6.6 and 8 of the SmPC are updated. The Labelling and Package Leaflet are updated in accordance. Version 1.2 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes and to update the list of local representatives in the Package Leaflet. As part of the application, the MAH is requesting a 1-year extension of the market protection.

The following Quality variations are also included as part of this application, applicable to the 1 mL PFP and PFS presentation, unless otherwise specified:

Type IA, A.5.b - To change the name of the site responsible for secondary packaging of the finished product from "Silvano Chiapparoli Logistica S.p.A" in Via Delle Industrie Snc, Livraga, LO, 26814, Italy to "Chiapparoli Logistica S.p.A". The address remains unchanged.

Type II, B.II.a.3.b.5 - To change the finished product composition (for Omvoh 100 mg strength presentations), by replacing the citrate buffer with a histidine-based buffer. This resulted in tightening

the pH specification and widening the osmolality specification in 3.2.P.5.1, Specification as a direct consequence of this change.

Type IB, B.II.b.4.a - To increase the finished product batch size (for Omvoh 100 mg strength presentations).

Type II, B.I.a.2.c - Changes in the active substance buffer manufacturing process to support the finished product formulation change:
- Optimization of several unit operations to increase the active substance manufacturing efficiency.
- Active substance changes to maximize process productivity/manufacturing efficiency and introduce a more caustic-resistant chromatography resin.
- Change in polishing column resin.
- As a consequence of the change in finished product composition, the active substance buffer and final matrix in Unit Operations 10 and 11 were changed to align with the new drug product formulation.
- Minor changes to the active substance specifications as a result of the reformulated active substance. The pH specification was tightened.
- Introduction of an automated dispensing train, which is applicable to both original and reformulated mirikizumab active substance. This change also applies to the active substance used in the 300 mg vial presentation.

Type IB, B.I.a.2.z - To update the unit operation 10 hold time for original mirikizumab active substance This change also applies to the active substance used in the 300 mg vial presentation.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0130/2024 on the agreement of a paediatric investigation plan (PIP.

At the time of submission of the application, the PIP P/0130/2024 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 MAH 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.

1.5. Additional Data exclusivity/Marketing protection

The MAH requested consideration of one year marketing protection in regards of its application for a

new indication in accordance with Article 14(11) of Regulation (EC) 726/2004. The request was withdrawn by the MAH during the procedure.

1.6. Scientific advice

The MAH received Scientific advice from the CHMP on 22 June 2017 (EMA/CHMP/SAWP/389521/2017). The Scientific advice pertained to non-clinical and clinical aspects.

1.7. Steps taken for the assessment of the product

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

Rapporteur: Finbarr Leacy Co-Rapporteur: N/A

The application was received by the EMA on	26 April 2024
The procedure started on	23 May 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	16 August 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	19 August 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	05 September 2024
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	19 September 2024
The MAH submitted the responses to the CHMP consolidated List of Questions on	10 October 2024
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	12 November 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	28 November 2024
The CHMP Rapporteurs circulated the updated CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	06 December 2024
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	12 December 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Crohn's disease (CD) is a chronic, immune-mediated disease of multifactorial aetiology that is characterized by transmural inflammation of the gastrointestinal tract that can involve any segment from the oral cavity to the perianal area. CD is a serious disease with associated morbidity and mortality when inadequately treated and has no cure.

2.1.2. Epidemiology

Prevalence of CD varies by geography, with higher rates observed in Western countries. According to a systematic, worldwide review of 61 population-based studies of CD from 1990 to 2016 (Ng et al. 2017), the highest estimates of prevalence were mostly found in regions in high income Western countries: 322 cases per 100,000 persons in Germany.

Prevalence of CD worldwide has been rising. In the US, CD prevalence increased with an annual percentage change of 3.4% among Medicare federal health-insurance beneficiaries between 2001 and 2018 (Xu et al. 2021).

Globally, the number of individuals with inflammatory bowel disease (IBD), primarily comprising CD, UC, and indeterminate colitis, increased from 3.7 million in 1990 to more than 6.8 million in 2017 (GBD 2017 Inflammatory Bowel Disease Collaborators 2020).

2.1.3. Biologic features

The pattern of CD activity is most often relapsing and remitting, with symptoms of active disease alternating with periods of clinical quiescence called remission (Lichtenstein et al. 2018). During periods of active CD, patients often suffer from diarrhoea, gastrointestinal bleeding, abdominal pain, weight loss, fever, fatigue, bowel urgency, and anaemia. Patients with CD may also suffer from dermatologic, orthopaedic or ophthalmic extra-intestinal manifestations (Lichtenstein et al. 2022).

2.1.4. Clinical presentation, diagnosis

Disease-related symptoms experienced by patients with CD contribute to decreased health-related quality of life (Lichenstein et al. 2018). In a large cross-sectional survey, diarrhoea, abdominal pain, fatigue, and bowel urgency were the most common symptoms reported by patients with CD (Rubin et al. 2021). Fatigue and bowel urgency were among the top-3 symptoms reported as being of high severity (Rubin et al. 2021) and very troublesome (Dibley et al. 2021) by patients with CD. Fatigue has a strong impact on daily activities, work productivity, social activities, and emotional health (van Gennep et al. 2021; Regueiro et al. 2023).

Patients with moderately to severely active CD have a high risk of disease-related complications, hospitalization, and surgical intervention (Nguyen et al. 2020). If not adequately controlled, the ongoing inflammation in patients with CD may result in cumulative, and sometimes irreversible, damage to the bowel and to the development of disease-related complications, such as structuring disease leading to intestinal obstructions, penetrating disease with intestinal fistulas and abscesses, and perianal disease

(Torres et al. 2020). Furthermore, patients with poorly controlled inflammation in CD and extensive involvement of the large intestine have an increased risk of colorectal cancer (Torres et al. 2017). Overall, mortality in CD is increased with a standardized mortality ratio of 1.4 times that of the general population (Lichtenstein et al. 2018).

Despite advances in medical therapy, up to 70% of patients eventually require a surgical intervention (Vilchez and Lightner 2022). However, these surgeries are not curative, and often lead to postoperative complications in these high-risk patients, related to the transmural nature of CD, malnutrition, and concomitant immune suppression (Li and Zhu 2018). Recent data show cumulative hospitalization rates for patients with CD were 23% to 49% in the first year following initial diagnosis and 44% to 54% after 5 years (Zhao et al. 2021).

2.1.5. Management

As CD is a lifelong disease, the overall goal in the treatment and management of CD is to induce remission and achieve mucosal healing with response maintained in the long term. It is recognized that early intervention and continued monitoring may prevent complications (Torres et al. 2020). There is emerging evidence that achieving both clinical and endoscopic remission in patients with moderate-to-severe CD results in a decreased risk of disease progression (Ungaro et al. 2020).

Existing treatment options for CD include

- conventional therapies such as corticosteroids (e.g. prednisone, budesonide) and immunomodulators (e.g. AZA, 6-MP, and MTX)
- biologic therapies (e.g. TNFα blockers, IL-12/23 and IL-23 inhibitors, integrin receptor antagonists)
- targeted oral therapies (e.g. JAK inhibitors), and
- surgery, for patients who fail available therapies or develop complications beyond the scope of medical management.

Limitations of conventional therapy:

Corticosteroids are used as first-line therapy but may not achieve mucosal healing. Their use is aimed at the acute control of symptoms. Corticosteroids are not recommended for long-term use given the known toxicities associated with chronic steroid exposure (Lichtenstein et al. 2018).

Thiopurines AZA and 6-MP may be used for maintenance of remission but are not recommended for induction therapy due to slow onset of full therapeutic effect. They have increased risk of certain malignancies, immune suppression, pancreatitis, and hepatotoxicity (Lichtenstein et al. 2018).

MTX use may be considered for maintenance of remission in patients with steroid-dependent CD or in combination with targeted therapy. Its role in induction treatment for CD is limited (Torres et al. 2020). MTX has increased risk of nausea and vomiting, hepatotoxicity, pulmonary toxicity, and myelosuppression (Lichtenstein et al. 2018).

Limitations of current biologic and targeted oral treatments

Multiple studies have shown patients becoming unresponsive to, failing to tolerate, or losing response to biologic and advanced oral therapies for CD:

- Approximately one-third of patients with CD treated with anti-TNFs are primary non-responders, and approximately one-third are secondary non-responders, meaning they lose response or develop intolerance after an initial benefit (Lichtenstein et al. 2018).

- Discontinuation rates of up to 25% in the first 3 months of treatment, and as high as 65% at 12 months, have been reported in the US for biologic treatments (Khan et al. 2019).
- Published data, including from recently approved therapies for CD, report a lower rate of efficacy for patients who previously experienced inadequate response, loss of response, or intolerance to biologic and advanced oral therapy (Sands et al. 2014; Derikx et al. 2023.

These limitations underscore the need for additional therapeutic options, such as mirikizumab, to provide benefit to patients with CD.

2.2. About the product

Mirikizumab, also known as Omvoh and LY3074828, was approved in the EU in May 2023 for the treatment of UC. The authorized dosing regimen includes an induction dose of 300 mg by IV infusion Q4W, for 3 doses; and maintenance dosing of 200 mg by SC injection Q4W (administered as 2 x 100 mg injections).

Mechanism of action

Mirikizumab is a humanized immunoglobulin G4 isotype monoclonal antibody that binds with high affinity and specificity to the p19 subunit of IL-23, a naturally occurring proinflammatory cytokine, and inhibits its interaction with the IL-23 receptor. The IL-23 pathway has been clinically demonstrated to play a central role in the pathogenesis of multiple immune-mediated and chronic inflammatory diseases, including CD.

2.3. Type of Application and aspects on development

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations:

- Line Extension Application
- Indication extension application (Variation Type II)
- Several grouped Module 3 Variations (Type II and IB) for Omvoh (INN: mirikizumab)

Background information on the group of variations

The proposed new indication for Omvoh is *the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic treatment*.

Mirikizumab is a recombinant humanised monoclonal antibody produced in CHO cells, first approved in the EU on 26 May 2023 with the following dose forms, strengths and pack sizes:

- Omvoh 300 mg concentrate for solution for infusion (pack size: 1 vial; EU/1/23/1736/001)
- Omvoh 100 mg pre-filled syringe (pack sizes: 2 pre-filled syringes; 6 pre-filled syringes, EU/1/23/1736/002 and 003)
- Omvoh 100 mg pre-filled pen (pack sizes: 2 pre-filled pens; 4 pre-filled pens 6 pre-filled pens;

EU/1/23/1736/004, 005 and 006)

The recommended Omvoh dose regimen for the new indication "treatment of Crohn's disease" has 2 parts:

1. Induction dose of 900 mg mirikizumab (3 vials) infused intravenously for at least 90 minutes at Week 0, 4 and 8
2. Maintenance dose of 300 mg mirikizumab injected subcutaneously every 4 weeks, starting at Week 12 and administered by subcutaneous injection of 100 mg (1 mL) and 200 mg (2 mL).

The maintenance treatment of CD requires the new dose form 200 mg in 2 mL (in a prefilled syringe or a prefilled pen), which will be co-packed with the dose form 100 mg in 1 mL (also prefilled syringe or prefilled pen).

Additionally, this submission seeks the approval for the simultaneous introduction of a reformulated, citrate free, buffer matrix which impacts:

- the drug substance manufacturing process and
- the 1 mL and 2 mL prefilled pen and prefilled syringe presentations supporting the subcutaneous maintenance dose.

2.4. Quality aspects

2.4.1. Introduction

The finished product Omvoh containing the active substance mirikizumab is currently authorised in six presentations (EU/1/23/1736/001-006) as 300 mg/15 ml concentrate for solution for infusion in glass vials; and 100 mg/1 ml solution for injection in pre-filled syringes and pre-filled pens.

Other ingredients, as listed in section 6.1 of the SmPC, are: sodium citrate dihydrate; citric acid, anhydrous; sodium chloride; polysorbate 80; water for injections. This list is being changed by this procedure for Omvoh 100 mg/1 ml.

A new strength of Omvoh 200 mg/2 ml solution for injection is proposed to be introduced to accommodate the recommended dose regimen for the new indication 'Treatment of Crohn's disease' that is added by this line extension. The new 200 mg strength is also manufactured in pre-filled syringes and pre-filled pens, hence constituting new integral drug-device combination products. As a result, four new Omvoh presentations (EU/1/23/1736/007-010) are proposed to be added where the new 200 mg/2 ml strength is co-packed with the already approved strength of 100 mg/ 1ml.

Additionally, five Quality variations have been grouped with this line extensions. The changes proposed notably impact the formulation of the finished product for the registered 100 mg/1 ml strength by replacing the current citrate buffer by a new histidine buffer, and the active substance manufacturing process to support this change in the finished product formulation. Moreover, the batch size of the finished product is increased for the registered 100 mg/ 1 ml strength; the Tangential Flow Filtration (TFF) hold time is updated in the active substance manufacturing process; and as an administrative change the name of a site responsible for secondary packaging of the finished product is updated.

2.4.2. Active substance

Changes grouped with this line extension affecting the active substance are presented below. The rest of the active substance dossier remains unchanged.

Type II - B.I.a.2.c: Changes in the active substance buffer manufacturing process to support the finished product formulation change:

- Optimization of several unit operations to increase the active substance manufacturing efficiency.
- Active substance changes to maximize process productivity/manufacturing efficiency and introduce a more caustic-resistant chromatography resin.
- Change in polishing column resin.
- As a consequence of the change in finished product composition, the active substance buffer and final matrix in Unit Operations 10 and 11 were changed to align with the new drug product formulation.
- Minor changes to the active substance specifications as a result of the reformulated active substance. The pH specification was tightened.
- Introduction of an automated dispensing train, which is applicable to both original and reformulated mirikizumab active substance. This change also applies to the active substance used in the 300 mg vial presentation.

Type IB - B.I.a.2.z: To update the unit operation 10 hold time for original mirikizumab active substance This change also applies to the active substance used in the 300 mg vial presentation.

2.4.2.1. General information

The general information for mirikizumab has a minor update to solubility criteria reflective of the reformulated buffer matrix. Mirikizumab is freely soluble in both the citrate and the histidine buffer used in the new formulation.

2.4.2.2. Manufacture, process controls and characterisation

The active substance remains manufactured at the Eli Lilly, IE43 facility located in Kinsale, Ireland.

Description of manufacturing process and process controls

Original active substance manufacturing process

The original active substance manufacturing process is maintained to produce the active substance used in Omvoh 300 mg/ 15 ml presented in a vial. To this process, the only change consists of the tangential flow filtration (TFF) concentrate process intermediate hold time that has been increased from not more than (NMT) 24 hours at 15-25 °C to NMT 81 hours at 15-25 °C. This change is already adequately supported by validation data presented in section 3.2.S.2.5 of the initial MAA dossier.

Reformulated active substance manufacturing process

To support the change in the finished product formulation of Omvoh 100 mg/1 ml from the citrate buffer to the histidine buffer, changes have been made to the active substance manufacturing process. In addition, to the required changes for this new formulation, the Applicant has made a number of changes to increase the scale in the upstream process and further changes in the downstream process to improve the clearance of impurities. This updated active substance manufacturing process will be used to produce the active substance used in the registered strength of Omvoh 100 mg as well as in the new strength of Omvoh 200 mg introduced by this line extension.

The changes to the manufacturing process of the active substance mirikizumab have been adequately described and are considered acceptable. The use of two active substance manufacturing processes (the original process maintained for the active substance used in Omvoh 300 mg/15 ml; and the new process hereby introduced for the active substance used in Omvoh 100 mg/1 ml and the new strength Omvoh 200 mg/2 ml) under the same marketing authorisation is considered acceptable as the new process is considered a technical adaptation which has been shown to be comparable to the original process with an adequate control strategy.

Control of materials

Sufficient information on raw materials and specifications associated with the reformulated mirikizumab active substance manufacturing process have been presented and include the new buffer composition, column, and raw material specifications. No raw materials used are sourced from animals.

Control of critical steps and intermediates

The control strategy for the reformulated manufacturing process is largely the same as the original process and is largely in line with what would be expected for a standard monoclonal antibody manufacturing process and the new limits are fully supported with data.

Process validation

A process validation approach has been performed 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). The process development changes introduced for the reformulated manufacturing and characterisation studies are presented and analysis results of PPQ batches manufactured at the commercial site and scale using the new manufacturing process are provided. The results presented for the PPQ batches include all tests registered. All results were within the established acceptance criteria. Overall, the applicant has provided sufficient data to provide assurance that the manufacturing process is appropriately validated and can produce active substance batches of consistent quality.

Manufacturing process development

The Applicant has introduced a new reformulated active substance matrix which consists of 5 mM histidine, 50 mM NaCl, 3.3% (w/v) mannitol, 0.03% (w/v) polysorbate 80, pH 5.4. The new manufacturing process of the active substance using the reformulated matrix was developed in Eli Lilly, Indianapolis and validated in the Eli Lilly, IE43 Kinsale commercial manufacturing facility. The Applicant has presented the manufacturing development history of the reformulated process along with a justification for the proposed change and a risk assessment of the impact of the proposed change. All changes were classified as low impact, and mitigations were implemented to mitigate risks identified.

Overall, the development of the control strategy proposed following the introduction of the new changes is logical and in line with the previous control strategy for the original manufacturing process.

Container closure

The reformulated active substance will be stored in the same 5L polycarbonate bottle with a silicone-lined, polypropylene copolymer (PPCO) screw cap closure as the original active substance formulation.

To confirm there was no safety or compatibility concerns with the new formulation and the PC container, a new leachable study was conducted. The study investigated the presence of volatile organic compounds, semi-volatile organic compounds and non-volatile organic compounds as long-term storage and accelerated conditions. The study for the long-term storage conditions is on-going but no leachables have been detected thus far or in the completed accelerated study. As the study is ongoing, the Applicant confirmed that any compound detected at a level above the AET would be reported to the EMA as requested.

<u>Comparability</u>

To support the new process the Applicant has performed several comparability studies which aimed to compare the original process to the reformulated manufacturing process. The comparability exercise was done in four studies. Finally, a stability comparability study comparing the commercial reformulated batches manufactured at Kinsale (post-change) which were placed on stability to three

original batches manufactured at Kinsale and the clinical reformulated batch manufactured at Kinsale (pre-change) was performed.

Overall, the results of the comparability exercise show that the new reformulated process is comparable to the original manufacturing process.

Characterisation

The main changes to this section were for the HCP section. Additional data from the new reformulated batches was presented which showed there was improved levels of the most abundant HCPs detected by LC-MS. The results showed that none of the top six HCPs could be determined following the improvements made to the process and this has led to a reduction of polysorbate hydrolysis in the reformulated finished product.

2.4.2.3. Specification

The mirikizumab active substance specification is shown in the dossier and remains mostly unchanged. The Applicant presented data that showed the reformulated active substance batches had similar results for release and over stability which demonstrates the acceptance criteria are suitable. The only changes consist of the addition of a narrowed pH release acceptance criteria for the new reformulated active substance matrix resulting from the change in active substance manufacturing process and finished product buffer; and the tightening of monomer purity and total aggregates acceptance criteria for the original active substance process. The proposed specifications are deemed acceptable.

Analytical methods

The analytical methods have been previously validated as part of the original MAA. Given there has been a change in the buffer formulation, the Applicant has presented additional acceptable validation data to demonstrate the use of this buffer does not impact the initial validation presented.

For the non-compendial methods, the Applicant has evaluated all the parameters performed to validate the methods originally and determined whether these parameters needed to be re-evaluated or could be leveraged from the original validation. This approach is considered acceptable. In most cases, the Applicant re-evaluated specificity to determine if the new reformulated buffer caused any interference in the method. This testing was done with the excipients at their highest concentration to further ensure there was no interference.

Batch analysis

Batch analysis data is provided for commercial and clinical batches. These data demonstrate that the commercial process is capable of manufacturing a consistent active substance.

Reference materials

The same reference standard is used for the reformulated active substance than the original as no impact was observed during the supplementary method validation for the new formulation and comparability between the two formulations has been shown.

2.4.2.4. Stability

Stability data are provided in support of a claimed shelf life of 36 months at ≤-65°C for the reformulated active substance. The studies are carried out in accordance with the ICH Q5C, and

suitable study protocols are provided which are aligned with the testing performed for the original formulation batches in procedure.

The data provided for the primary stability study shows that all batches meet specification. There are no trends or out of specifications observed at either condition. There are minor differences in values compared to the results obtained for the original batches but as the two processes have been shown comparable, this is not considered significant.

In the supporting stability study, the data provided shows there were no out of specifications at the long term, accelerated or stressed conditions for all the time points studied. In conclusion, the claimed shelf-life of 36 months at ≤-65°C is adequately supported by the stability data provided over the tested time periods.

2.4.3. Finished medicinal product

A new 200 mg/2 ml strength of the finished product Omvoh in a pre-filled syringe or pre-filled pen is introduced to address dosage requirements for the new indication added by this line extension. Furthermore, a type II variation grouped with this line extension was submitted to change the formulation of the registered Omvoh 100 mg strength replacing the citrate buffer by a histidine buffer. The reformulation of Omvoh 100 mg/1 ml is identical to the formulation of the new Omvoh 200 mg/2 ml strength. Other changes than the introduction of the new Omvoh 200 mg/2 ml strength grouped with this line extension and affecting the finished product are listed below. The rest of the finished product dossier remains unchanged.

Type IA - A.5.b: To change the name of the site responsible for secondary packaging of the finished product from "Silvano Chiapparoli Logistica S.p.A" in Via Delle Industrie Snc, Livraga, LO, 26814, Italy to "Chiapparoli Logistica S.p.A". The address remains unchanged.

Type II - B.II.a.3.b.5: To change the finished product composition (for Omvoh 100 mg strength presentations), by replacing the citrate buffer with a histidine-based buffer. This resulted in tightening the pH specification and widening the osmolality specification in 3.2.P.5.1, Specification as a direct consequence of this change.

Type IB - B.II.b.4.a: To increase the finished product batch size (for Omvoh 100 mg strength presentations).

2.4.3.1. Description of the product and Pharmaceutical development

Description of the finished product

The reformulated Omvoh 100 mg/1 ml and new strength Omvoh 200 mg/2 ml finished product compositions were presented in the dossier.

The reformulated Omvoh 100 mg/1 ml contains 100 mg of the active substance mirikizumab in 1 mL solution. The new strength Omvoh 200 mg/2 ml contains 200 mg of the active substance mirikizumab in 2 mL solution. The excipients listed in the SmPC are the same between the reformulated Omvoh 100 mg/1 ml and Omvoh 200 mg/2 ml: histidine, histidine monohydrochloride, sodium chloride, mannitol (E421), polysorbate 80 (E433), water for injections.

The finished product composition is identical to the active substance matrix composition. All excipients are well-known pharmaceutical ingredients, and their quality is compliant with Ph. Eur. standards.

There are no novel excipients used in the finished product formulation. The formulation data presented shows the commercial composition is suitable to maintain the quality of the finished product.

The primary packaging is a type I clear glass syringe encased in a disposable, single-dose syringe or pen with bromobutyl rubber plunger, which is unchanged for Omvoh 100 mg/1 mL but constitute new integral drug-device combination products for the new strength Omvoh 200 mg/2 mL. The material of the container closure system complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. The container closure system filled with the finished product is referred to as the semi-finished syringe (SFS). The SFS is assembled with device components to form either the prefilled syringe (PFS) or the autoinjector pen (AI) presentation.

Pharmaceutical development

The Quality Target Product Profile (QTPP) has been updated to take into account the reformulation of Omvoh 100 mg/1 ml and the new Omvoh strength of 200 mg/2 ml.

During the development of the original finished product, clinical studies indicated subjects may be experiencing undesirable injection site pain while receiving their subcutaneous dose. To improve the patient experience, a development program was initiated to reformulate the original finished products (both 1 mL and 2 mL presentations) into a buffer matrix that reduced injection site pain while maintaining the quality aspects and pharmacokinetics of the original finished product formulation. To facilitate the reformulation, human clinical trials were conducted to assess injection site pain after administration of buffer matrices lacking an active pharmaceutical ingredient. These study results coupled with the QTPP, CQAs and historical development experience were used to design formulation studies. The formulation studies included formulation screening, stability and formulation robustness studies demonstrated a commercial finished product formulation that was stable with an improved injection experience.

The new manufacturing process contains the same unit operations as the original and was developed by performing a risk assessment on each unit operation to determine their impact on the finished product critical quality attributes (CQAs) which remain the same as the original. The results from the risk assessment led to development of process characterisation studies to try mitigating identified risks and/or develop process ranges for the unit operations. The chosen process characterisation studies are considered acceptable, and the acceptance ranges determined from these studies are considered appropriate.

An extractables and leachables study has been performed on the container closure system. No extractables were identified above the AET limit and leachable studies are ongoing, and the Applicant has confirmed they will report any leachable identified above the calculated AET over the duration of the studies. The container closure systems used for Omvoh 100 mg/1 mL and 200 mg/2 mL has been shown to be suitable to protect the product from physiochemical and microbiological factors.

The Notified Body opinion for the original 100 mg/ 1mL PFS and AI is provided in 3.2.R, Regional Information which was approved as part of the initial MAA. A Major Objection was raised during the procedure to request a new Notified Body Opinion for the 2 mL PFS and autoinjector that the Applicant provided in their responses and the MO was resolved.

2.4.3.2. Manufacture of the product and process controls

Manufacturing process

The addresses of the manufacturing, packaging, labelling, and control facilities are provided in the dossier and are unchanged from the original MAA.

The manufacturing process 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 finished product manufacturing process of the reformulated Omvoh 100 mg/1 ml and of the new 200 mg/2 ml strength is typical for a monoclonal antibody and is essentially the same as the original Omvoh 100 mg/1 mL with minor differences in the filling operations (fill volume) and the assembly and dimensions of the PFS and PFP container.

Process controls

The process control strategy for the finished product manufacturing process is identical to the original Omvoh 100 mg/1 mL finished product with minor acceptable differences. Hold times have been proposed for each of the finished product manufacturing steps at ambient temperatures.

Process validation / verification

To validate the finished product manufacturing processes, three consecutive finished product validation batches were manufactured at commercial scale for both the reformulated Omvoh 100 mg/1 mL and 200 mg/2 mL finished products. A summary of the process validation for the PPQ batches is provided and all batches met the acceptance criteria. Bacterial retention, membrane compatibility, product specific bubble point studies were performed, and all were considered acceptable. Filter extractables testing was performed and was acceptable. The results of the media studies show that no contaminations were discovered in any of the syringes from four batches initially tested and the nine batches tested since 2019. A shipping study was performed from Indiana (USA) to Seishin (Japan) for the finished devices, the semi-finished devices and the PFS and AI. The shipping study was conducted at 2 °C to 15 °C for the worst-case duration of the intended commercial supply chain. All results met the acceptance criteria.

2.4.3.3. Product specification

New Omvoh 200 mg/2 ml

The finished product specifications for the new strength of Omvoh 200 mg/2 ml were presented in the dossier for the SFS, the assembled PFS and for the assembled AI (pre-filled pen)**.**

Reformulated Omvoh 100 mg/1 ml

The specification of the reformulated Omvoh 100 mg/1 ml are identical to the new Omvoh 200 mg/ 2 ml except for the volume of injection (NLT 1.0 ml for the reformulated Omvoh 100 mg/1 ml; NLT 2.0 ml for the new Omvoh 200 mg/2 ml) and syringe functionality (Compared to the original Omvoh 100 mg/1 ml, the specification of the reformulated Omvoh 100 mg/1 ml have been updated for pHand osmolality () due to the reformulation.

Original Omvoh 300 mg/15 ml

Upon request, the Applicant tightened the specification of Omvoh 300 mg/15 ml using the original process for mirikizumab for total aggregates. As the induction dosage of the Crohn's disease has been increased from 300 mg to 900 mg the Applicant was requested to justify the specifications for the vial presentation given that there is a potential for higher levels of impurities (total aggregates by SEC, and particulate matter) and endotoxins to be present in the final 900 mg dose. The Applicant justified the

specifications for the particulate matter (2X safety factor relative to the pharmacopeial requirements) and the endotoxin level (aligned with the acceptable calculated tolerance limit in Ph. Eur. and incorporates a minimum 2X safety factor) hence these remain unchanged. The limit for total aggregates by SEC was tightened in line with the highest levels observed in the clinical studies to support the new dose. Thus, the updated specifications have been suitably justified and can be considered clinically qualified and acceptable.

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. Batch analysis data on 10 commercially representative batches manufactured with the original mirikizumab process, and 6 commercially representative batches manufactured with the reformulated mirikizumab process, using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product covering both citrate and histidine formulations has been performed 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. Therefore, no additional control measures are deemed necessary.

Analytical methods

The analytical procedures for testing the 2 mL SFS, PFS and autoinjector are the same as the methods used for testing the 1mL SFS, PFS and autoinjector. The break loose and glide force method for the 2.25 mL Filled Syringe is the only method presented as there are no changes to any of the other methods compared to the original 100 mg/1 ml presentation.

Specific verifications for the reformulated mirikizumab have been provided for endotoxin, in-process bioburden, sterility, break loose and glide force, AI injection time and dose accuracy, AI injection time and button activation force and PFS dose accuracy.

Batch analysis

<u>New Omvoh 200 mg/2 ml</u>

Batch analysis data is provided for Omvoh 200 mg/2 mL Additionally, data was provided for autoinjector batches and prefilled syringe. The data presented met the proposed specifications.

<u>Reformulated Omvoh 100 mg/1 ml</u>

Batch analysis data is provided for reformulated Omvoh 100 mg/1 mL batches. All batches met the acceptance criteria. Additionally, data was provided for autoinjector and prefilled syringe batches. The data presented met the proposed specifications.

Reference materials

The reference standards are identical to those already approved for the original Omvoh 100 mg/1 mL presentation therefore no update was required.

2.4.3.4. Stability of the product

Primary stability studies were performed on three reformulated 100 mg/1 mL and three reformulated 200 mg/2 mL SFS batches. Nine months of stability data are currently available at the long-term storage condition at 2-8 °C for these batches. Long-term storage data shows the FP is stable with no trends or out of specification observed. Supporting data is provided at 2-8 °C for Omvoh 100 mg/1 mL SFS finished product and Omvoh 200 mg/2 mL SFS finished product. The data shows no trends or out of specification.

Stability studies are currently being conducted on PFS syringe for each of the reformulated Omvoh 100 mg/1 mL and 200 mg/2 mL and autoinjector for each of the Omvoh 100 mg/1 mL and 200 mg/ 2 mL of assembled finished product. The currently available results are within specification.

It is known that the product is photolabile and should be protected from light due to photostability studies performed for the approved original 100 mg/1 mL presentation.

Based on the primary and supporting data provided a shelf-life of 24 months protected from light at the long-term condition of 2-8 °C with a patient use period of two weeks at NMT 30 °C as stated in SmPC (sections 6.3 and 6.4) is supported.

2.4.3.5. Adventitious agents

There have been no updates made to the materials of biological origin or testing for the cell banks, this is deemed acceptable given the changes to the manufacturing process. Testing of the unprocessed bulk has been performed, the testing is acceptable, and all batches met the acceptance criteria.

Viral clearance has been re-evaluated based on the changes made to the manufacturing process. Supportive viral clearance data was provided. The results of the study showed the clearance was comparable to the original clearance study results.

Overall, the results of viral clearance study at set point conditions demonstrated the production process has sufficient capacity to inactivate or remove viruses.

2.4.3.6. GMO

Not applicable.

2.4.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The provided information supports the proposed changes in the active substance manufacturing process and supports the introduction of the new strength of the finished product 200 mg/2 ml, the reformulation of the registered 100 mg/1 ml finished product presentations, and changes affecting the original 300 mg/15 ml finished product in vial as a result of this line extension.

During the procedure, a Major Objection was raised requesting a new Notified Body Opinion on the new 2 ml devices (pre-filled syringe and auto-injector pen) used with the new 200 mg/2 ml strength. The Applicant provided the NBO on the new devices thus resolving the issue. Other issues raised during the procedure were adequately addressed.

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.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of the new finished product strength 200 mg/2 ml, as well as the reformulated finished product strength 100 mg/1 ml and the original 300 mg/15 ml, is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendations for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

Mirikizumab is a humanized IgG4 monoclonal, anti-interleukin-23 (anti-IL-23) antibody that binds with high affinity and specificity to the p19 subunit of human IL-23 cytokine and inhibits its interaction with the IL-23 receptor and is approved for use in adults with moderate to severe ulcerative colitis.

A comprehensive package of nonclinical pharmacology, PK, and toxicology studies was conducted to support the original MAA in ulcerative colitis.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

One additional in vitro pharmacology study has been conducted.

In Vitro Characterization, Binding Kinetics, and Affinity of LY3074828 to Human IL-23, IL-12, IL-27, and IL-35 (BTDR542)

A surface plasmon resonance assay was used to determine the binding kinetics and affinity of commercially manufactured mirikizumab to human IL-23. The binding of commercially manufactured mirikizumab to human IL-12, human IL-27, and human IL-35 was also determined to assess selectivity. The equilibrium dissociation constant (KD) of mirikizumab to human IL-23 was determined to be 328 pM. The K_D of mirikizumab to human IL-12, human IL-27, and human IL-35 was determined to be >333 nM, >500 nM, and >833 nM, respectively.

2.5.3. Ecotoxicity/environmental risk assessment

The active substance is a protein composed of natural amino acids. Proteins are expected to biodegrade in the environment. Based on the environmental fate and common presence in the environment, the use of mirikizumab 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.

2.5.4. Discussion on non-clinical aspects

A comprehensive package of nonclinical pharmacology, PK, and toxicology studies was conducted to support the original MAA in ulcerative colitis. To support the new indication for the treatment of moderately to severely active CD, the Applicant relies on the nonclinical package submitted and assessed during the original MAA (EMEA/H/C/005122).

Only an additional in vitro study to investigate the binding of commercially manufactured mirikizumab has been performed since the authorisation of mirikizumab for ulcerative colitis. That study demonstrates the specificity of mirikuzumab to bind human IL-23 with no significant binding to other related cytokines such as IL-12, IL-27 and IL-35.

No new nonclinical pharmacokinetic or toxicology studies have been performed. Margins of exposure have been recalculated based on the population PK data generated from the CD trials taking into account the higher dose used in the induction and maintenance phases. Based on the identified NOAEL in the chronic repeat dose toxicity study performed in cynomolgus monkeys a margin of exposure of at least 6-fold has been calculated.

Considering the nonclinical studies performed previously and in the context of the clinical experience with mirikizumab, the absence of additional nonclinical studies is acceptable to the CHMP.

The active substance is a protein composed of natural amino acids. Proteins are expected to biodegrade in the environment. Therefore, the use of mirikizumab will not alter the concentration or distribution of the substance in the environment and is not expected to pose a risk to the environment.

2.5.5. Conclusion on the non-clinical aspects

The nonclinical package is acceptable to the CHMP to support the extension of indication for mirikizumab in CD.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

The MAH 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**

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
Bioavailability and Bioequivalence Studies in Healthy Subjects						
I6T-MC-AMBT; 5.3.4.1; Completed; Full	**Primary Objective:** To evaluate the bioequivalence of a single 200-mg SC dose of mirikizumab in a citrate-free solution formulation using a 2 x 1-mL AI (test) compared to the mirikizumab solution formulation using a 2 x 1-mL AI (reference) **Secondary Objective:** To describe the safety and tolerability of a single 200-mg SC dose of mirikizumab in a citrate-free solution formulation using a 2 x 1-mL AI (test) compared to the mirikizumab solution formulation using a 2 x 1-mL AI (reference) .	Phase 1, participant-blind, randomized, 2-arm, 2-formulation, parallel-design, single-dose, multi-center study in healthy participants.	• Mirikizumab solution AI: Solution for injection, 2 x 100 mg/mL in a 1-mL AI. Route of Administration: 1 × 1-mL SC injections at the injection site (arm, thigh, or abdomen) according to the randomization • Mirikizumab citrate-free solution formulation AI: Solution for injection, 2 x 100 mg/mL in a 1-mL AI. Route of Administration: 1 × 1-mL SC injections at the injection site (arm, thigh, or abdomen) according to the randomization	Healthy subjects: 411 • 200 mg mirikizumab SC AI: 199 • 200 mg mirikizumab citrate-free formulation SC AI: 197	Healthy subjects.	On Day 1, participants received the mirikizumab SC dose of their assigned treatment. Participants were allowed to leave the CRU after completing the 4-hour safety assessments on Day 1, or later at the investigator's discretion, and returned for PK and immunogenicity sampling and safety assessments at predefined times up to 12 weeks post dose.

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
I6T-MC-AMBX; 5.3.3.1; Completed; Full	To evaluate the PK of SC injections of 300 mg mirikizumab solution administered using 1-mL and 2-mL PFS, and 1-mL and 2-mL AIs in healthy participants	Phase 1, open-label, 2-arm, randomized, parallel-design, single-dose, multi-site study.	• Mirikizumab PFS: Solution for injection; 100 mg/mL in a 1-mL and 2-mL PFS/300 mg. Route of Administration: 1 × 1-mL and 1 × 2-mL SC injections at the injection site (arm, thigh, or abdomen) according to the randomization • Mirikizumab AI: Solution for injection; 100 mg/mL in a 1-mL and 2-mL AI/300 mg. Route of Administration: 1 × 1-mL and 1 × 2-mL SC injections at the injection site (arm, thigh, or abdomen) according to the randomization	Healthy subjects: 237 • 300 mg mirikizumab SC PFS: 117 • 300 mg mirikizumab SC AI: 120	Healthy subjects	On Day 1, subjects received the mirikizumab SC dose of their assigned treatment. Subjects were allowed to leave the CRU after completing the 4-hour safety assessments on Day 1, and returned for PK and immunogenicity sampling and safety assessments at predefined times up to 12 weeks post dose.

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
I6T-MC-AMBY; 5.3.1.2; Completed; Full	To evaluate the bioequivalence of a single 300-mg SC dose of mirikizumab in a citrate-free solution formulation using a 1-mL and 2-mL PFS (test) compared to the mirikizumab solution formulation using a 1-mL and 2-mL PFS (reference).	Phase 1, participant-blind, randomized, 2-arm, 2-formulation, parallel-design, single-dose, multi-center study	• Mirikizumab citrate-free solution formulation PFS: Solution for injection, 100 mg/mL in a 1-mL and 2-mL PFS/300 mg. Route of Administration: 1 × 1-mL and 1 × 2-mL SC injections at the injection site (arm, thigh, or abdomen) according to the randomization • Mirikizumab PFS: Solution for injection, 100 mg/mL in a 1-mL and 2-mL PFS/300 mg. Route of Administration: 1 × 1-mL and 1 × 2-mL SC injections at the injection site (arm, thigh, or abdomen) according to the randomization	Healthy subjects: 456 • 300 mg mirikizumab citrate-free formulation SC PFS: 224 • 300 mg mirikizumab SC PFS: 226	Healthy subjects	On Day 1, subjects received mirikizumab SC dose of their assigned treatment. Subjects were allowed to leave the CRU after completing the 4-hour safety assessments on Day 1, and returned for PK and immunogenicity sampling and safety assessments at predefined times up to 12 weeks post dose.
Controlled Clinical Studies in Patients with Crohn's disease						
I6T-MC-AMAG; 5.3.5.1; Completed; Full	To test the hypothesis that treatment with mirikizumab is superior to placebo in the proportion of participants with endoscopic response at Week 12, defined as 50% reduction from baseline in SES-CD Score	Phase 2, multicenter, randomized, parallel-arm, double-blind, 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	Patients: 191 • 1000 mg mirikizumab: 64 • 600 mg mirikizumab: 32 • 200 mg mirikizumab: 31 • 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 208

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
			Period 2 (Double Blind and Double Dummy): • Mirikizumab-treated participants with Week 12 SES-CD improvement were evenly randomized to continue Period 1 treatment (described above) or to 300 mg SC Q4W[a] • Mirikizumab-treated participants with no Week 12 SES-CD improvement 1000 mg mirikizumab IV Q4W[a] • Placebo-treated participants in Period 1: 1000 mg mirikizumab IV Q4W[a] **Period 3 (Open Label):** • All participants who continued study treatment and achieved clinical benefit in the opinion of the investigator received open-label mirikizumab 300 mg SC Q4W. • Participants who did not achieve clinical benefit discontinued treatment and entered the Follow-Up period.			

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
I6T-MC-AMAM; 5.3.5.1; Ongoing[b]; Full	To evaluate whether the efficacy of treatment with mirikizumab is superior to placebo as assessed by • clinical response by PRO at Week 12 and endoscopic response at Week 52, and • clinical response by PRO at Week 12 and clinical remission by CDAI at Week 52	Phase 3, multicenter, randomized, double-blind, double-dummy, parallel-group, active- and placebo-controlled, treat-through study	• Mirikizumab 900 mg IV Q4W for 3 doses, then 300 mg SC Q4W • Ustekinumab 6 mg/kg IV for 1 dose, then 90 mg SC Q8W • Placebo o When Period 1 concludes (Week 12), responders continue receiving placebo, and NR at Week 12 will receive mirikizumab as described above. o NR is defined as failing to achieve at least a 30% decrease in SF and/or AP and be no worse than baseline.	Patients: 1152 • Mirikizumab: 631 • Ustekinumab: 309 • Placebo: 212	Patients with moderately to severely active Crohn's disease	52 weeks
Uncontrolled Studies in Patients with Ulcerative Colitis						
I6T-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	Mirikizumab 200 mg SC Q4W	Patients: 1006	Patients with moderately to severely active ulcerative colitis	A maximum of 3 years for each patient until the patient discontinues from the study, or until mirikizumab is commercially available in the country in which the patient resides, whichever occurs first.

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
Uncontrolled Studies in Patients with Crohn's disease						
I6T-MC-AMAX; Not applicable; Ongoing	The primary objective of Study AMAX is to evaluate the long-term effect of mirikizumab in clinical remission and endoscopic response at Week 52 of treatment in Study AMAX.	Phase 3, multicenter, open-label, long-term extension study	• Study AMAM responders and participants from Study AMAG receive open-label mirikizumab 300 mg SC Q4W. • Study AMAM non-responders receive an induction dose of IV mirikizumab 900 mg Q4W for 3 doses. o All participants having clinical benefit post-IV induction treatment continue 300 mg SC Q4W. o Participants considered to have no clinical benefit post-IV induction discontinue from the study at Week 12 and enter the 12- to 16-week posttreatment follow-up period.	Patients: 868	Patients with moderately to severely active Crohn's Disease	A maximum of 3 years per participant, until the participant discontinues from the study, or until mirikizumab is commercially available in the country in which the participant resides, whichever occurs first.

Abbreviations: AI = auto injector; AP = abdominal pain; CDAI=Crohn's Disease Activity Index; CRU = clinical research unit; IV = intravenous; NR = non-responders; PFS = pre-filled syringe; PK = pharmacokinetic; PRO = patient reported outcomes; Q4W = once every 4 weeks; Q8W = once every 8 weeks; SC = subcutaneous; SES-CD = Simple Endoscopic Score for Crohn's Disease; SF = stool frequency.

[a] Placebo administered by the appropriate route; for example, if active LY is administered intravenously, then placebo is administered via SC route and vice versa.

[b] Data presented corresponds to primary outcome database lock, at which time Induction and Maintenance Periods were complete, and the Post-treatment Follow-up Period was still ongoing.

2.6.2. Clinical pharmacology

For the present extension of indication submission, characterisations of pharmacokinetics (PK), pharmacodynamics (PD), and exposure-response (ER) relationships, for mirikizumab in the treatment of moderately to severely active Crohn's disease (CD), were conducted with new data from:

- 1 Phase 2 Study I6T-MC-AMAG (AMAG) and
- 1 Phase 3 Study I6T-MC-AMAM (AMAM).

In addition, 3 bioequivalence (BE) studies were conducted to support the approval of the citrate-free formulation administered by 1-mL and 2-mL AI or PFS for CD: Study I6T-MC-AMBX (AMBX), Study I6T-MC-AMBY (AMBY), and Study I6T-MC-AMBT (AMBT).

2.6.2.1. Pharmacokinetics

Bioanalytical methods

The method used for determination of mirikizumab serum concentrations in the clinical studies to support the CD indication was previously assessed during the initial MAA submission, where specificity was determined using serum from healthy subjects, CD and UC subjects. Hence the assay was previously shown to be suitable for use with CD patient serum and was fully validated as per ICH guidance M10 on bioanalytical method validation, and study sample analysis is considered acceptable.

Similarly, the 4-tier assay for ADA and Nabs is the same assay used in clinical studies to support the initial MAA submission, which included assessment of CD specific cut points. Hence the assay was previously shown to be suitable for use with CD patient analysis and is considered fully validated in accordance with the Guideline on Immunogenicity assessment of biotechnology-derived therapeutic proteins (EMEA/CHMP/BMWP/14327/2006 Rev.1).

Overall, the bioanalytical methods have been described in sufficient detail in the dossier and sufficient data on the validation of these assay have been provided. No queries are raised.

Absorption

Following SC administration of mirikizumab in participants with CD, peak concentrations were achieved within 3 to 6.83 days with a median of 5 days, which was consistent with the data on participants with UC.

Based on the popPK analysis of data from the Phase 3 Study AMAM, SC bioavailability of mirikizumab across injection sites (abdomen, arm or thigh) was estimated to be 36.3% (CV: 31%). This estimate was consistent with results from previous analyses in participants with CD (Study AMAG) and UC (Studies AMAN and AMBG). Injection site effect on SC bioavailability was not identified as a significant covariate.

Bioequivalence

Study 16-MC-AMBX

Study AMBX was a Phase 1, open-label, 2-arm, randomized, parallel design, single-dose, multisite study in 231 healthy participants who completed the study. The study was conducted to evaluate the PK, safety, and tolerability of SC injections of 300 mg mirikizumab (original formulation) administered using 1-mL and 2-mL pre-filled syringes (PFS) and 1-mL and 2-mL autoinjectors (AI).

Following dosing by AI, the 90% CIs for the ratios of the GLSM values compared with PFS for AUC(0-tlast) and AUC(0-∞) were contained within the prespecified confidence limits of 0.80 and 1.25; the 90% CIs for the ratios of the GLSM values for Cmax were 1.07 and 1.27. The difference in Cmax is not expected to have clinically meaningful impact on safety. No statistically significant difference was observed in tmax between AI and PFS (Table 2.7.1.5).

Table 2.7.1.5. Statistical Analysis of the Pharmacokinetic Parameters of Mirikizumab Following a Single Dose of 300 mg Administered by PFS or AI – Study AMBX

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)	111	359		
	AI (Test)	117	415	1.16	(1.07, 1.25)
AUC(0-∞) (ug.day/mL)	PFS (Reference)	116	363		
	AI (Test)	120	415	1.15	(1.06, 1.24)
Cmax (ug/mL)	PFS (Reference)	114	20.3		
	AI (Test)	119	23.7	1.17	(1.07, 1.27)

Parameter	Treatment	n	Median	(AI - PFS)	(Lower, Upper)	P-value
tmax (day)	PFS (Reference)	114	4.02			
	AI (Test)	119	4.02	0.00	(-0.06, 0.04)	0.8707

Abbreviations: AI = 300 mg Mirikizumab 1 x 1-mL + 1 x 2-mL (100 mg/mL) autoinjector (Test); CI = confidence interval; n = number of observations; PFS = 300 mg Mirikizumab 1 x 1-mL + 1 x 2-mL (100 mg/mL) prefilled syringe (Reference); tmax = time of maximum observed drug concentration
tmax is analysed using the procedure PROC NPAR1WAY and p-values reported from the Wilcoxon rank sum test

Status of Program: Production
Program Location: /cvn/projects/prj/ecb/programs/000000218212/dev/tables/t_pkanall.sas
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Although the study was not powered for the comparison by injection site, the 90% CIs of the ratios of GLSMs of AUC(0-tlast), AUC(0-∞), and Cmax were completely contained within the confidence limits of 0.80 to 1.25 following administration into the arm and thigh. The GLSM ratio of AUCs was approximately 40% higher and Cmax was 53% higher for AI compared with PFS, with the upper bound of the 90% CI for the various PK parameters falling above 1.25 following administration into the abdomen. This higher exposure is not considered clinically relevant. There was no difference in tmax between AI and PFS at any of the injection sites.

Of the 237 participants evaluable for treatment emergent-antidrug antibodies (TE-ADA), the incidences of TE-ADA were numerically higher in the AI treatment group (19.2%) compared to the PFS-treated participants (12.8%).

The incidence of all treatment emergent adverse effects (TEAEs) reported during the study was generally similar between the 2 devices [PFS (33.3%) and AI (37.5%)]. The incidence of ISRs was higher when mirikizumab was administered by AI (10.0%) compared to PFS (2.6%). Overall, the mean changes in clinical laboratory values and vital signs were similar between the PFS and AI.

Study 16-MC-AMBY

Study AMBY was a Phase 1, participant-blind, randomized, 2-arm, 2-formulation, parallel-design, single-dose, multi-center study in healthy participants. The purpose of the study was to assess the PK, safety, and tolerability of a 300-mg dose of mirikizumab in solution formulation or citrate-free solution formulation, both administered SC as 1 × 100-mg using an investigational 1-mL PFS and 1 × 200-mg using an investigational 2-mL PFS.

Bioequivalence was observed between the two formulations, as the 90% CIs of the ratios of GLSMs included unity and were contained within the equivalence range of 0.80 to 1.25. No statistically significant difference in median tmax was observed (Table AMBY.5.22).

Table AMBY.5.22. Statistical Analysis of Pharmacokinetic Parameters of Mirikizumab by Formulation

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

Population: Pharmacokinetic

Parameter	Solution formulation	n	Geometric least squares mean	Ratio of geometric least squares mean (CF Solution PFS:Solution PFS)	90% CI for the ratio (Lower, Upper)
AUC(0-tlast) (ug.day/mL)	Solution PFS (Reference)	205	320		
	CF Solution PFS (Test)	208	313	0.979	(0.926, 1.03)
AUC(0-∞) (ug.day/mL)	Solution PFS (Reference)	205	325		
	CF Solution PFS (Test)	208	318	0.980	(0.927, 1.04)
Cmax (ug/mL)	Solution PFS (Reference)	207	20.5		
	CF Solution PFS (Test)	208	20.5	0.998	(0.939, 1.06)

Parameter	Solution formulation	n	Median	PFS)	(Lower, Upper)	P-value
tmax (day)	Solution PFS (Reference)	207	3.98			
	CF Solution PFS (Test)	208	3.97	-0.01	(-0.03, 0.00)	0.2113

CF Solution PFS = 1 × 1-mL (100 mg) and 1 × 2-mL (200 mg) Mirikizumab Citrate-free Solution SC PFS (Test)
Solution PFS = 1 × 1-mL (100 mg) and 1 × 2-mL (200 mg) Mirikizumab Solution SC PFS (Reference)
Abbreviations: CF = citrate-free; CI = confidence interval; n = number of observations; PFS = prefilled syringe; tmax = time of maximum observed drug concentration
tmax is analyzed using the procedure PROC NPAR1WAY and p-values reported from the Wilcoxon rank-sum test

Although not powered for comparisons by injection site, the GLSMs of AUC(0-tlast), AUC(0-∞), and Cmax were similar between the 2 formulations for each individual injection site separately (arm, thigh and abdomen). All 90% CIs of the ratios of GLSMs were within the range of 0.80 to 1.25. Median tmax values were similar between formulations for the abdomen and arm injection sites. Median of differences in tmax values was 0.04 days shorter for the citrate-free formulation for the thigh injection site. This tmax difference is not considered clinically meaningful.

Of the 416 participants evaluable for TE ADAs a similar proportion of participants were TE ADA-positive between the 2 formulations (14.5% for the solution and 12.9% for the citrate-free solution).

The incidence of all TEAEs reported during the study was higher following administration of mirikizumab solution (48.7%) when compared to citrate-free solution (31.3%). No deaths or serious adverse events (SAEs) occurred during the study. Overall, the mean changes in clinical laboratory values and vital signs were similar throughout the study.

Study 16-MC-AMBT

Study AMBT was a Phase 1, participant-blind, randomised, 2-arm, 2 formulation, parallel design, single-dose, multicentre study in healthy participants. The study was conducted to evaluate the PK, safety, and tolerability of a 200 mg dose of mirikizumab solution formulation administered as 2 × 100 mg SC injections using an investigational 1-mL AI or mirikizumab citrate-free solution formulation administered as 2 × 100 mg SC injections using an investigational 1-mL AI.

Bioequivalence was demonstrated between the reference and test formulations as the 90% CIs of the ratios of geometric LS mean included unity and were contained within the equivalence range of 0.80 to 1.25. No statistically significant difference in median tmax was observed (Table AMBT.5.8).

Table AMBT.5.8. Statistical Analysis of Pharmacokinetic Parameters of Mirikizumab by Formulation

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

Population: Pharmacokinetic

Parameter	Solution formulation	n	Geometric least squares mean	Ratio of geometric least squares mean (CF Solution AI:Solution AI)	90% CI for the ratio (Lower, Upper)
AUC(0-tlast) (ug.day/mL)	Solution AI (Reference)	193	222		
	CF Solution AI (Test)	187	227	1.02	(0.960, 1.09)
AUC(0-∞) (ug.day/mL)	Solution AI (Reference)	195	226		
	CF Solution AI (Test)	192	228	1.01	(0.948, 1.08)
Cmax (ug/mL)	Solution AI (Reference)	196	12.9		
	CF Solution AI (Test)	192	12.7	0.986	(0.929, 1.05)

Parameter	Treatment	n	Median	Median of differences (CF Solution AI-Solution AI)	Approximate 90% CI for the difference (Lower, Upper)	P-value
tmax (day)	Solution AI (Reference)	196	3.98			
	CF Solution AI (Test)	192	3.98	0.00	(0.00, 0.02)	0.4011

CF Solution AI = 200 mg Mirikizumab 2 x 1-mL Citrate-free Solution SC AI (Test)
Solution AI = 200 mg Mirikizumab 2 x 1-mL Solution SC AI (Reference)
Abbreviations: AI = autoinjector; CI = confidence interval; n = number of observations; tmax = time of maximum observed drug concentration
tmax is analyzed using the procedure PROC NPAR1WAY and p-values reported from the Wilcoxon rank sum test

The study was not powered for the comparisons when statistical analyses were conducted on data for each injection site separately. However, when comparing AUC(0-tlast), AUC(0-∞), and Cmax between mirikizumab solution and citrate-free solution all 90% CIs of the ratios of GLSMs were within the range of 0.8 to 1.25. Median tmax values were similar between the two formulations at all injection sites were similar.

Of the 392 participants evaluable for TE-ADA, a slightly lower proportion of participants were TE-ADA positive following administration of mirikizumab citrate-free solution (12.3%) compared to mirikizumab solution (19.8%).

The incidence of all TEAEs reported during the study was similar following administration of mirikizumab solution (29.6%) and citrate-free solution (28.9%). No deaths or SAEs occurred during the study. The incidence of ISRs was lower following administration of mirikizumab citrate-free solution (9.6%) compared to mirikizumab solution (16.1%). Overall, the mean changes in clinical laboratory values and vital signs were similar throughout the study.

Distribution

The PK profile of mirikizumab follows 2-compartment characteristics. The estimated geometric mean (CV) central and peripheral volume of distribution were 2.79 L (16%) and 1.60 L (16%) resulting in a total volume of distribution at steady state of 4.40 L (14%) (AMAM PopPK analysis), similar to the values in CD (Study AMAG) and UC (Studies AMAN and AMBG).

Elimination

The estimated geometric mean (CV) systemic clearance was 0.0202 L/h (38%) and the t1/2 for mirikizumab in participants with Study AMAM was estimated as 9.3 days (26%) (AMAM PopPK analysis), both were similar to the values in CD (Study AMAG) and UC (Studies AMAN and AMBG).

Pharmacokinetics in the target population

Study 16T-MC-AMAG population PK analysis

Study AMAG was a Phase 2, multicenter, randomised, parallel-arm, double-blind, placebo-controlled study to evaluate the efficacy and safety of mirikizumab IV dosing (200, 600, and 1000 mg) and mirikizumab SC dosing (300 mg) in participants with moderately to severely active CD.

A total of 3440 serum mirikizumab concentration samples in 186 participants were included in the popPK analysis. A 2-compartment model with first-order absorption for the SC maintenance doses best described the data. Table AMAG.5.19 presents the estimated PK parameters. The estimated mean half-life in patients with CD (9.9 days) and other key PK parameter estimates are consistent with those characterised previously for patients with UC.

Table AMAG.5.19. Summary of Population Pharmacokinetic Model-Estimated Parameters for Mirikizumab

Parameter Description	Population Estimate (95% CI, %SEE)[a]	Inter-individual Variability (95% CI, %SEE)[a,b]
Rate of Absorption		
Parameter for Ka (hr^{-1})	0.00647 (0.00561 – 0.00961, 8.72)	–
Clearance		
Parameter for CL[c] (L/hr)	0.0217 (0.0203 – 0.0306, 6.27)	21.9% (19.1–25.6%, 12.9)
Albumin effect on CL	-0.754 (-0.976 – -0.598, 12.0)	–
Baseline SES-CD effect on CL	0.227(0.160 – 0.309, 15.9)	–
Parameter for Q[d] (L/hr)	0.00884 (0.00605 – 0.202, 42.3)	–
Baseline weight effect on CL and Q	0.538(0.348 – 0.745, 19.7)	–
Volume of Distribution		
Parameter for V_2[d] (L)	3.31 (3.08 – 3.45, 2.21)	17.2% (12.4–22.5%, 26.7)
Parameter for V_3[d] (L)	1.75 (1.49 – 5.67, 18.2)	37.3% (15.1–50.1%, 40.9)
Baseline weight effect on V_2 and V_3	0.543 (0.330 – 0.721, 18.1)	–
Bioavailability		
Parameter for F1[e]	0.334 (0.296 – 0.445, 8.44)	35.7% (28.1–41.6%, 17.5)
Baseline BMI effect on F1	-0.0318 (-0.0434 – -0.0206, 18.2)	–
Residual Error		
Proportional (%)	26.1% (24.4–27.5%, 2.90)	
Additive (ng/mL)	87.4 (10.6–183, 35.5)	

Abbreviations: BMI = body mass index; CI = confidence interval; CL = clearance; F1 = bioavailability; Ka = absorption rate constant; Q = inter-compartmental clearance; SEE = standard error of the estimate; SES-CD = Simple Endoscopic Score for Crohn's Disease; 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 Inter-individual variability (IIV) was 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.

c The table provides the population estimate. To obtain individual clearance estimates, use the following equation: $CL,individual = CL \times (Baseline\ weight/71.8)^{0.538} \times (Baseline\ SES\text{-}CD/12)^{0.227} \times (Albumin/44.0)^{-0.754}$

d The table provides the population estimate. To obtain individual volume estimates, use the following equations: $Q,individual = Q \times (Baseline\ weight/71.8)^{0.538}$; $V_2,individual = V_2 \times (Baseline\ weight/71.8)^{0.543}$; $V_3,individual = V_3 \times (Baseline\ weight/71.8)^{0.543}$

e The table provides the population estimate. To obtain individual volume estimates, use the following equation: $F1,individual = F1 \times [1+(Baseline\ BMI-24.75) \times -0.0318]$

Factors found to have a statistically significant impact on mirikizumab PK were body weight, serum albumin concentration, baseline SES-CD, and baseline BMI; however, the magnitude of the impact of these factors on the PK was small relative to variability, indicating that the impact was not clinically meaningful. Thus, no dose adjustments on the basis of these covariates are warranted. There was no impact of immunogenicity on the PK of mirikizumab.

Study I6T-MC-AMAM population PK analysis

Study AMAM was a Phase 3 study of participants designed to evaluate the efficacy and safety of mirikizumab in participants with moderately to severely active CD. The objectives of the popPK analysis were to characterise the PK of mirikizumab in adults with CD and to identify demographic factors, laboratory parameters, immunogenicity, prior and concomitant therapies, and disease characteristics that may influence mirikizumab disposition in this patient population.

A total of 5318 postbaseline serum mirikizumab concentration samples collected from 711 participants from the Induction and Maintenance Periods were included in the final PK analyses dataset. A 2-compartment model, with first-order absorption for the SC maintenance doses, was found to best describe the PK profile of mirikizumab in patients with CD. The estimated PK parameters for the final model are shown in Table 8.1. Bootstrap and VPC (Figure 8.5) supported the validity of the model and demonstrated that all parameters were well estimated. The estimated half-life was 9.3 days. The key PK parameter estimates are consistent with those characterized previously for participants with UC and CD.

Table 8.1. Summary of Final Population Pharmacokinetic Model-Estimated Parameters for Mirikizumab in Crohn's Disease Based on Study AMAM

Parameter Description	Population Estimate (95% CI, %SEE)[a]	Interindividual Variability (95% CI, %SEE)[a,b,f]
Clearance		
Parameter for CL[c] (L/hr)	0.0197 (0.0179 to 0.0230, 4.53)	32.3% (29.9% to 34.6%, 7.08)
Time-varying albumin effect on CL	-0.0200 (-0.0228 to -0.0173, 7.25)	---
Baseline CRP effect on CL	0.0853 (0.0701 to 0.0997, 9.23)	---
Parameter for Q[c] (L/hr)	0.00921 (0.00529 to 0.0252, 26.6)	---
Baseline weight effect on CL and Q	0.268 (0.150 to 0.378, 23.1)	---
Volume of Distribution		
Parameter for V_2[d] (L)	2.78 (2.71 to 2.82, 0.978)	17.1% (12.5% to 20.5%, 22.8)
Parameter for V_3[d] (L)	1.61 (1.13 to 2.85, 16.5)	23.6% (14.1% to 30.8%, 30.4)
Baseline weight effect on V_2 and V_3	0.445 (0.372 to 0.517, 9.53)	---
Covariance between CL and V_2	0.0187 (0.0100 to 0.0268, 22.0)	
Bioavailability		
Parameter for F_1 (%)[e]	38.8 (33.8 to 45.8, 5.62)	51.7% (46.0% to 57.5%, 10.6)
Baseline BMI effect on F_1	-0.0354 (-0.0469 to -0.0263, 13.9)	---
First Order Absorption Rate Constant		
Parameter for K_a (h^{-1})	0.00693 (0.00609 to 0.00834, 6.16)	---
Residual Error		
Proportional (%)	23.7% (22.2% to 25.2%, 3.17)	
Additive (ng/mL)	96.7 (0.00246 to 173, 29.3)	

Abbreviations: AMAM = I6T-MC-AMAM; BMI = body mass index; CI = confidence interval; CL = clearance; CRP = C-reactive protein; Eta = random effect; F_1 = 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.

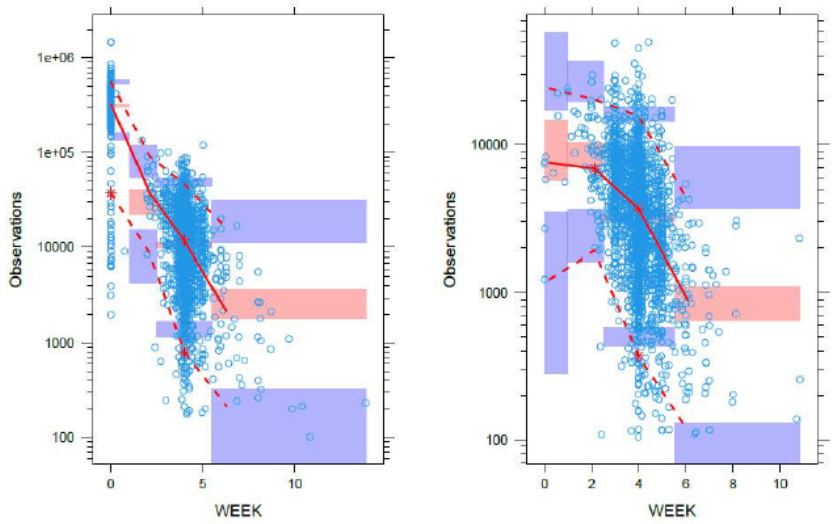
b IIV for CL, V_2, and V_3 was calculated using the following equation for log-normal distributions of the random effects for $\%IIV = 100 \times \sqrt{(e^{OMEGA_N} - 1)}$, where $OMEGA_N$ is the variance of the parameter. Interindividual variability for bioavailability (F_1) was incorporated in an additive manner in the logit domain, hence the following equation was used to calculate the IIV for F_1: $\%IIV_F = 100 \times \sqrt{OMEGA_{F_1}}$.

c The table provides the population estimate. To obtain individual clearance estimates, use the following equation: $CL_{,individual} = CL^*(\text{Baseline weight}/65.0)^{0.268}*(1+(\text{Albumin}-44.57)*-0.02)*(\text{Baseline CRP}/7.41)^{0.0853}$; $Q_{,individual} = Q^*(\text{Baseline weight}/65.0)^{0.268}$

d The table provides the population estimate. To obtain individual volume estimates, use the following equations: $V_{2,individual} = V_2^*(\text{Baseline weight}/65.0)^{0.445}$; $V_{3,individual} = V_3^*(\text{Baseline weight}/65.0)^{0.445}$

e Estimate is on the logit parameter for bioavailability. This translates to bioavailability of 43% and 32% for participants with baseline BMI of 17 kg/m^2 (10th percentile of analysis population) and 31 kg/m^2 (90th percentile of the analysis population).

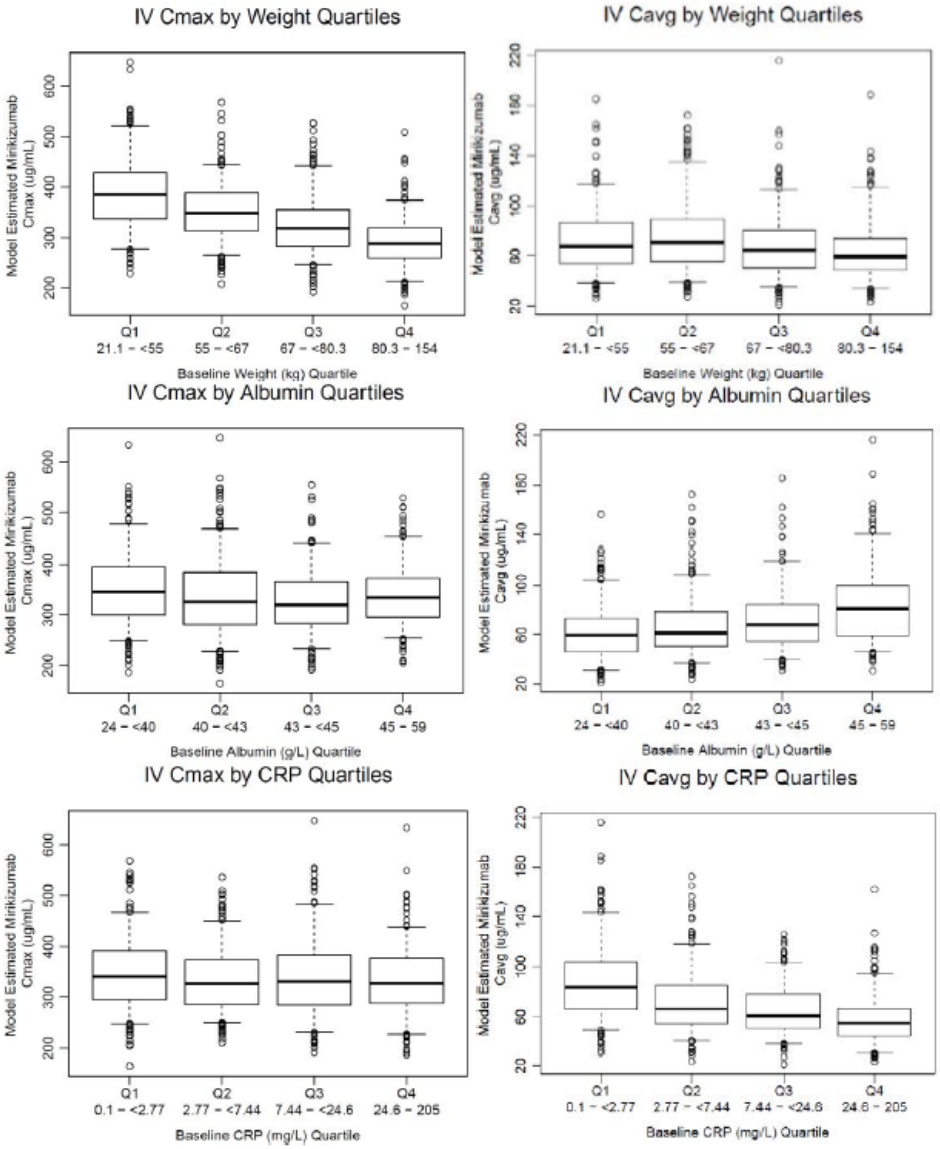
f Eta shrinkage for CL, V_2, V_3, and F_1 are 4.70%, 37.9%, 51.1%, and 18.0%, respectively.



Abbreviations: IV = intravenous; PK = pharmacokinetics; SC = subcutaneous.
Blue circle: 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 area: confidence intervals for the 5th and 95th percentiles of simulated data.

Figure 8.5. **Visual predictive check for mirikizumab final PK model for Study AMAM stratified by route of administration (IV left panel and SC right panel).**

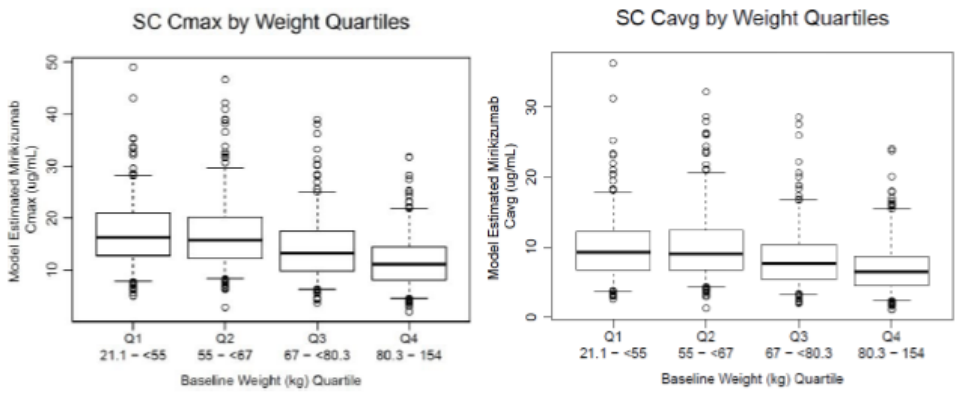
Simulations were performed to illustrate the impact of significant covariates in the final model (baseline body weight, serum albumin concentration, baseline CRP, and baseline BMI) on mirikizumab exposures. Figure 10.2 and Figure 10.3 show quartile boxplots of significant baseline covariates versus Cavg,ss and Cmax,ss for the IV and SC dose regimens. Overall, these boxplots show significant overlap of Cavg,ss and Cmax across the patient covariate quartiles. Further, for both the IV and SC dose regimens, given that the current range of exposures is on the near-maximal efficacy portion of the ER relationship for efficacy outcomes from Study AMAG results, no dose adjustment based on any covariate is warranted.



Abbreviations: C_{avg} = average drug concentration under steady state conditions during multiple dosing; C_{max} = maximum concentration during one dosing interval at steady state; IV = intravenous; PK = pharmacokinetic(s); PopPK = population pharmacokinetics; Q = Quartile.

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

Figure 10.2. **Boxplots of covariate effects on the PK profile of mirikizumab postintravenous administration from the PopPK analysis.**



Abbreviations: C_{avg} = average drug concentration under steady state conditions during multiple dosing; C_{max} = maximum concentration during one dosing interval at steady state; PK = pharmacokinetic(s); PopPK = population pharmacokinetics; Q = Quartile; SC = subcutaneous.

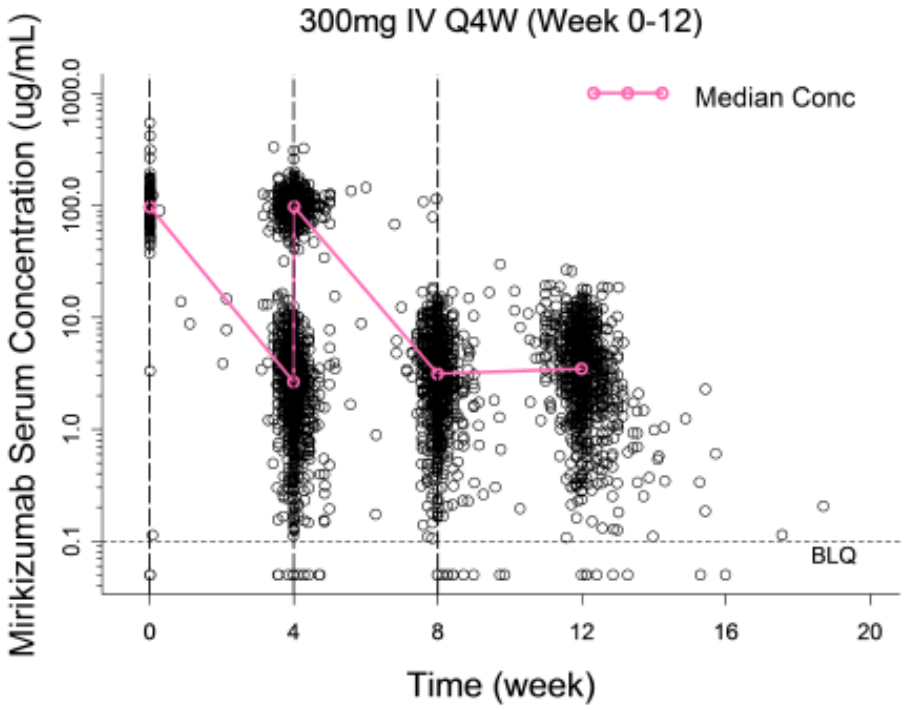
Note: The horizontal line in each box represents the median; the top and bottom sides of the box represent the 75th and 25th percentiles, respectively; the whiskers extend to the 95th and 5th percentiles; and circles represent data points outside of the 5th or 95th percentile.

Figure 10.3. **Boxplots of covariate effects on the PK profile of mirikizumab postsubcutaneous administration from the PopPK analysis.**

Dose proportionality and time dependencies

In the Phase 1 clinical studies, mirikizumab exposure increased proportionally over a dose range of 5 to 2400 mg given IV or 120 to 400 mg given as an SC injection. A PK model with linear clearance best described the data in all PopPK analyses, which supports that the PK of mirikizumab is linear with regard to dose.

Figure 2.7.2.6 presents the observed mirikizumab concentrations following 300-mg IV Q4W dosing regimen in the induction period of the Phase 3 Study AMAN. 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.



Abbreviations: BLQ = below limit of quantitation; IV = intravenous; LLOQ = lower limit of quantitation; PK = pharmacokinetics; Q4W = every 4 weeks.
Note: The vertical dashed lines represent the scheduled mirikizumab dose administration; the horizontal dashed line represents assay LLOQ of 0.1 µg/mL; the pink line represents the median predose and postdose PK concentrations, where predose concentration is defined as PK samples taken ≥96 hours after dosing and postdose is defined as PK samples taken <96 hours after dosing and only data points based on the Schedule of Activities are plotted; BLQ concentrations were represented as LLOQ/2.

Figure 2.7.2.6. **Observed mirikizumab concentrations during the induction period following mirikizumab 300 mg IV Q4W.**

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.

Special populations

Impaired renal and hepatic function

AMAM popPK analysis revealed that creatinine clearance and baseline bilirubin level did not affect mirikizumab clearance for participants with CD. No specific clinical pharmacology studies to evaluate the effects of renal or hepatic impairment on the PK of mirikizumab have been conducted.

Gender

In AMAM popPK analysis, gender (56.5% male and 43.5% female) was identified as a statistically significant covariate on central volume of distribution, but it was not included in the final AMAM popPK model due to the small magnitude of effect on reduction of IIV (<15%).

Ethnic factors

Ethnicity and race were not identified as statistically significant covariates in AMAM popPK analysis.

Weight

Higher body weight was associated with higher systemic clearance and volume of distribution, which would reduce Cavg,ss. In the IV dose regimen, every 1 kg of baseline body weight increase results in less than 1% decrease in Cavg,ss. This difference is small compared to random unexplained variability of Cavg,ss.

Since BMI affects SC bioavailability and body weight affects clearance, the exposure with the SC regimen would be impacted by both patient factors in combination. With the SC dose regimen, the combined effect resulted in approximately 35% of exposure decrease when body weight increased approximately 57% from Quartile 1 median to Quartile 4 median. The difference is within the random unexplained variability of SC Cavg,ss; therefore, no dose adjustments on the basis of body size factors including body weight and BMI are needed.

Elderly

Age was not found to be a clinically significant covariate in the AMAM popPK analysis, which is consistent with UC (Studies AMAN and AMBG) Of the 711 participants with CD exposed to mirikizumab in Study AMAM, 25 (3.5%) participants were 65 years or older and 0 (0.0%) participants were 75 years.

2.6.2.2. Pharmacodynamics

No clinical pharmacodynamic studies were conducted in patients with CD.

Mechanism of action

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

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

Immunogenicity

Study 16T-MC-AMAG

During mirikizumab Treatment and Follow-Up (up to 208 weeks), 6.0% of evaluable mirikizumab-treated participants were TE-ADA positive and 5.4% were NAb positive. Postbaseline TE-ADA titers ranged from 1:20 to 1:160 where 1:160 was reported for 1 participant during Period 1. There was no impact of immunogenicity on the PK of mirikizumab based on the popPK analysis.

Study I6T-MC-AMAM

Of the 622 evaluable participants in Study AMAM through 52 weeks of treatment with mirikizumab, the incidence of TE ADA was 12.7% (n=79). The incidence of NAb was 12.5% (n=78) (Table ISI.9.1).

Table ISI.9.1. Incidence of Antidrug Antibody and Neutralizing Antidrug Antibodies Status – Safety Population – Mirikizumab Only – I6T-MC-AMAM – Study Treatment Period

Incidence of Anti Drug Antibody and Neutralizing Anti-Drug Antibodies Status — Page 1 of 1
Safety Population - mirikizumab only — 04:46 13DEC2023
I6T-MC-AMAM - Study Treatment Period — PDPM

Category	miri (N=630) n (%)
Patients Evaluable for TE ADA	622 (100.0)
Evaluable Patients with ADA Present at Baseline	28 (4.5)
Neutralizing Antibodies at Baseline	16 (2.6)
Patients with Postbaseline TE ADA+	79 (12.7)
Neutralizing Antibodies Present	78 (12.5)
Neutralizing Antibodies Inconclusive	0 (0.0)
Treatment-Induced TE ADA+	76 (12.2)
Treatment-Boosted TE ADA+	3 (0.5)
Patients with Postbaseline TE ADA Inconclusive	0 (0.0)
Patients with Postbaseline TE ADA-	543 (87.3)

Abbreviations: miri = mirikizumab; N = number of participants in the analysis population; n = number of participants in the specified category; TE = treatment-emergent; ADA = anti-drug antibodies; % = All percentages are relative to the total number of TE ADA evaluable participants.

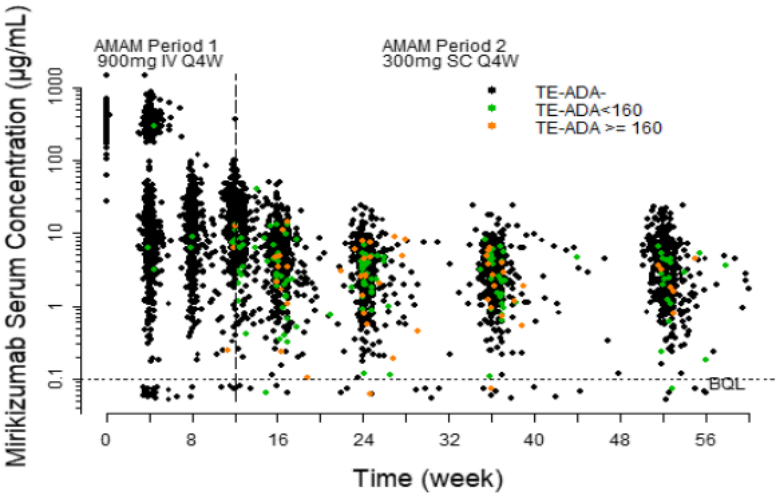
Notes:
A patient is TE ADA evaluable if there is at least one non-missing test result for mirikizumab ADA for baseline period and the postbaseline period.
A TE ADA evaluable patient is considered to be TE ADA+ if the patient has at least one postbaseline titer that is a 4-fold or greater increase in titer from the baseline measurement (treatment-boosted). If the baseline result is ADA not present, then the patient is TE ADA+ if there is at least one postbaseline result of ADA present with a titer >= 1:20 (treatment-induced).
A TE ADA evaluable patient is TE ADA inconclusive if 20% of the patient's postbaseline samples, drawn pre-dose, are ADA inconclusive and the patient is not otherwise TE ADA+. A TE ADA evaluable patient is TE ADA- if not TE ADA+ and not TE ADA inconclusive.

The majority of TE ADA-positive participants treated with mirikizumab recorded a maximum titer of 1:160 or less (82.3%). The highest recorded titer was 1:5120, which occurred in 1 participant. 81.0%

(n=64) of TE ADA-positive participants treated with mirikizumab had their titers decline over time, including 63% (n=50) returning to TE ADA-negative levels at their last sample.

Effect of immunogenicity on PK

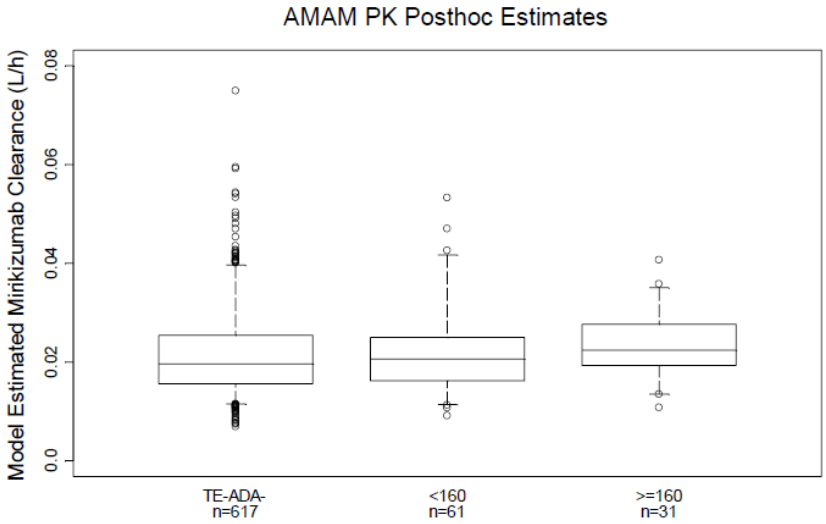
The relationship between immunogenicity titer and mirikizumab concentrations was explored graphically using observed mirikizumab trough concentrations and immunogenicity data from Study AMAM. Neither the presence of TE ADA nor the titer levels demonstrated an impact on exposures associated with mirikizumab in both the mirikizumab treatment regimen group (Figure ISI.9.1) and the placebo non-responder group who received mirikizumab starting at Week 12.



Abbreviations: BQL = below the quantifiable lower limit of the assay; IV = intravenous; LLOQ = lower limit of quantitation of the LY3074828 (mirikizumab) bioanalytical assay; PK = pharmacokinetics; Q4W = every 4 weeks; SC = subcutaneous; TE ADA = treatment-emergent antidrug antibody.
Note: Individual dots represent individual PK samples. The Week 4 visit in Study AMAM included samples taken both before and after the mirikizumab infusion. Horizontal dashed line represents LLOQ (=BQL) value (0.1µg/mL) reported from bioanalytical results.

Figure ISI.9.1. Observed mirikizumab concentrations in Study AMAM Induction and Maintenance Phase following mirikizumab 900 mg IV Q4W and 300 mg SC Q4W by TE ADA titer categories.

In the popPK analysis, immunogenicity (TE ADA, TE ADA titer, and NAb status) was not a statistically significant factor that impacted mirikizumab PK. When the individual model-estimated CL values were compared among TE ADA titer groups, no difference in the CL estimates was found among the TE ADA negative, TE ADA higher titer (1:160), or TE ADA lower titer (<1:160) groups (Figure ISI.9.3). The interpretation of TE ADA effect on CL should be approached with caution due to the sparsity of participants who developed higher TE ADA titers (TE ADA titer ≥1:160).



Abbreviations: n = number of participants; PK = pharmacokinetics; TE ADA = treatment-emergent antidrug antibody.
Note: participants were categorized by the maximum observed TE ADA 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 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 ISI.9.3. **Boxplots of model-estimated post hoc clearance values versus treatment-emergent antidrug antibody titers in Study AMAM.**

Effect of immunogenicity on efficacy

Neither the presence of TE ADA nor the titer levels demonstrated an impact on efficacy measures associated with mirikizumab. In addition, the impact of immunogenicity (TE ADA-positive status) was tested as a covariate in models evaluating the relationships between mirikizumab exposure and efficacy in the Study AMAM. These models found that immunogenicity did not have a significant impact on the mirikizumab treatment effect parameters.

Effect of immunogenicity on safety

Overall, despite a few numerical differences, no clinically meaningful differences in the frequencies of hypersensitivity, infusion site, and injection site reactions were observed in TE ADA-positive participants compared with TE ADA-negative participants.

The frequency of participants reporting at least 1 treatment emergent (TE) infusion site reaction was higher in TE ADA-positive participants compared with TE ADA-negative participants (n=2, N = 79 [2.5%] and n=3, N = 543 [0.6%], respectively). However, given the small number of participants with these events, this difference is not considered clinically meaningful, and a causative link between infusion site reactions and ADA status could not be made.

The frequency of participants reporting at least 1 TE injection site reaction was higher in TE ADA-positive participants compared with TE ADA-negative participants (n=12, N = 79 [15.2%] and n=51, N = 543 [9.4%], respectively). However, given the small number of participants with these events, this difference is not considered clinically meaningful, and a causative link between injection site reactions and TE ADA status could not be made.

Exposure-response analyses

Study 16T-MC-AMAG exposure-efficacy analyses

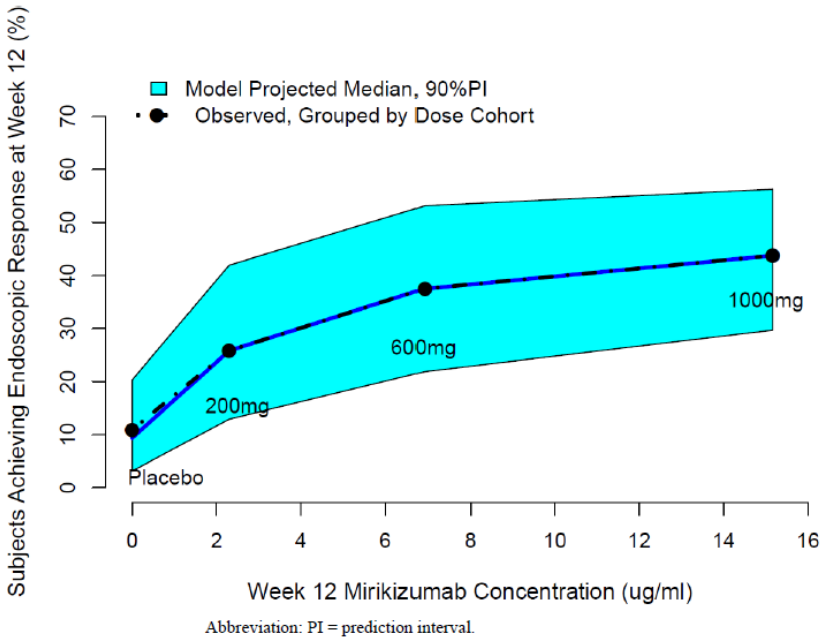
The ER analyses were based on data from the Phase 2 (dose-finding) Study AMAG in patients with participants with moderately to severely active CD.

Period 1 (induction)

In period 1, participants received 3 doses of mirikizumab IV Q4W (200, 600, and 1000 mg), or placebo, at Weeks 0, 4, and 8. Logistic regression models were used to evaluate the relationships between mirikizumab exposure in individual participants and the probability of achieving either endoscopic response or patient-reported outcome (PRO) remission at Week 12. Models were also used to evaluate the relationship between the change from baseline in Simple Endoscopic Score for Crohn's Disease (SES-CD) at Week 12 and mirikizumab exposure.

In the dose range of 200 to 1000 mg Q4W IV, the observed Week 12 efficacy measures (including clinical response, clinical remission, endoscopic response, and endoscopic remission) indicated near-maximal efficacy between 600 and 1000 mg IV. The efficacy profile was relatively flat between 600 and 1000 mg for endoscopic response and clinical remission by PRO. The efficacy profile indicated that doses higher than 1000 mg would likely lead to minimal added benefit.

The endoscopic response model was able to detect a significant treatment effect relative to placebo ($p<0.001$) and a significant exposure-efficacy ($p=0.001$) in the exposure range tested. None of the evaluated covariates were noted to have a significant impact on placebo effect or treatment effect or to provide a significant improvement in the fit of the data in the endoscopic response model. A visual predictive check was used to validate the model (Figure 2.7.2.1) and it showed good agreement between the observed and model-predicted endoscopic response rates across the treatment arms and justified that 900-mg IV dose would produce a near-maximal effect.



Abbreviation: PI = prediction interval.

Figure 2.7.2.1. Visual predictive check of model fit of Week 12 endoscopic response.

No significant relationship mirikizumab exposure (model-estimated Cavg) and the change from baseline in SES-CD was detected at Week 12. The change from baseline in PRO and Crohn's Disease Activity Index (CDAI) at Week 12 also showed no significant E-R and no modelling was performed.

Period 2 (maintenance)

In period 2, participants either remained on their Period 1 treatment or switched to either mirikizumab 300 mg SC Q4W dosing or mirikizumab 1000 mg IV Q4W. A logistic regression model was used to evaluate the relationships between mirikizumab exposure in individual participants and the probability of achieving endoscopic response at Week 52.

In the dose range studied (200 mg IV Q4W, 600 mg IV Q4W, 1000 mg IV Q4W, and 300 mg SC Q4W), efficacy was observed through Week 52 as measured by clinical response, clinical remission, endoscopic response, and endoscopic remission but there was no discernible exposure-efficacy trend across the Period 2 exposure ranges. Participants in the lowest mirikizumab dose group of 300 mg SC Q4W (estimated from popPK model simulation to be equivalent to ~100 to 120 mg IV Q4W) demonstrated similar efficacy to participants who continued to receive mirikizumab IV treatment. These results supported the selection of 300 mg mirikizumab SC Q4W for the Maintenance Period in Study AMAM.

Since Week 52 efficacy measures did not exhibit a significant exposure-efficacy relationship in the dose range tested, analyses between exposure (model-estimated Cavg) and efficacy were performed using the absolute change from Week 12 to Week 52 in SES-CD, PRO, and CDAI scores. Similar to Period 1, the observed relationships showed large overlap in the score changes and there was no discernible exposure-efficacy relationship across Period 2 treatment arms.

Study I6T-MC-AMAM

The ER analyses were based on data from the Phase 3 Study AMAM with participants with moderately to severely active CD.

Exposure-efficacy analyses

Static exposure-efficacy logistic regression models were developed for

1) Week 12 endoscopic response by SES-CD

2) Week 12 clinical response by PRO

3) Clinical response by PRO at Week 12 and endoscopic response by SES-CD at Week 52, and

4) Clinical response by PRO at Week 12 and clinical remission by CDAI at Week 52.

The final exposure-efficacy model dataset contained observations from 839 participants. All the exposure-efficacy logistic regression models found that linear relationships rather than Emax relationships were best able to describe the observed data. The mirikizumab exposure measure used in all final models was Cavg.

Induction period

In Study AMAM, mirikizumab 900 mg IV at Weeks 0, 4, and 8 achieved all Week 12 major secondary endpoints. This result was consistent with the relationship between exposure and efficacy observed and model predicted from the dose-ranging Phase 2 Study AMAG.

The model-estimated parameters for the relationship between Induction Period Cavg and Week 12 endoscopic response by SES-CD and clinical response by PRO are presented in Table 8.2 and Table 8.3, repectively. VPCs for each final model are presented in Figures ATT.13.5 and ATT.13.8.

Table 8.2. Week 12 Endoscopic Response by SES-CD Exposure-Efficacy Model Parameters

Parameter	Estimate (%SEE)
Baseline Logit Intercept	-2.00 (8.45)
Slope	0.0158 (14.8)
Baseline Body Weight on Slope[a]	0.000241 (28.1)
Baseline SES-CD on Slope[a]	0.000646 (29.3)

Abbreviations: %SEE = percent standard error of estimate; SES-CD = Simple Endoscopic Score for Crohn's Disease.

[a] To obtain individual slope estimate with baseline body weight and baseline SES-CD on slope, use the following equation:

Slope,individual = Slope + {0.000241 * (Baseline Body Weight – 65) + 0.000646 * (Baseline SES-CD – 11)}.

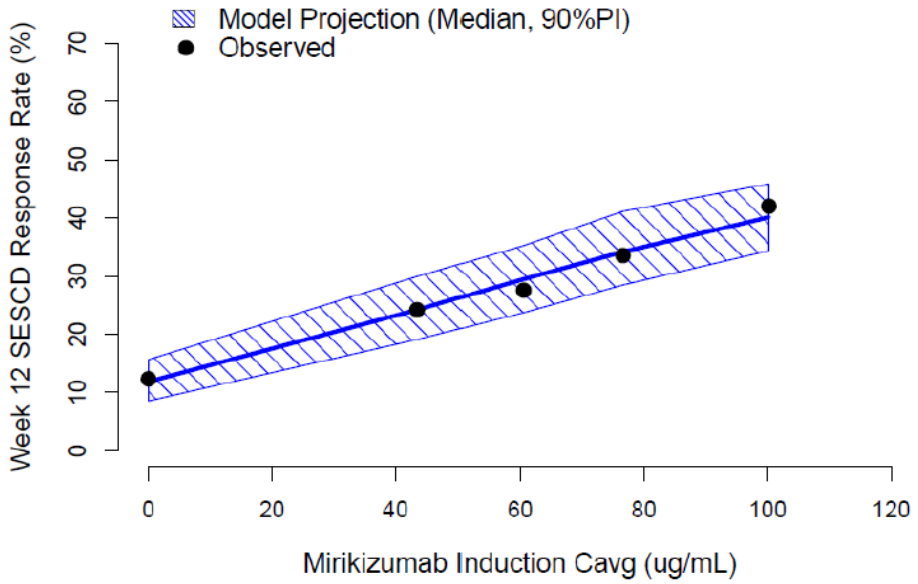
Table 8.3. Week 12 Clinical Response by PRO Exposure-Efficacy Model Parameters

Parameter	Estimate (%SEE)
Baseline Logit Intercept	0.0283 (438)
Slope	0.0111 (18.5)
Baseline SES-CD on Slope[a]	0.000757 (29.9)

Abbreviations: PRO = patient-reported outcome; %SEE = percent standard error of estimate.

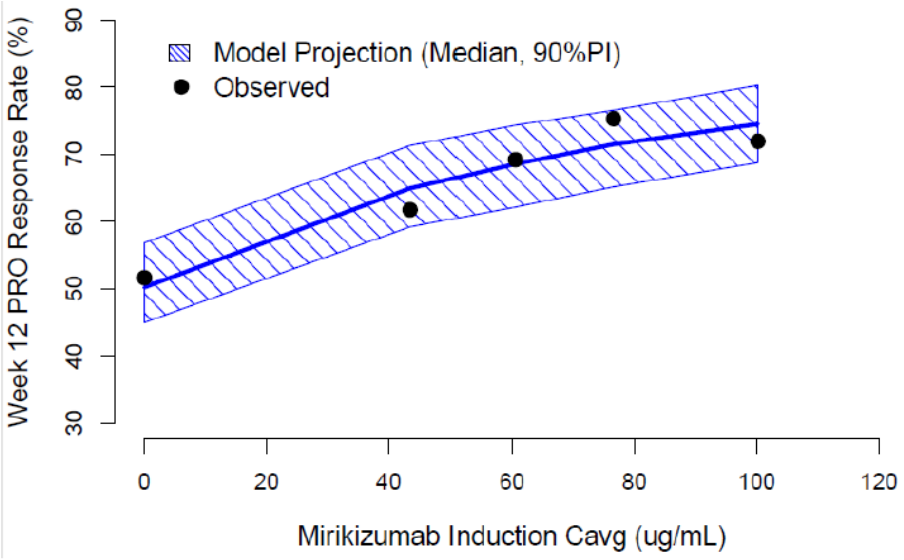
[a] To obtain individual slope estimate with baseline SES-CD on slope effect, use the following equation:

Slope,individual = Slope + 0.000757 * (Baseline SES-CD – 11).



Abbreviations: C_{avg} = average mirikizumab concentration during 1 dosing interval; Miri = mirikizumab; PI = prediction interval; SES-CD = Simple Endoscopic Score for Crohn's Disease.

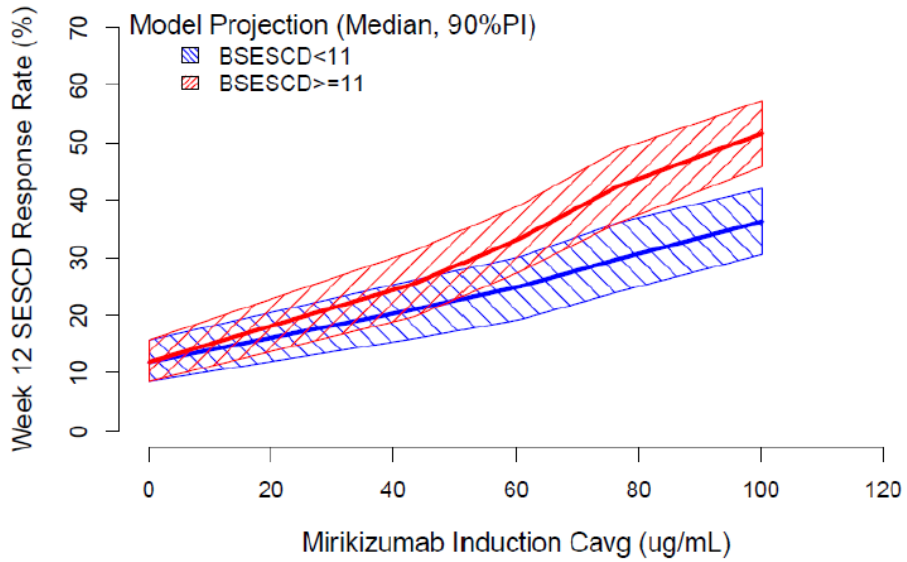
Figure ATT.13.5. Visual predictive check of model fit of endoscopic response by SES-CD at Week 12 model in Study AMAM.



Abbreviations: PRO = patient-reported outcome; C_{avg} = average mirikizumab concentration during 1 dosing interval; PI = Prediction interval

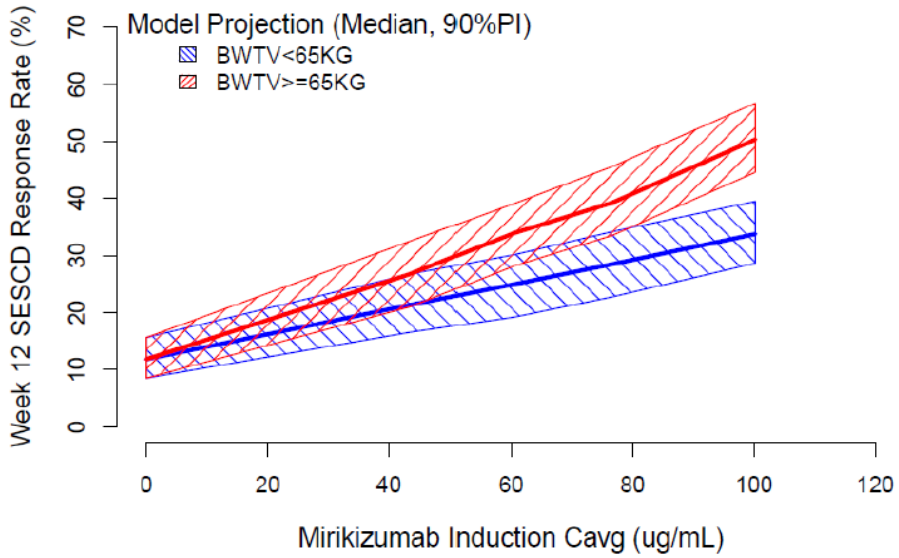
Figure ATT.13.8. Visual predictive check of model fit of clinical response by PRO at Week 12 model in Study AMAM.

In the model focusing on Week 12 endoscopic response by SES-CD, higher baseline SES-CD (more severe disease state) and higher baseline body weight were associated with a higher chance to achieve endoscopic response with mirikizumab treatment. Simulation exposure-efficacy plots stratified by median baseline SES-CD and median baseline body weight are presented in Figure 9.2 and Figure 9.3, respectively. The simulation results suggest that at median exposure range, for participants with higher SES-CD (≥11) or higher baseline body weight (≥ 65 kg), the response rate is expected to be approximately 17% higher than that in those with lower SES-CD (<11) or lower baseline body weight (<65 kg).



Abbreviations: AMAM = I6T-MC-AMAM; BSES-CD = Baseline Simple Endoscopic Score for Crohn's Disease; C_{avg} = average mirikizumab concentration during 1 dosing interval in the Induction Period; CD = Crohn's disease; PI = prediction interval; SES-CD = Simple Endoscopic Score for Crohn's Disease;.

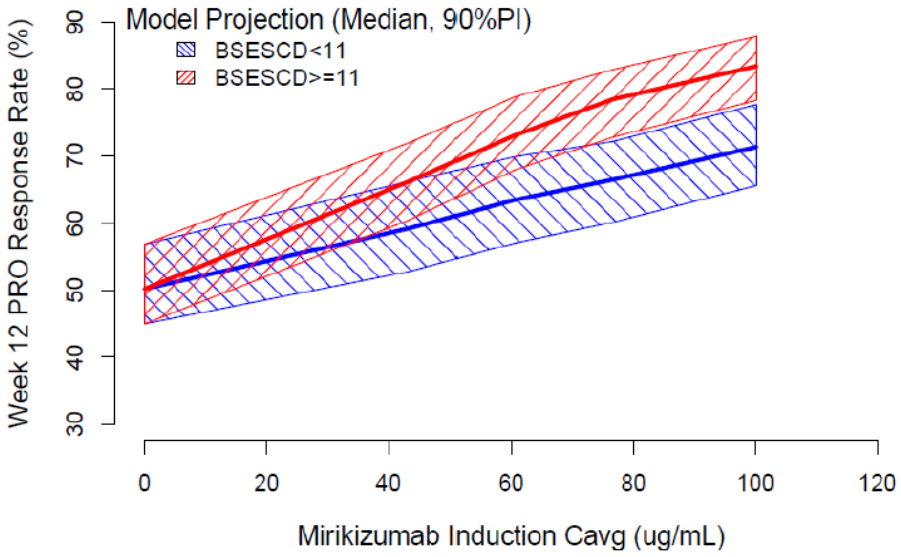
Figure 9.2. Simulation exposure-efficacy relationship plots for endoscopic response by SES-CD at Week 12 in participants with CD in Study AMAM stratified by median baseline SES-CD.



Abbreviations: AMAM = I6T-MC-AMAM; BWTV = baseline body weight (kg); C_{avg} = average mirikizumab concentration during 1 dosing interval in the Induction Period; CD = Crohn's disease; PI = prediction interval; SES-CD = Simple Endoscopic Score for Crohn's Disease.

Figure 9.3. **Simulation exposure-efficacy relationship plots for endoscopic response by SES-CD at Week 12 in participants with CD in Study AMAM stratified by median baseline BWTV.**

In the model focusing on Week 12 clinical response by PRO, higher baseline SES-CD (more severe disease state) was associated with a higher chance to achieve clinical response with mirikizumab treatment. The simulation exposure-efficacy plot stratified by median baseline SES-CD is presented in Figure 9.5 and shows that baseline SES-CD changes the slope in a similar fashion to the endoscopic response by SES-CD.



Abbreviations: AMAM = I6T-MC-AMAM; BSES-CD = Baseline Simple Endoscopic Score for Crohn's Disease; BWTV = Baseline body weight (kg); C_{avg} = average mirikizumab concentration during 1 dosing interval in the Induction Period; CD = Crohn's disease; PI = prediction interval; PRO = patient-reported outcome; SES-CD = Simple Endoscopic Score for Crohn's Disease.

Figure 9.5. **Simulation exposure-efficacy relationship plots for clinical response by PRO at Week 12 in participants with CD in Study AMAM stratified by median baseline SES-CD.**

Overall, baseline SES-CD and baseline body weight are not considered clinically relevant, and no dose adjustment based on these factors is needed.

Maintenance period

In Study AMAM, greater proportions of participants in the mirikizumab treatment group achieved the co-primary endpoints and all Week 52 major secondary endpoints than those in the placebo group. These results are supported by Study AMAG, in which efficacy achieved at Week 52 with mirikizumab 300 mg SC Q4W, the lowest dose selected, was similar to that observed with mirikizumab 600 or 1000 mg IV Q4W.

The model-estimated parameters for the relationship between Week 52 mirikizumab Cavg and Week 52 endoscopic response by SES-CD and clinical remission by CDAI are presented in Table 8.4 and Table 8.5, respectively. VPCs for each final model are presented in Figures ATT.13.11 and ATT.13.14.

Table 8.4. Week 52 Endoscopic Response Exposure-Efficacy Model Parameters

Parameter	Estimate (%SEE)
Baseline Logit Intercept	-1.89 (8.10)
Slope	0.127 (13.5)
Baseline SES-CD on Slope[a]	0.00733 (21.4)

Abbreviations: %SEE = percent standard error of estimate; SES-CD = Simple Endoscopic Score for Crohn's Disease.

[a] To obtain individual slope estimate with baseline SES-CD on slope, use the following equation: Slope,individual = Slope + 0.00733 * (Baseline SES-CD – 11).

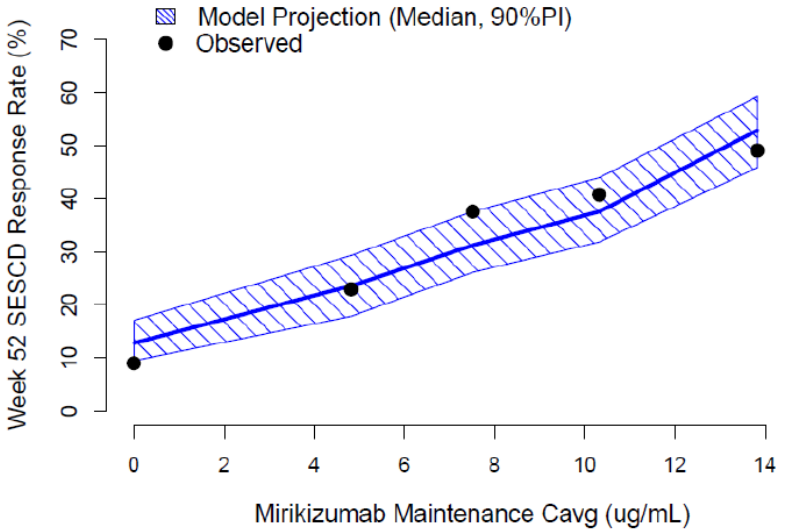
Table 8.5. Week 52 Clinical Remission by CDAI Exposure-Efficacy Model Parameters

Parameter	Estimate (%SEE)
Baseline Logit Intercept	-1.30 (10.2)
Slope	0.0996 (15.2)
Baseline CDAI on Intercept[a]	-0.00391 (25.6)
Baseline SES-CD on Slope[b]	0.00775 (19.7)

Abbreviations: CDAI = Crohn's Disease Activity Index; %SEE = percent standard error of estimate; SES-CD = Simple Endoscopic Score for Crohn's Disease.

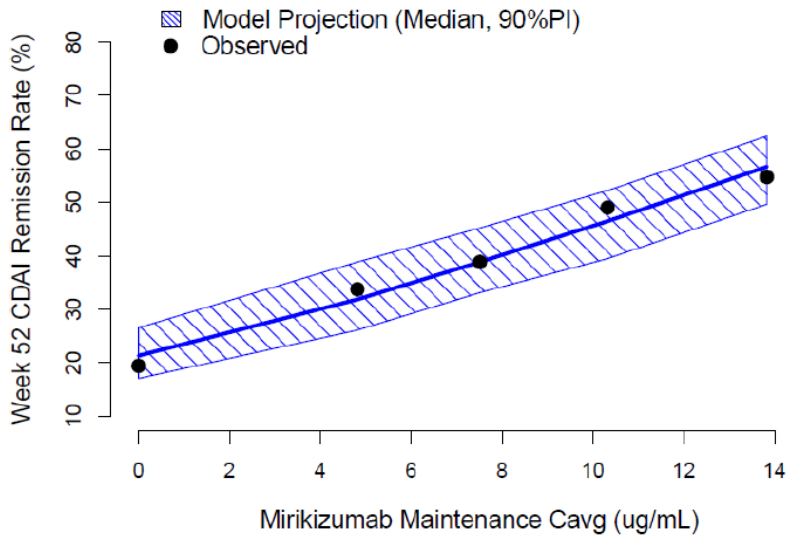
[a] To obtain individual intercept estimate with baseline CDAI on intercept, use the following equation: Intercept,individual = Intercept + {-0.00391 * (Baseline CDAI – 316.29)}.

[b] To obtain individual slope estimate with baseline SES-CD on slope, use the following equation: Slope,individual = Slope + 0.00775 * (Baseline SES-CD – 11).



Abbreviations: C_{avg} = average mirikizumab concentration during 1 dosing interval; PI = prediction interval; PRO = patient-reported outcome; SES-CD = Simple Endoscopic Score for Crohn's Disease.

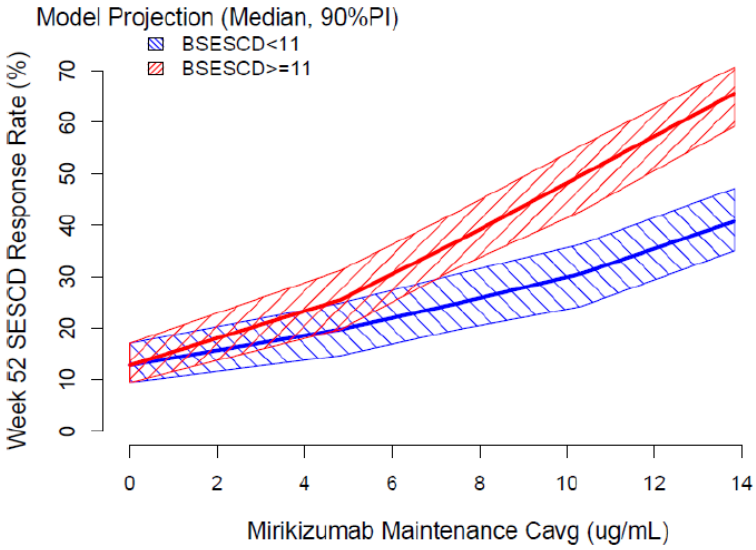
Figure ATT.13.11. **Visual predictive check of model fit of endoscopic response by SES-CD at Week 52 for those participants with clinical response by PRO at Week 12 model in Study AMAM.**



Abbreviations: C_{avg} = average mirikizumab concentration during 1 dosing interval; CDAI = Crohn's Disease Activity Index; PI = prediction interval; PRO = patient-reported outcome;.

Figure ATT.13.14. **Visual predictive check of model fit of clinical remission by CDAI score at Week 52 in participants with clinical response by PRO at Week 12 model in Study AMAM.**

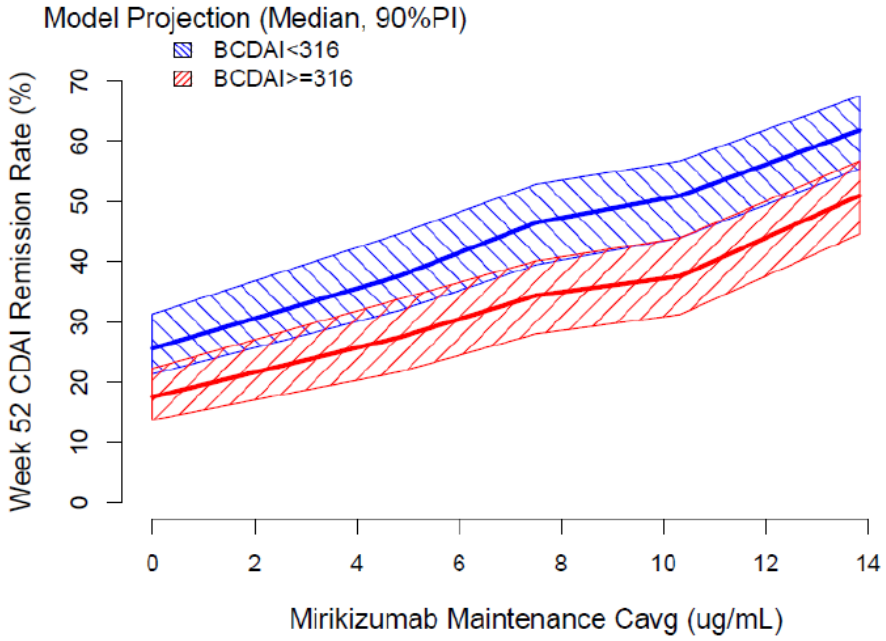
In the co-primary endpoint model focusing on endoscopic response by SES-CD at Week 52, higher baseline SES-CD (more severe disease state) was associated with a higher chance to achieve endoscopic response with mirikizumab treatment. The simulation exposure-efficacy plot stratified by median baseline SES-CD for the clinical response by PRO at Week 12 and endoscopic response by SES-CD at Week 52 is presented in Figure 9.8.



Abbreviations: AMAM = I6T-MC-AMAM; BSES-CD = Baseline Simple Endoscopic Score for Crohn's Disease; C_{avg} = average mirikizumab concentration during 1 dosing interval in the Maintenance Period; PRO = patient-reported outcome; PI = prediction interval; SES-CD = Simple Endoscopic Score for Crohn's Disease.

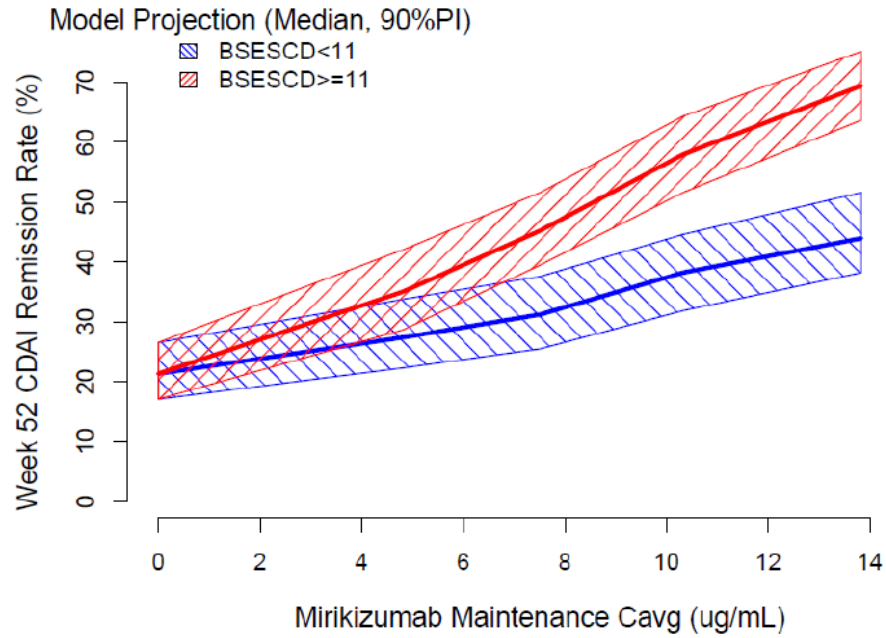
Figure 9.8. **Simulation exposure-efficacy relationship plots for endoscopic response by SES-CD at Week 52 in participants who achieved clinical response by PRO at Week 12 in Study AMAM stratified by median baseline SES-CD.**

In the co-primary endpoint model focusing on clinical remission by CDAI at Week 52, participants with lower baseline CDAI (less severe disease state) who were clinical responders by PRO at Week 12 had a higher chance to achieve clinical remission at Week 52 in both placebo and mirikizumab treatment groups (Figure 9.6). Similarly, participants with higher baseline endoscopic response by SES-CD (more severe disease state) who were clinical responders by PRO at Week 12 also had a better chance to achieve clinical remission at Week 52 defined by CDAI in the mirikizumab treatment group (Figure 9.7).



Abbreviations: AMAM = I6T-MC-AMAM; C_{avg} = average mirikizumab concentration during 1 dosing interval in the Maintenance Period; CDAI = Crohn's Disease Activity Index; PI = prediction interval; PRO = patient-reported outcome.

Figure 9.6. **Simulation Exposure-Efficacy relationship plots for clinical remission by CDAI at Week 52 in participants who achieved clinical response by PRO at Week 12 in Study AMAM stratified by median baseline CDAI.**



Abbreviations: AMAM = I6T-MC-AMAM; BSES-CD = Baseline Simple Endoscopic Score for Crohn's Disease; C_{avg} = average mirikizumab concentration during 1 dosing interval in the Maintenance Period; CDAI = Crohn's Disease Activity Index; PI = prediction interval; PRO = patient-reported outcome; SES-CD = Simple Endoscopic Score for Crohn's Disease;.

Figure 9.7. **Simulation exposure-efficacy relationship plots for clinical remission by CDAI at Week 52 in participants who achieved clinical response by PRO at Week 12 in Study AMAM stratified by median baseline SES-CD.**

Overall, these baseline patient factors were not considered clinically relevant from a dose adjustment perspective.

Exposure-safety analyses

Plots comparing the rates of safety events of interest versus model-predicted Cavg for each exposure quartiles were prepared.

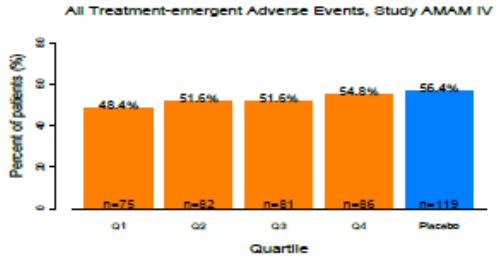
No apparent mirikizumab concentration relationship was identified with the following categories of AEs:

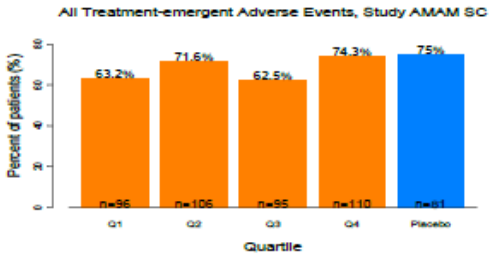
- All TEAEs
- SAEs
- injection site reactions and infusion site reactions, and
- infections, opportunistic infections, and serious infections.

For hypersensitivity reactions after SC injection in the Maintenance Period, an apparent positive trend for an increased frequency of TEAEs with increased exposure was observed, but this trend was not statistically significant (p=0.08507, Cochran Armitage Test for trend). Further, hypersensitivity reactions were reported by 9.3% of participants in the placebo group, which was similar to the Quartile 4 Cavg TEAE frequency (9.5%). Finally, the difference between the incidence of hypersensitivity reactions in the lowest quartile (5.3%) and the highest quartile (9.5%) was small. Overall, an association between exposure and the incidence of hypersensitivity reactions could not be established.

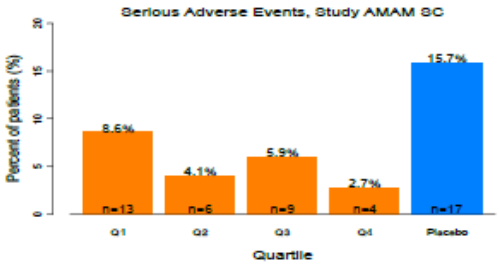
For hepatic events after SC injection in the Maintenance Period, a positive trend was observed for an increased frequency of TEAEs with increased exposure, but this trend was not statistically significant (p=0.1388, Cochran Armitage Test for trend). Additionally, the difference between the incidence of hepatic events in the average of lower 2 quartiles and higher 2 quartiles was small. Considering the small numbers of hepatic events, mainly hepatic lab increases, and the mild transient nature of these lab excursions, an association between exposure and the incidence of these TEAEs could not be established.

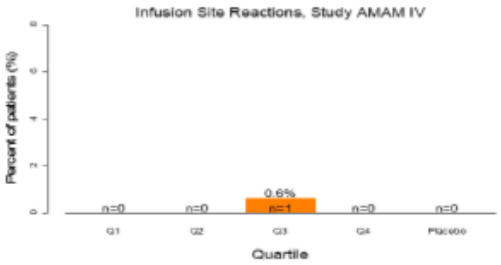
The percentage of participants reporting AEs for each exposure quartile up to Week 12 and up to Week 52 are presented in Figure 8.10.


All Treatment-emergent Adverse Events, Study AMAM IV
Percent of patients (%)
48.4%
51.6%
51.6%
54.8%
56.4%
n=75
n=82
n=81
n=86
n=119
Q1
Q2
Q3
Q4
Placebo
Quartile

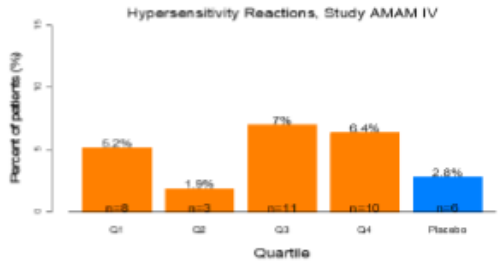

All Treatment-emergent Adverse Events, Study AMAM SC
Percent of patients (%)
63.2%
71.6%
62.5%
74.3%
75%
n=96
n=106
n=95
n=110
n=81
Q1
Q2
Q3
Q4
Placebo
Quartile


Serious Adverse Events, Study AMAM IV
Percent of patients (%)
9.7%
5.7%
4.5%
3.8%
9%
n=15
n=9
n=7
n=6
n=19
Q1
Q2
Q3
Q4
Placebo
Quartile

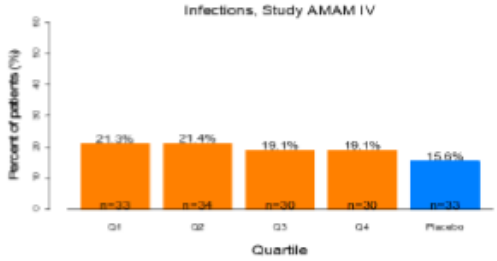

Serious Adverse Events, Study AMAM SC
Percent of patients (%)
8.6%
4.1%
5.9%
2.7%
15.7%
n=13
n=6
n=9
n=4
n=17
Q1
Q2
Q3
Q4
Placebo
Quartile

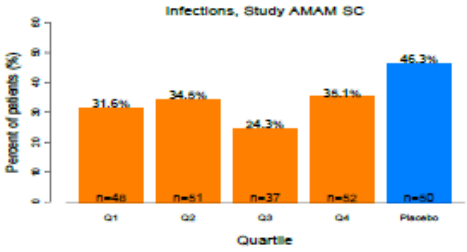

Infusion Site Reactions, Study AMAM IV
Percent of patients (%)
n=0
n=0
0.6%
n=0
n=0
n=1
Q1
Q2
Q3
Q4
Placebo
Quartile

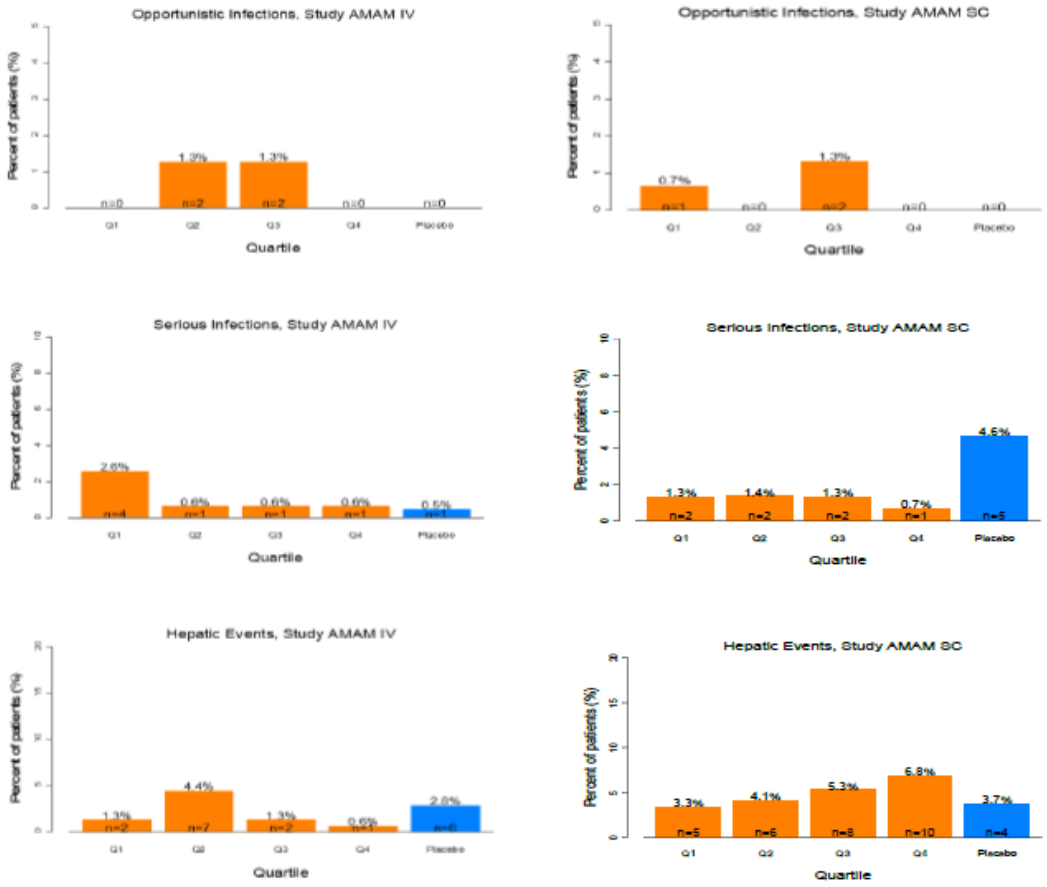

Injection Site Reactions, Study AMAM SC
Percent of patients (%)
9.2%
8.1%
13.8%
12.2%
6.5%
n=14
n=12
n=21
n=18
n=7
Q1
Q2
Q3
Q4
Placebo
Quartile


Hypersensitivity Reactions, Study AMAM IV
Percent of patients (%)
5.2%
1.9%
7%
6.4%
2.8%
n=8
n=3
n=11
n=10
n=6
Q1
Q2
Q3
Q4
Placebo
Quartile


Hypersensitivity Reactions, Study AMAM SC
Percent of patients (%)
5.3%
5.4%
9.2%
9.5%
9.3%
n=8
n=8
n=14
n=14
n=10
Q1
Q2
Q3
Q4
Placebo
Quartile


Infections, Study AMAM IV
Percent of patients (%)
21.3%
21.4%
19.1%
19.1%
15.6%
n=33
n=34
n=30
n=30
n=33
Q1
Q2
Q3
Q4
Placebo
Quartile


Infections, Study AMAM SC
Percent of patients (%)
31.6%
34.5%
24.3%
36.1%
46.3%
n=48
n=51
n=37
n=52
n=50
Q1
Q2
Q3
Q4
Placebo
Quartile



Abbreviations: IV = intravenous; n = number of participants who experienced the adverse event; Q = quartile; SC = subcutaneous; Q4W = every 4 weeks.
AMAM IV average concentration quartiles: Q1: <53.0 µg/mL; Q2: 53.0 to 67.1 µg/mL; Q3: 67.1 to 85.4 µg/mL; Q4: ≥85.4 µg/mL.
AMAM SC average concentration quartiles: Q1: <6.11 µg/mL; Q2: 6.11 to 8.70 µg/mL; Q3: 8.70 to 11.2 µg/mL; Q4: ≥11.2 µg/mL.
Note: The mirikizumab Induction Period included data from the mirikizumab group participants who received 900 mg mirikizumab IV Q4W. The mirikizumab Maintenance Period included data from the mirikizumab group participants who received 900 mg mirikizumab IV Q4W followed by 300 mg mirikizumab SC.
All the plots in this analysis that has either the broad or the narrow terms (for example, Hypersensitivity reactions, Opportunistic infections, and Hepatic events) are done with narrow search term.

Figure 8.10. **Exposure-response analyses: summary of adverse events by exposure quartile up to Week 12 for induction dosing and up to Week 52 for maintenance dosing in Study AMAM.**

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

Bioanalytical methods

The method used for determination of mirikizumab serum concentrations in the clinical studies to support the CD indication was previously assessed during the initial MAA submission, where specificity was determined using serum from healthy subjects, CD and UC subjects. Hence, the assay was previously shown to be suitable for use with CD patient serum and was fully validated as per ICH guidance M10 on bioanalytical method validation, and study sample analysis. This is acceptable to the CHMP.

Similarly, the 4-tier assay for ADA and Nabs is the same assay used in clinical studies to support the initial MAA submission, which included assessment of CD specific cut points. Hence, the assay was previously shown to be suitable for use with CD patient analysis and is considered fully validated in accordance with the Guideline on Immunogenicity assessment of biotechnology-derived therapeutic proteins (EMEA/CHMP/BMWP/14327/2006 Rev.1). This is acceptable to the CHMP.

Bioequivalence

Three (3) bioequivalence (BE) studies were conducted to support the approval of the citrate-free formulation administered by 1-mL and 2-mL AI or PFS for CD.

Study 16-MC-AMBX

Phase 3 studies for CD utilised the solution drug product containing a citrate buffer (original formulation), administered using a PFS. Therefore, Study AMBX was conducted to evaluate the bioequivalence of Mirikizumab Injection (original formulation) delivered by an AI with Mirikizumab Injection (original formulation) delivered by a PFS.

The design and methodology of Study AMBX are acceptable to the CHMP. Data handling and exclusions were detailed and are also acceptable to the CHMP.

In the statistical comparison (AI:PFS), bioequivalence was demonstrated for AUC(0-tlast) and AUC(0-∞). This was not the case for Cmax, where the 90% CI limits for the ratio of GLSMs were 1.07 and 1.27. However, this slightly higher peak exposure for the AI is unlikely to impact safety given that exposure following administration by AI is significantly less than exposure with the recommended IV induction dose in the Phase 3 studies, and the higher exposures with IV dosing were not associated with an increase in clinical safety findings. Further, there was no apparent ER relationship for key adverse events.

Whilst this study was not powered for the comparison of devices by injection site, bioequivalence was shown for AUC(0-tlast), AUC(0-∞), and Cmax following administration into the arm and thigh. For the abdomen, AUC was approximately 40% higher and Cmax was 53% higher for AI compared with PFS. The CHMP agreed that this higher exposure is not of clinical relevance.

Similar proportions of participants reported TEAEs following administration of mirikizumab by PFS (33.3%) and AI (37.5%). However, a higher proportion of participants reported ISRs for the AI (10.0%) compared to the PFS (2.6%) and the incidence of TE-ADA were numerically higher in the AI group compared to the PFS. There were no other notable differences in safety/immunogenicity of the 2 delivery devices. However, this was a single dose study of short duration with small group sizes. Therefore, safety and immunogenicity data are descriptive only.

Study I6T-MC-AMBY

Phase 3 studies for CD utilised the solution drug product containing a citrate buffer (original formulation), administered using a PFS. Therefore, Study AMBY was conducted to evaluate the bioequivalence of a single 300-mg SC dose of mirikizumab citrate-free solution (citrate-free formulation [test]) using a 1-mL and 2-mL PFS compared with the mirikizumab solution (original formulation [reference]) using a 1-mL and 2-mL PFS.

The design and methodology of Study AMBX are acceptable. Data handling and exclusions were detailed and are also acceptable. Bioequivalence was demonstrated between 300 mg mirikizumab solution and mirikizumab citrate-free solution, as assessed by AUC(0-tlast), AUC(0-∞), and Cmax.

Whilst this study was not powered for the comparison of formulations by injection site, bioequivalence was also shown between mirikizumab solution and mirikizumab citrate-free solution for each individual injection site separately (arm, thigh and abdomen), as assessed by AUC(0-tlast), AUC(0-∞), and Cmax.

A similar proportion of participants were TE ADA-positive following administration of 300 mg mirikizumab solution or 300 mg mirikizumab citrate-free solution. A higher proportion of participants reported ISRs following administration of mirikizumab solution when compared to mirikizumab citrate-free solution. Excluding ISRs, the incidence of all TEAEs during the study was similar between mirikizumab solution and mirikizumab citrate-free solution, and similar between injection-site locations. Overall, the mean changes in clinical laboratory values and vital signs were similar between formulations. There were no SAEs, no discontinuations due to TEAEs, and no unexpected safety and tolerability findings. However, this was a single dose study of short duration with small group sizes. Therefore, safety and immunogenicity data are descriptive only.

Study 16-MC-AMBT

Phase 3 studies for CD used the mirikizumab solution drug product that contains a citrate buffer (original formulation), administered using a PFS. Therefore, study 16-MS-AMBT provided bioequivalence data on the mirikizumab citrate-free solution formulation compared to the original formulation administered by AI (2 x 1 mL of 100-mg/mL injections for a 200-mg dose).

The design and methodology of Study AMBT are acceptable to the CHMP. Data handling and exclusions were detailed and are also acceptable to the CHMP.

Bioequivalence was observed between mirikizumab solution and citrate-free solution, as assessed by AUC(0-tlast), AUC(0-∞), Cmax, and tmax.

Although this study was not powered for comparison of formulations by injection site, when comparing mirikizumab solution and citrate-free solution for the abdomen, arm, and thigh injection sites separately, the 90% CIs of the ratios of GLSMs included unity for AUC(0-tlast), AUC(0-∞), and Cmax, except for the 90% CIs of the ratios for Cmax following administration of mirikizumab citrate-free solution at the thigh, which were below unity.

The incidence of TE-ADA-positive participants during the study was slightly lower following administration of mirikizumab citrate-free solution compared to mirikizumab solution. Overall, the proportion of participants reporting treatment-emergent adverse events (TEAEs) was similar following administration of mirikizumab solution or citrate-free solution. The incidence of ISRs was lower following administration of mirikizumab citrate-free solution (9.6%) compared to mirikizumab solution (16.1%). No deaths or SAEs occurred during the study. However, this was a single dose study of short duration with small group sizes. Therefore, safety and immunogenicity data are descriptive only.

Overall conclusion

The CHMP concluded that the totality of evidence from the 3 BE studies (AMBX, AMBY, and AMBT) supports the approval of the citrate-free formulation administered by 1-mL and 2-mL AI or PFS in patients with CD.

Pharmacokinetics in the target population

For Crohn's Disease the mean (coefficient of variation in %) C_{max} and area under the curve (AUC) after induction dosing (900 mg every 4 weeks administered by intravenous infusion) in patients with Crohn's disease were 332 µg/mL (20.6 %) and 1820 µg*day/mL (38.1 %), respectively. The mean (CV %) C_{max} and AUC after maintenance dosing (300 mg every 4 weeks by subcutaneous injection) were 13.6 µg/mL (48.1 %) and 220 µg*day/mL (55.9 %), respectively.

To support the indication of moderately to severely active CD, popPK analyses were conducted based on new data from the Phase 2 Study I6T-MC-AMAG and 1 Phase 3 Study I6T-MC-AMAM.

Study 16T-MC-AMAG

The methods used to develop the popPK model using data from Study AMAG are acceptable to the CHMP. The results of this analysis, together with the ER analyses, provide support for the doses evaluated in the Phase 3 Study AMAG: induction dose of 900 mg IV Q4W for the first 12 weeks followed by 300 mg SC Q4W for maintenance dosing.

Study I6T-MC-AMAM

This popPK analysis was based on data from the pivotal Phase 3 study AMAM in adult patients with CD. The methods used for model development and data exclusions are acceptable to the CHMP.

The final model was a 2-compartment model, with first-order absorption for the SC maintenance doses. The parameter estimates of the final model were consistent with those obtained in previous analyses for participants with CD (Study AMAG) and UC (Studies AMAN and AMBG). Model diagnostics showed good agreement between observed and model-predicted mirikizumab concentrations. Bootstrap demonstrated that all parameters were adequately estimated. The presented VPC indicated that the predictive performance of the model was adequate.

Baseline body weight, serum albumin concentration, baseline CRP, and baseline body mass index were found to be statistically significant covariates in the final model. However, simulations of mirikizumab exposure using the final popPK model showed that changes in mirikizumab exposure related to changes in patient covariates were either similar or within random unexplained variability of the exposures, and none of the covariates elicited clinically meaningful impact. Therefore, no dose adjustment based on any patient factor is warranted.

Of note, injection site was not identified as a significant covariate on SC bioavailability. This suggests that SC injection site location (abdomen. arm or thigh) does not have a significant impact on mirikizumab exposure.

Special populations

In both IV and SC dose regimens, all intrinsic patient factors included as statistically significant covariates were assessed for their effect size and clinical relevance. Overall, the impact of patient factors on both the PK profile of mirikizumab and exposure-efficacy models was either small or not considered clinically relevant. Therefore, the CHMP is agreed that no dose adjustment based on any patient factor is warranted.

Pharmacodynamics

No specific clinical PD studies were performed in patients with CD which was considered acceptable by the CHMP.

Immunogenicity

In Study AMAG, 6.0% of evaluable mirikizumab-treated participants were TE-ADA positive and 5.4% were NAb positive. In Study AMAM, 12.7% of evaluable mirikizumab-treated participants were TE-ADA positive and 12.5% were NAb positive.

Overall, using both graphical and model-based evaluations of TE ADA and mirikizumab exposure, no discernible difference was noted in mirikizumab exposure between TE ADA-positive and TE ADA-negative participants. Further, the magnitude of titer in participants with TE ADA showed no impact on exposure.

Similar proportions of TE ADA-positive and TE ADA-negative participants achieved successful clinical outcomes after treatment with mirikizumab in the Phase 3 study (AMAM). The presence of TE ADA and the magnitude of titer in participants with TE ADA showed no apparent impact on efficacy.

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

Pharmacokinetics-Pharmacodynamics

Study I6T-MC-AMAM

Exposure-efficacy analyses

The methods used for model development and evaluation are acceptable to the CHMP. For both the Induction and Maintenance Periods, all exposure-efficacy models found that linear relationships rather than Emax relationships were best able to describe the observed data. The parameters for each final model were estimated reasonably well. VPCs for each final model showed that the models described the observed data adequately.

In the Induction Period of Study AMAM, a single dose of 900 mg IV Q4W was evaluated, and all Week 12 major secondary endpoints were achieved with this dose at Weeks 0, 4, and 8. This result was consistent with the E-R relationship from the dose-ranging Phase 2 Study AMAG, in which endoscopic response and PRO remission measures indicated near-maximal responses for doses between 600 and 1000 mg and that the 900 mg IV dose would produce a near-maximal effect.

In the exposure-efficacy logistic regression model focusing on Week 12 endoscopic response by SES-CD, higher baseline body weight and higher baseline SES-CD were associated with a higher chance to achieve endoscopic response with mirikizumab treatment. Further, in the model on Week 12 clinical response by PRO, higher baseline SES-CD was associated with a higher chance to achieve clinical response with mirikizumab treatment. These results suggest that patients with worse baseline disease status have a better chance of responding to mirikizumab treatment when administered the same dose. Therefore, these patient factors were not deemed clinically relevant, which is agreed by the CHMP. As such, the 900 mg IV Q4W studied in AMAM Induction Period was shown to be appropriate and no dose adjustments are warranted based on patient factors.

In Maintenance Period of Study AMAM, the 300 mg SC Q4W dose showed a robust efficacy in participants with CD, which was consistent with results of Study AMAG, in which efficacy achieved at Week 52 with mirikizumab 300 mg SC Q4W, the lowest dose selected, was similar to that observed with mirikizumab 600 or 1000 mg IV Q4W.

In the model-based exposure-efficacy analyses for co-primary endpoints focusing on endoscopic response by SES-CD at Week 52, higher baseline SES-CD was associated with a higher chance to achieve endoscopic response with mirikizumab treatment. In the co-primary endpoint model focusing on clinical remission by CDAI at Week 52, participants with lower baseline CDAI (less severe disease

state) who were clinical responders by PRO at Week 12 had a higher chance to achieve clinical remission at Week 52 in both placebo and mirikizumab treatment groups. Similarly, participants with higher baseline endoscopic response by SES-CD (more severe disease state) who were clinical responders by PRO at Week 12 also had a better chance to achieve clinical remission at Week 52 defined by CDAI in the mirikizumab treatment group. These patient factors were not deemed clinically relevant, which is agreed by the CHMP. As such, the 300 mg SC Q4W maintenance dosing regimen for mirikizumab was shown to be appropriate and no dose adjustments are warranted based on patient factors.

Exposure-safety analyses

There was no apparent mirikizumab exposure relationship with all TEAEs, SAEs, injection site reactions (for SC dosing), infusion site reactions (for IV dosing), infections, opportunistic infections, and serious infections.

An apparent positive trend for increased frequency of hypersensitivity reactions with increased exposure in the Maintenance Period was observed. However, this trend was not statistically significant. Further, hypersensitivity reactions were reported in 9.3% of participants in the placebo group, which was similar to the Quartile 4 Cavg TEAE frequency of 9.5%. In addition, the difference between the incidence of hypersensitivity reactions in the lowest quartile (5.3%) and the highest quartile (9.5%) was relatively small. As such, an association between mirikizumab exposure and the incidence of hypersensitivity reactions could not be established.

An apparent positive trend for increased frequency of hepatic events with increased exposure in the Maintenance Period was observed, but this trend was also not statistically significant. Additionally, the difference between the incidence of hepatic events in the average of lower 2 quartiles and higher 2 quartiles was relatively small. Considering the small numbers of hepatic events, mainly hepatic laboratory test result increases, and the mild transient nature of these laboratory excursions, an association between exposure and the incidence of these TEAEs could not be established.

Overall, the results of the exposure-efficacy and exposure-safety analyses of data from the pivotal Phase 3 Study AMAM provide justification for the proposed mirikizumab dose regimen in CD of 900-mg IV Q4W dose for the Induction Period and 300 mg SC Q4W dose for the Maintenance Period, in either biologic-failed or not-biologic-failed adults with moderately to severely active CD.

2.6.4. Conclusions on clinical pharmacology

The Clinical Pharmacology of mirikizumab in adults with moderately to severely active CD has been sufficiently characterised.

2.6.5. Clinical efficacy

The clinical development of mirikizumab for the treatment of Crohn's disease includes

- 1 pivotal Phase 3 study (Study I6T-MC-AMAM [AMAM])
- 1 supportive Phase 2 study (Study I6T-MC-AMAG [AMAG]), and
- 1 long-term extension Phase 3 study (Study I6T-MC-AMAX [AMAX] - ongoing

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

Controlled Clinical Studies in Patients with Crohn's disease						
I6T-MC-AMAG; 5.3.5.1; Completed; Full	To test the hypothesis that treatment with mirikizumab is superior to placebo in the proportion of participants with endoscopic response at Week 12, defined as 50% reduction from baseline in SES-CD Score	Phase 2, multicenter, randomized, parallel-arm, double-blind, 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	Patients: 191 • 1000 mg mirikizumab: 64 • 600 mg mirikizumab: 32 • 200 mg mirikizumab: 31 • 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 208
			Period 2 (Double Blind and Double Dummy): • Mirikizumab-treated participants with Week 12 SES-CD improvement were evenly randomized to continue Period 1 treatment (described above) or to 300 mg SC Q4W[a] • Mirikizumab-treated participants with no Week 12 SES-CD improvement 1000 mg mirikizumab IV Q4W[a] • Placebo-treated participants in Period 1: 1000 mg mirikizumab IV Q4W[a] **Period 3 (Open Label):** • All participants who continued study treatment and achieved clinical benefit in the opinion of the investigator received open-label mirikizumab 300 mg SC Q4W. • Participants who did not achieve clinical benefit discontinued treatment and entered the Follow-Up period.			

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
I6T-MC-AMAM; 5.3.5.1; Ongoing[b]; Full	To evaluate whether the efficacy of treatment with mirikizumab is superior to placebo as assessed by • clinical response by PRO at Week 12 and endoscopic response at Week 52, and • clinical response by PRO at Week 12 and clinical remission by CDAI at Week 52	Phase 3, multicenter, randomized, double-blind, double-dummy, parallel-group, active- and placebo-controlled, treat-through study	• Mirikizumab 900 mg IV Q4W for 3 doses, then 300 mg SC Q4W • Ustekinumab 6 mg/kg IV for 1 dose, then 90 mg SC Q8W • Placebo o When Period 1 concludes (Week 12), responders continue receiving placebo, and NR at Week 12 will receive mirikizumab as described above. o NR is defined as failing to achieve at least a 30% decrease in SF and/or AP and be no worse than baseline.	Patients: 1152 • Mirikizumab: 631 • Ustekinumab: 309 • Placebo: 212	Patients with moderately to severely active Crohn's disease	52 weeks
Uncontrolled Studies in Patients with Crohn's disease						
I6T-MC-AMAX; Not applicable; Ongoing	The primary objective of Study AMAX is to evaluate the long-term effect of mirikizumab in clinical remission and endoscopic response at Week 52 of treatment in Study AMAX.	Phase 3, multicenter, open-label, long-term extension study	• Study AMAM responders and participants from Study AMAG receive open-label mirikizumab 300 mg SC Q4W. • Study AMAM non-responders receive an induction dose of IV mirikizumab 900 mg Q4W for 3 doses. o All participants having clinical benefit post-IV induction treatment continue 300 mg SC Q4W. o Participants considered to have no clinical benefit post-IV induction discontinue from the study at Week 12 and enter the 12- to 16-week posttreatment follow-up period.	Patients: 868	Patients with moderately to severely active Crohn's Disease	A maximum of 3 years per participant, until the participant discontinues from the study, or until mirikizumab is commercially available in the country in which the participant resides, whichever occurs first.

2.6.5.1. Dose response study(ies)

The mirikizumab 900 mg IV Q4W induction and 300 mg SC Q4W maintenance dose regimens was selected based primarily on analyses of pharmacokinetics (PK), safety, and efficacy data from the Phase 2 Study AMAG, safety data from other clinical studies evaluating mirikizumab, and nonclinical safety data.

Study I6T-MC-AMAG

Study title: A Phase 2, Multicenter, Randomized, Parallel-Arm, Placebo-Controlled Study of LY3074828 in Participants with Active Crohn's Disease

Study design

The study was comprised of 3 treatment periods followed by a 16-week Post-Treatment Follow-Up period. The total treatment period in this study was up to 208 weeks; the total duration of participation in this study was up to 224 weeks.

Period 1 (Weeks 0 to 12):

After a 28-day Screening Period, participants were randomized with a 2:1:1:2 allocation across 4 treatment arms: placebo, **mirikizumab 200 mg, mirikizumab 600 mg, or mirikizumab 1000 mg administered intravenously Q4W at Weeks 0, 4, and 8**. Participants were stratified by previous exposure to biologic therapy for the treatment of CD.

Period 2 (Weeks 12 to 52):

Participants received both IV and SC dosing to maintain blinding from Weeks 12 through 48.

All participants who received mirikizumab treatment in Period 1 and who achieved at least a 1-point improvement from baseline in their SES-CD score at Week 12 (determined by the central reader) were stratified based upon endoscopic response and randomized 1:1 to

- continue Period 1 IV treatment assignment with placebo administered subcutaneously, or
- receive mirikizumab 300 mg SC Q4W with placebo administered intravenously.

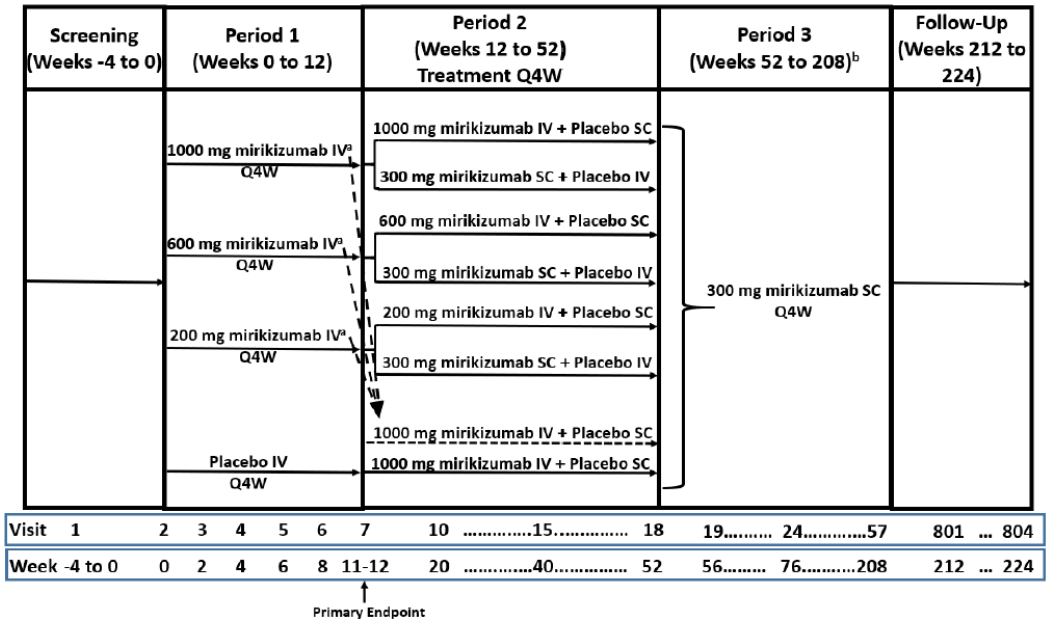
All participants who received mirikizumab treatment in Period 1 and who did not achieve at least a 1-point improvement from baseline in their SES-CD score at Week 12 received mirikizumab 1000 mg IV and placebo SC Q4W.

All participants who received placebo in Period 1 received mirikizumab 1000 mg IV and placebo SC Q4W.

Period 3 (Weeks 52 to 208):

At Week 52, all participants having clinical benefit per the judgment of the investigator proceeded to Period 3 and received mirikizumab 300-mg SC Q4W open-label treatment starting at Week 52. Participants not receiving clinical benefit at Week 52 discontinued treatment and entered the Follow-Up period.

Figure: I6T-MC-AMAG Study design.



Abbreviations: IV = intravenous; Q4W = every 4 weeks; SC = subcutaneous; SES-CD = Simple Endoscopic Score for Crohn's Disease.

[a] Participants who had not had any improvement in SES-CD score from baseline at Week 12, as determined by the central reader, received mirikizumab 1000 mg IV + placebo SC.

[b] Once Study AMAX opened for enrollment, participants in Period 3 were asked to consider participation in Study AMAX, or they discontinued from Study AMAG.

Main inclusion criteria:

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

- had a diagnosis of CD ≥3 months before baseline visit
- had active CD at baseline visit defined as absolute stool frequency ≥4 (loose and watery stools defined as Bristol Stool Scale Category 6 or 7), and/or abdominal pain ≥2, andwithin 14 days before the first dose of study treatment, had a centrally read SES-CD score of ≥7 for participants with ileal-colonic disease, or ≥4 for participants with isolated ileal disease.

Study participants must have received prior treatment fro CD

- with a history of inadequate response to, or failure to tolerate treatment with aminosalicylates, 6-mercaptopurine or azathioprine, oral or IV corticosteroids, or a history of corticosteroid dependence, or
- have received treatment with≥1 biologic agent (such as TNF antagonists, vedolizumab, experimental biologic CD therapeutics) with or without documented history of failure to respond to or tolerate such treatment. The treatment must have been discontinued according to the following timeline:
    - anti-TNF therapy at least 8 weeks before baseline
    - vedolizumab treatment at least 12 weeks before baseline
    - experimental biologic CD therapy at least 8 weeks before baseline, or
- a combination of both.

Study participants were excluded from study enrollment if they had previous exposure to any biologic therapy targeting IL-23 p19 either licensed or investigational, or prior exposure to ustekinumab within the screening period.

Study intervention

Study Interventions, Dose, and Mode of Administration:

Treatment Arm	Description
Period 1 (Double Blind)	
Mirikizumab Dose Arm 1	Mirikizumab 1000 mg IV Q4W
Mirikizumab Dose Arm 2	Mirikizumab 600 mg IV Q4W
Mirikizumab Dose Arm 3	Mirikizumab 200 mg IV Q4W
Placebo	Placebo IV Q4W
Period 2 (Double Blind and Double Dummy)	
Mirikizumab Dose Arm 1	Mirikizumab 1000 mg IV Q4W* or mirikizumab 300 mg SC Q4W*
Mirikizumab Dose Arm 2	Mirikizumab 600 mg IV Q4W* or mirikizumab 300 mg SC Q4W*
Mirikizumab Dose Arm 3	Mirikizumab 200 mg IV Q4W* or mirikizumab 300 mg SC Q4W*
Mirikizumab participants with no Week 12 SES-CD improvement	Mirikizumab 1000 mg IV Q4W + placebo SC Q4W
Placebo	Mirikizumab 1000 mg IV Q4W + placebo SC Q4W
Period 3 (Open Label)	
Mirikizumab Dose Arm 1	Mirikizumab 300 mg SC Q4W
Mirikizumab Dose Arm 2	Mirikizumab 300 mg SC 4W
Mirikizumab Dose Arm 3	Mirikizumab 300 mg SC Q4W
Placebo	Mirikizumab 300 mg SC Q4W

Abbreviations: IV = intravenous; LY = LY3074828; Q4W = every 4 weeks; SC = subcutaneous; SES-CD = Simple Endoscopic Score for Crohn's Disease.

* Placebo administered 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.

Primary and Secondary Objective and Endpoints

Objectives	Endpoints
Primary	
• To test the hypothesis that treatment with mirikizumab is superior to placebo in the proportion of participants with endoscopic response at Week 12, defined as at least 50% reduction from baseline in SES-CD Score	• Proportion of participants achieving endoscopic response at Week 12
Secondary	
• To evaluate the safety and tolerability of treatment with mirikizumab	• AEs and discontinuation rates; mean change vital signs; laboratory values
• To evaluate the effect of mirikizumab on the proportion of participants with endoscopic response at Week 52, defined as at least 50% reduction from baseline in SES-CD score	• Proportion of participants achieving endoscopic response at Week 52
• To evaluate the efficacy of treatment with mirikizumab as superior to placebo in endoscopic remission (defined as an SES-CD score of <4 ileal-colonic or <2 for isolated ileal disease, and no subscore >1) at Week 12	• Proportion of participants achieving endoscopic remission at Week 12
• To evaluate the effect of mirikizumab on the proportion of participants with endoscopic remission (defined as an SES-CD score of <4 ileal-colonic or <2 for isolated ileal disease, and no subscore >1) at Week 52	• Proportion of participants achieving endoscopic remission at Week 52
• To evaluate the efficacy of treatment with mirikizumab as superior to placebo in PRO remission (defined as SF ≤2.5and AP ≤1) at Week 12	• Proportion of participants achieving PRO remission at Week 12
• To evaluate the effect of mirikizumab on the proportion of participants with PRO remission (defined as SF ≤2.5 and AP ≤1) at Week 52	• Proportion of participants achieving PRO remission at Week 52
• To evaluate the effect of mirikizumab on health outcomes/quality-of-life measures (including PGRS score, PGRC score, IBDQ score, SF-36 score, and FACIT-Fatigue) at Weeks 12 and 52	• The mean change from baseline for PGRS score, IBDQ score, FACIT-Fatigue, and SF-36, and the mean PGRC at Weeks 12 and 52
• To characterize the PK of mirikizumab	• Clearance and volume of distribution

Allowed medications

During the study, use of the following medications was allowed: oral 5-ASA or sulfasalazine, AZA or 6-MP, MTX, and oral corticosteroid therapy (prednisone at a stable dosage ≤20 mg/day or equivalent oral steroid)

Results

Participant flow and numbers analysed

A total of 191 participants were randomized to 1 of 4 groups as the ITT population. A total of 176 participants (92.1%) completed the 12-week Period 1 and entered Period 2. 143 (81.3%) participants completed the 52-week Period 2 and 137 participants entered into Period 3.

Demography and Baseline Characteristics

The mean age was 38.6 years, 51.3% of participants were female, and the mean BMI was 25.2 kg/m2. The mean duration since CD onset among participants was 9.5 years, 62.8% of participants reported prior biologic use, and 29.8% of participants reported oral corticosteroid use at baseline.

Outcomes and estimation

Period 1

Mirikizumab 200 mg IV Q4W, 600 mg IV Q4W, and 1000 mg IV Q4W demonstrated superiority compared with placebo at its Week 12 primary endpoint of endoscopic response, defined as at least 50% reduction from baseline in SES-CD score (response rates of 25.8% for 200 mg IV, 37.5% for 600 mg IV, 43.8% for 1000 mg IV, and 10.9% for placebo).

In addition, the mirikizumab 600-mg and 1000-mg IV groups were superior compared with placebo on all secondary endpoints measuring clinical response, health outcomes, and quality of life at Week 12. Mirikizumab 200 mg IV was superior compared with placebo on all secondary endpoints measuring health outcomes and quality of life at Week 12 but did not demonstrate superiority compared with placebo on the secondary clinical endpoints of endoscopic remission and PRO remission.

Table: Objectives, Endpoints, Statistical Methods, and Results for Period 1

Objectives	Endpoints	Statistical Methods	Results				
				PBO N = 64	Miri 200 mg IV N = 31	Miri 600 mg IV N = 32	Miri 1000 mg IV N = 64
Primary Endpoint Analysis							
To test the hypothesis that treatment with mirikizumab is superior to placebo in the proportion of participants with endoscopic response at Week 12, defined as at least 50% reduction from baseline in SES-CD Score	Proportion of participants achieving endoscopic response at Week 12	Logistic regression analysis with NRI	Response, n (%)	7 (10.9)	8 (25.8)	12 (37.5)	28 (43.8)
			P-value vs. PBO	–	0.079	0.003	<0.001
Secondary Endpoint Analysis at Week 12							
To evaluate the efficacy of treatment with mirikizumab as superior to placebo in endoscopic remission (defined as an SES-CD score of <4 ileal-colonic or <2 for isolated ileal disease, and no subscore >1) at Week 12	Proportion of participants achieving endoscopic remission at Week 12	Logistic regression analysis with NRI	Response, n (%)	1 (1.6)	2 (6.5)	5 (15.6)	13 (20.3)
			P-value vs. PBO	–	0.241	0.032	0.009
To evaluate the efficacy of treatment with mirikizumab as superior to placebo in PRO remission (defined as SF ≤2.5and AP ≤1) at Week 12	Proportion of participants achieving PRO remission at Week 12	Logistic regression analysis with NRI	Response, n (%)	4 (6.3)	4 (12.9)	9 (28.1)	14 (21.9)
			P-value vs. PBO	–	0.330	0.006	0.029

Period 2

For participants treated continuously with mirikizumab 600 mg IV or 1000 mg IV in Period 1 and Period 2, the gains observed at Week 12 were maintained at Week 52. Response rates observed at Week 52 for endoscopic response, endoscopic remission, and PRO remission were similar for participants who received any of the mirikizumab IV regimens in Period 1, followed by mirikizumab 300 mg SC in Period 2 and participants who continuously received mirikizumab 600 mg IV or 1000 mg IV in Period 1 and Period 2.

Table: Objectives, Endpoints, Statistical Methods, and Results for Period 2

				Miri 200 mg IV/200 mg IV N = 9	Miri 600 mg IV/600 mg IV N = 9	Miri 1000 mg IV/1000 mg IV N = 23	Miri IV/ 300 mg SC N = 46	Miri 1000 mg IV for NI N = 30	PBO/ Miri 1000 mg IV N = 59
Secondary Endpoint Analysis at Week 52									
To evaluate the effect of mirikizumab on the proportion of participants with endoscopic response at Week 52, defined as at least 50% reduction from baseline in SES-CD score	Proportion of participants achieving endoscopic response at Week 52	Descriptive Statistics with NRI	Response, n (%)	4 (44.4)	7 (77.8)	13 (56.5)	27 (58.7)	6 (20.0)	25 (42.4)
			90% CI	(17.2,71.7)	(55.0, 100)	(39.5, 73.5)	(46.8, 70.6)	(8.0, 32.0)	(31.8, 53.0)
To evaluate the effect of mirikizumab on the proportion of participants with endoscopic remission (defined as an SES-CD score of <4 ileal-colonic or <2 for isolated ileal disease, and no subscore >1) at Week 52	Proportion of participants achieving endoscopic remission at Week 52	Descriptive Statistics with NRI	Response, n (%)	0 (0.0)	2 (22.2)	6 (26.1)	15 (32.6)	4 (13.3)	11 (18.6)
			90% CI	(0.0, 0.0)	(0.0, 45.0)	(11.0, 41.1)	(21.2, 44.0)	(3.1, 23.5)	(10.3, 27.0)
To evaluate the effect of mirikizumab on the proportion of participants with PRO remission (defined as SF ≤2.5 and AP ≤1) at Week 52	Proportion of participants achieving PRO remission at Week 52	Descriptive Statistics with NRI	Response, n (%)	7(77.8)	5(55.6)	7(30.4)	21(45.7)	11(36.7)	24(40.7)
			90% CI	(55.0, 100)	(28.3,82.8)	(14.7, 46.2)	(33.6, 57.7)	(22.2, 51.1)	(30.2, 51.2)

Considerations of Efficacy and Exposure–Response Relationships

Period 1

A model-based analysis of the relationship between individual subject mirikizumab systemic exposures and Week 12 endoscopic response revealed a significant relationship, with higher mirikizumab exposures associated with higher rates of endoscopic response. The proposed 900 mg IV induction dose is expected to produce near-maximal effect based on this exposure-response analysis. The exposure of mirikizumab changes in proportion to dose, which means that the induction dose of 900 mg IV selected for the pivotal phase 3 study is expected to produce an exposure that is 10% lower than the 1000 mg IV dose evaluated in Study AMAG. A 10% decrease in systemic exposure is not expected to result in a decrease in efficacy relative to what was observed in Study AMAG.

Period 2

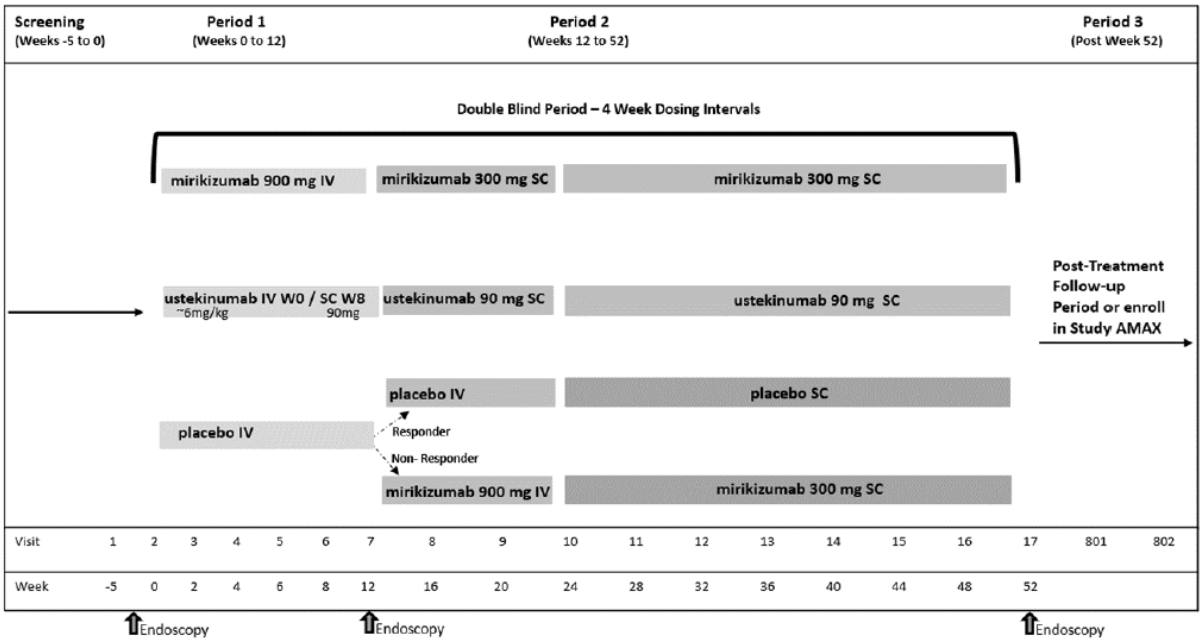
In the Week 12 to Week 52 maintenance period of Study AMAG, the mirikizumab dose regimens that were evaluated ranged from 300 mg SC Q4W to 1000 mg IV Q4W. These dose regimens produced approximately an 8-fold range in the median mirikizumab exposures across the treatment groups. The Week 52 endoscopic response and PRO remission rates across the maintenance treatment groups were similar and did not appear to have any relationship to dose or mirikizumab exposure within any of the doses and range of exposures evaluated in Study AMAG. There were also no observed differences in the time course of SF or AP scores across the treatment groups during the maintenance period. Based on these data, a mirikizumab maintenance dose of 300 mg SC Q4W was selected for the pivotal phase 3 study.

2.6.5.2. Main study

Study: I6T-MC-AMAM

Study title: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo- and Active Controlled, Treat-Through Study to Evaluate the Efficacy and Safety of Mirikizumab in Patients with Moderately to Severely Active Crohn's Disease

Figure 1: Study schema



Abbreviations: IV = intravenous; SC = subcutaneous; W = week.
Note: From Week 8 through Week 20, all participants received their assigned treatment and matching placebo via both IV and SC administration.

Methods

- **Study Participants**

The study population included male or female participants ≥18 and ≤80 years of age at the time of initial screening who had

- a diagnosis of CD or fistulizing CD established at least 3 months prior to enrollment, confirmed by clinical, endoscopic, and histological criteria
- moderately to severely active CD as defined by an unweighted daily average SF ≥4 (loose and watery stools defined as Bristol Stool Scale Category 6 or 7), AND/OR an unweighted daily average AP ≥2 at baseline
- a SES-CD score ≥7 in participants with ileal-colonic or ≥4 in participants with isolated ileal disease within 21 days before randomization

Note: Enrollment of participants with a SES-CD score ≥3 and <7 (SES-CD <4 for participants with isolated ileal disease) and presence of at least 1 large ulcer (in the ileum, colon, or both) that resulted in a minimum score of 2 for the component of "size of ulcers" and a minimum score of 1 for the component of "ulcerated surface was limited to approximately 10% of total enrollment. Participants from this subset were excluded from the PAS.

Prior Medication Failure Criteria

Participants must have an inadequate response to, loss of response to, or intolerance to at least 1 of the medications described in Inclusion Criterion [8a] OR [8b]. For the relevant medication specified in these criteria, documentation of dose, frequency, route of administration, and duration of the qualifying failure was required.

[8a] **Conventional-failed participants:** Participants who have an inadequate response to, loss of response to, or are intolerant to at least one of the following medications:

- **corticosteroids**

o corticosteroid-refractory disease, defined as signs and/or symptoms of active CD despite a minimum of 4 weeks of:

- oral prednisone (or equivalent) at doses of at least 30 mg/day, or

- budesonide at doses of at least 9 mg/day

o corticosteroid-dependent disease:

a. defined as an inability to reduce corticosteroids below the equivalent of prednisone 10 mg/day or budesonide below 3 mg/day within 3 months of starting corticosteroids without a return of signs and/or symptoms of active CD; or

b. a relapse within 3 months of completing a course of corticosteroids; or

o history of intolerance of corticosteroids (which includes evidence of a side-effect sufficiently serious as to precluding continued treatment with corticosteroids including, but not limited to, Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, or neuropsychiatric side-effects, including insomnia, associated with corticosteroid treatment).

- **immunomodulators:**

o signs and/or symptoms of persistently active disease despite at least 3 months' treatment with one of the following:

- oral AZA (≥1.5 mg/kg/day) or 6-MP (≥0.75 mg/kg/day) or MTX 25 mg (intramuscular or SC weekly) or
- oral AZA or 6-MP within a therapeutic range as judged by thioguanine metabolite testing, or
- a combination of a thiopurine and allopurinol within a therapeutic range as judged by thioguanine metabolite testing.

o history of intolerance to at least 1 immunomodulator (including but not limited to nausea/vomiting, AP, pancreatitis, liver function test abnormalities, and lymphopenia).

AND

o have neither failed nor demonstrated an intolerance to a biologic medication (anti-TNF antibody or anti-integrin antibody) that is approved for the treatment of CD.

Discontinuation despite clinical benefit does not qualify as having failed or being intolerant to CD conventional therapy.

[8b] Biologic-failed participants: Participants who have an inadequate response to, loss of response to, or are intolerant to an approved biologic therapy for CD (such as anti-TNF antibodies or anti-integrin antibodies). Investigators must be able to document an adequate history of induction and/or maintenance dose use. Participants should fulfill 1 of the following criteria:

- Inadequate response: Signs and symptoms of persistently active disease despite induction treatment at the approved induction dosing, that was indicated in the product label at the time of use,

OR

- Loss of response: Recurrence of signs and symptoms of active disease following prior clinical benefit during treatment with approved maintenance dosing,

OR

- Intolerance: History of intolerance to infliximab, adalimumab, certolizumab pegol, vedolizumab, natalizumab, or other approved biologics (including but not limited to infusion-related event, demyelination, congestive heart failure, or any other drug-related AE that led to a reduction in dose or discontinuation of the medication).

Key exclusion criteria

Participants were excluded from the study enrolment if they had

- a current diagnosis of UC or IBD unclassified
- currently or were suspected to have an abscess
- a bowel resection within 6 months or intra-abdominal surgery within 3 months of baseline
- complications of CD such as symptomatic strictures or stenosis, short bowel syndrome, or any other manifestation that would possibly confound assessment of treatment effect
- discontinued an anti-IL 12/23p40 antibody (for example, ustekinumab) due to primary nonresponse or secondary loss of response or intolerance OR who received more than the IV induction dose and 1 SC dose
- a history or current evidence of cancer of the gastrointestinal tract
- current infections such as tuberculosis, hepatitis B, hepatitis C, Clostridium difficile, and opportunistic extraintestinal infections.

- **Treatments**

Participants were randomized in a 6:3:2 ratio to receive mirikizumab, ustekinumab, or placebo, in Induction Period (Weeks 0 to 12). In Maintenance Period, there were 4 intervention groups (Weeks 12 to 52). A double-dummy design was maintained throughout the study to mask differences in treatment and in frequency of treatment administration.

Induction Period (Weeks 0 to 12)

- Mirikizumab: 900 mg IV Q4W (Weeks 0, 4, and 8)
- Ustekinumab: ~6 mg/kg IV at Week 0 and 90 mg SC at Week 8
- Placebo

Maintenance Period (Weeks 12 to 52)

- Mirikizumab: 300 mg SC Q4W
- Ustekinumab: 90 mg SC Q8W
- Placebo:

When the Induction Period concluded at Week 12,

- responders continued to receive IV and SC placebo dosing as applicable, at Weeks 12 to 20, then SC placebo Weeks 24 to 52, and
- nonresponders received blinded mirikizumab therapy: 3 doses of 900 mg IV Q4W followed by 300 mg SC Q4W

Nonresponse was defined as failing to

- achieve at least a 30% decrease in SF, AP, or both, and
- be no worse than baseline.

Concomitant and rescue therapies

Table: Permitted Prior/Concomitant Medications with Dose Stabilization

Drug Class	Stabilization
Oral 5-ASAs	○ Prescribed dose must have been stable for at least 2 weeks before screening endoscopy; doses should remain stable throughout the study unless medication is discontinued due to a toxicity related to the medication.
Oral corticosteroids (prednisone ≤30 mg/day or equivalent, or budesonide ≤9 mg/day)	○ Prescribed dose must have been stable for at least 2 weeks before screening endoscopy and should remain stable until Week 12.
Immunomodulators (for example, AZA, 6-MP, or MTX)	○ Prescribed at stable dose for at least 8 weeks before screening endoscopy; doses should remain stable throughout study unless medication is discontinued due to a toxicity related to the medication.
Antibiotics (for treatment of CD)	○ May continue if the prescribed dose has been stable 4 weeks prior to baseline or stopped treatment at least 3 weeks prior to screening endoscopy.

Abbreviations: 5-ASA = 5-aminosalicylic acid; 6-MP = 6-mercaptopurine; AZA = azathioprine; CD = Crohn's disease; MTX = methotrexate.

Corticosteroid taper

At Week 12, participants who were receiving corticosteroids and who achieved clinical response, as assessed by PRO, initiated corticosteroid tapering as instructed in the protocol. Participants who achieved clinical response after Week 12 initiated the corticosteroid taper at the visit in which clinical response was achieved.

The recommended tapering schedule for oral corticosteroids (other than budesonide) was as follows:

- Dose >10 mg/day prednisone or equivalent: taper daily dose by 5 mg/week until receiving 10 mg/day, and then continue tapering at 2.5 mg/week until 0 mg/day.
- Dose ≤10 mg/day prednisone or equivalent: taper daily dose by 2.5 mg/week until 0 mg/day.

For participants receiving oral budesonide, the recommended tapering schedule was to have their dose tapered by 3 mg every 3 weeks until 0 mg/day.

Rescue medicine

The study did not include rescue therapy for participants who were assigned to active study drug. Participants in the placebo group who were non-responder at Week 12 received mirikizumab.

- **Objectives**

The primary hypothesis tested in this study is that mirikizumab is superior to placebo with regards to the co-primary endpoints. Please also refer to below chapter on Outcomes/endpoints.

- **Outcomes/endpoints**

Co-primary endpoint:

To evaluate the efficacy of mirikizumab is superior to placebo as assessed by

- clinical response by PRO at **Week 12** and endoscopic response at **Week 52**
- clinical response by PRO at **Week 12** and clinical remission by CDAI at Week 52

Clinical response by PRO is defined as at least a 30% decrease in SF and/or AP with neither score worse than baseline.

Endoscopic response is defined as ≥50% reduction from baseline in SES-CD Total Score.

Clinical remission by CDAI is defined as CDAI total score <150.

Secondary objectives and endpoints

There were several secondary endpoints in the study. Main secondary endpoints were under multiplicity adjustment.

Table: Main secondary objective and endpoints

Major Secondary[a,b]	
To evaluate the efficacy of mirikizumab is superior to placebo at Week 52 as assessed by • endoscopic response • clinical remission by CDAI	• Proportion of participants achieving endoscopic response[d] at Week 52 • Proportion of participants achieving clinical remission by CDAI[e] at Week 52
To evaluate the efficacy of mirikizumab is superior to placebo at Week 12 as assessed by • endoscopic response • endoscopic remission • clinical response by PRO • clinical remission by CDAI • FACIT-Fatigue scores	• Proportion of participants achieving endoscopic response[d] at Week 12 • Proportion of participants achieving endoscopic remission SES-CD ≤4[i] at Week 12 • Proportion of participants achieving clinical response by PRO[c] at Week 12 • Proportion of participants achieving clinical remission by CDAI[e] at Week 12 • Change from baseline in FACIT-Fatigue scores at Week 12
To evaluate the efficacy of mirikizumab is superior to placebo as assessed by both clinical response by PRO at Week 12 and each below, individually: • clinical remission by PRO at Week 52 • endoscopic remission at Week 52 • corticosteroid-free clinical remission by CDAI	Proportion of participants achieving clinical response by PRO[c] at Week 12 and each below, individually: • Clinical remission by PRO[f] at Week 52 • Endoscopic remission SES-CD ≤4[i] at Week 52 • Corticosteroid-free from Week 40 to Week 52 and clinical remission by CDAI[e] at Week 52
To evaluate the efficacy of mirikizumab in comparison to ustekinumab at Week 52 as assessed by • endoscopic response (superior) • clinical remission by CDAI (non-inferior)	Proportion of participants achieving • Endoscopic response[d] at Week 52 • Clinical remission by CDAI[e] at Week 52

Table: Other secondary objective and endpoints

Other Secondary	
To evaluate the efficacy of mirikizumab is superior to placebo at Week 12 as assessed by • clinical remission by PRO • clinical response by CDAI • endoscopic remission SES-CD Total Score 0-2 • endoscopic response and clinical response by CDAI • endoscopic response and clinical remission by CDAI • Urgency NRS ≤2 in participants with baseline Urgency NRS ≥3	Proportion of participants achieving • Clinical remission by PRO[f] at Week 12 • Clinical response by CDAI[g] at Week 12 • Endoscopic remission[h] at Week 12 • Endoscopic response[d] and clinical response by CDAI[g] at Week 12 • Endoscopic response[d] and clinical remission by CDAI[e] at Week 12 • Urgency NRS ≤2 at Week 12 in participants with baseline Urgency NRS ≥3
To evaluate the efficacy of mirikizumab is superior to placebo as assessed by both clinical response by PRO at Week 12 and each below, individually: • Clinical response by CDAI at Week 52 • Clinical response by PRO at Week 52 • Endoscopic remission SES-CD Total Score 0-2 at Week 52 • Stability of clinical remission by CDAI from Week 12 to Week 52 • Durability of endoscopic response at Week 12 and Week 52 • Durability of endoscopic remission at Week 12 and Week 52 • Endoscopic remission and clinical remission by CDAI at Week 52 • Endoscopic response and clinical remission by CDAI at Week 52 • Corticosteroid-free clinical remission by CDAI among participants who used corticosteroids at baseline • Urgency NRS ≤2 at Week 52 in participants with baseline Urgency NRS ≥3	Proportion of participants achieving clinical response by PRO[c] at Week 12 and each below, individually: • Clinical response by CDAI[g] at Week 52 • Clinical response by PRO[c] at Week 52 • Endoscopic remission[h] at Week 52 • Stability of clinical remission by CDAI[e] from Week 12 to Week 52 • Durability of endoscopic response[d] at Week 12 and Week 52 • Durability of endoscopic remission[i] at Week 12 and Week 52 • Endoscopic remission[i] and clinical remission by CDAI[e] at Week 52 • Endoscopic response[d] and clinical remission by CDAI[e] at Week 52 • Corticosteroid-free from Week 40 to Week 52 and clinical remission by CDAI[e] at Week 52 in participants who used corticosteroids at baseline • Urgency NRS ≤2 at Week 52 in participants with baseline Urgency NRS ≥3.
To evaluate the efficacy of mirikizumab is superior to placebo at Week 52 as assessed by Urgency NRS	Change from baseline in Urgency NRS at Week 52
To evaluate the efficacy of mirikizumab is superior to placebo in clinical response by CDAI at Week 4	Proportion of participants achieving clinical response by CDAI[g] at Week 4

Objectives	Endpoints
To evaluate the efficacy of mirikizumab is superior to placebo in mITT population as assessed by • clinical response by PRO at Week 12 and endoscopic response at Week 52 • clinical response by PRO at Week 12 and clinical remission by CDAI at Week 52	• Proportion of participants achieving clinical response by PRO[c] at Week 12 and endoscopic response[d] at Week 52 • Proportion of participants achieving clinical response by PRO[c] at Week 12 and clinical remission by CDAI[e] at Week 52
To evaluate the efficacy of mirikizumab is superior to placebo in not-biologic-failed and biologic-failed subgroups	Proportion of participants achieving • Endoscopic response[d] at Week 12 • Clinical remission by CDAI[e] at Week 12 Proportion of participants achieving clinical response by PRO[c] at Week 12 and each below at Week 52, individually: • Endoscopic response[d] • Endoscopic remission SES-CD ≤4[i] • Clinical remission by CDAI[e]
To evaluate the efficacy of mirikizumab in comparison to placebo in health outcomes and quality of life measures, symptomatic endpoints, inflammatory biomarkers	Proportion of participants achieving each below over time • Clinical remission by CDAI[e] • Clinical response by CDAI[g] • Clinical remission by PRO[f] • Clinical response by PRO[c] Change from baseline at Week 12 and Week 52 of each below: • C-reactive protein • Fecal calprotectin • FACIT-Fatigue scores (Week 52 only) • EQ-5D-5L • WPAI:CD scores • Medical Outcomes SF-36 Version 2 acute scores • IBDQ
To evaluate the efficacy of mirikizumab in comparison to placebo for other assessments	Proportion of participants • had no EIMs among those who had EIMs at baseline • CD-related emergency room visits • CD-related hospitalization • CD-related surgeries Proportion of participants achieving clinical response by PRO[c] at Week 12 and each below evaluated at Week 24, and at Week 52, individually: • ≥50% reduction from baseline in the number of draining cutaneous fistulae

Objectives	Endpoints
	• Closure of all draining cutaneous fistulae in participants who had any draining cutaneous fistulae at baseline
To evaluate the efficacy of mirikizumab in comparison to ustekinumab as assessed by • Endoscopic response at Week 12 (superior) • Endoscopic remission at Week 52 (superior) • Clinical remission by CDAI at Week 12 (non-inferior) • Clinical response by CDAI at Week 12 (non-inferior) • Clinical response by CDAI at Week 52 (non-inferior) • Corticosteroid-free clinical remission by CDAI at Week 52 (non-inferior) • Clinical response by PRO at Week 12 • Clinical response by PRO at Week 52 • Clinical remission by PRO at Week 12 • Clinical remission by PRO at Week 52	Proportion of participants achieving • Endoscopic response[d] at Week 12 • Endoscopic remission SES-CD ≤4[i] at Week 52 • Clinical remission by CDAI[e] at Week 12 • Clinical response by CDAI[g] at Week 12 • Clinical response by CDAI[g] at Week 52 • Corticosteroid-free clinical remission by CDAI[e] at Week 52 • Clinical response by PRO[c] at Week 12 • Clinical response by PRO[c] at Week 52 • Clinical remission by PRO[f] at Week 12 • Clinical remission by PRO[f] at Week 52
To evaluate the efficacy of mirikizumab in comparison to ustekinumab in not-biologic-failed and biologic-failed subgroups	Proportion of participants achieving • Endoscopic response[d] at Week 52 • Endoscopic remission SES-CD ≤4[i] at Week 52 • Clinical remission by CDAI[e] at Week 52 • Endoscopic response[d] at Week 12 • Clinical remission by CDAI[e] at Week 12
To evaluate the pharmacokinetic and pharmacokinetic/pharmacodynamic relationships of mirikizumab	• Clearance and volume of distribution of mirikizumab • Relationship between mirikizumab exposure and efficacy

- **Sample size**

Approximately 3000 participants may be screened to achieve a total of approximately 1100 participants randomly assigned to study intervention. Based on a 6:3:2 randomization ratio, approximately 600 participants will be randomized to mirikizumab, 300 participants to ustekinumab, and 200 participants to placebo.

Approximately 90% of randomized participants are expected to meet the Primary Analysis Set definition. A sample size of 990 participants (540 participants in mirikizumab and 180 participants in placebo) provides >90% power to demonstrate that mirikizumab is superior to placebo for the co-primary endpoint of (1) clinical response by PRO at Week 12 and clinical remission by CDAI at Week 52 and (2) clinical response by PRO at Week 12 and endoscopic response at Week 52. This estimated power is based on a 2-sided chi-square test with alpha = 0.005 and the assumed treatment response rates of the co-primary endpoint are 33% for mirikizumab and 10% for placebo. The sample size based on the Primary Analysis Set also provides >90% power to demonstrate that mirikizumab is superior to ustekinumab for endoscopic response at Week 52. This calculation is based on a 2-sided chi-square test with alpha =

0.045 and assuming a difference of at least 16% between mirikizumab and ustekinumab in endoscopic response at Week 52.

Blinded sample-size re-estimation may be performed before the last participant has been enrolled in the study. For this re-estimation, response rates using blinded data will be evaluated and compared with the assumed response rates. The sample size from the study is estimated to be between a minimum sample size, 1100 participants, and a predefined, maximum sample size up to 1210 participants. If the re-estimated sample size is smaller than the planned minimum sample size, the study may enroll to the recalculated sample size. If the re-estimated sample size is larger than the planned minimum sample size, the team will decide whether to increase the sample size, up to a predefined maximum, or to accept the re-assessed reduced power reduction in power.

- **Randomisation and Blinding (masking)**

Assignment to treatment groups was determined by a computer-generated random sequence using an IWRS.

Blinding

This was a double-blind study. All treatments were blinded. To maintain the blind, placebo were administered as appropriate, either by IV, SC, or both. All study assessments were done by study personnel who were blinded to the participant's treatment assignment.

Emergency unblinding for AEs could be performed through the IWRS, which may supplement or take the place of emergency codes generated by a computer drug-labeling system. This option was to be used ONLY if the participant's well-being required knowledge of the participant's treatment assignment. All notifications resulting in an unblinding event were recorded and reported by the IWRS.

If an investigator, site personnel performing assessments, or participant was unblinded, the participant discontinued from the study drug and must complete the ETV and post-treatment follow-up visits. In cases where there was ethical reasons to have the participant continue on the study drug, the investigator had to obtain specific approval from the sponsor or designee for the participant continue.

A limited number of preidentified individuals could gain access to unblinded data, as specified in the unblinding plan, prior to the database lock, in order to initiate the final population PK/pharmacodynamic (PD) model development processes for analyses. Information which could unblind the study during the analyses were not shared with study sites or the blinded study team until the study has been unblinded. Unblinding details were specified in the unblinding plan section of the statistical analysis plan (SAP) or a separate unblinding plan document.

- **Statistical methods**

Estimands

For the binary co-primary endpoints, a composite strategy was used where intercurrent events (ICEs) are included in the endpoint definition. Successful response defined only if:

- response criteria definition met (as defined in the SAP)
- no study intervention discontinuation prior to time point of interest, and
- do not meet any of the specified changes in the concomitant CD medication prior to time point of interest

The MAH also defines in the same SAP the following as ICEs:

- Discontinuation of study intervention prior to time point of interest. Note: participants who take prohibited medications are required to discontinue the study treatment.

- Specified changes in concomitant CD medications (Appendix 10 [Section 6.10]) prior to time point of interest.
- Non-responders at Week 12 in Placebo arm switch to mirikizumab

For the two major secondary binary endpoints, proportion of participants achieving endoscopic response at Week 52 and proportion of participants achieving clinical remission by CDAI at Week 52, a hybrid strategy was used to accommodate the additional ICE where participants in the placebo group switch to mirikizumab at Week 12. For this ICE a hypothetical scenario was envisaged in which these participants remained on placebo for the rest of the study and measurements after this ICE were imputed (i.e. as non-responders). For all other ICEs the composite strategy as above was used.

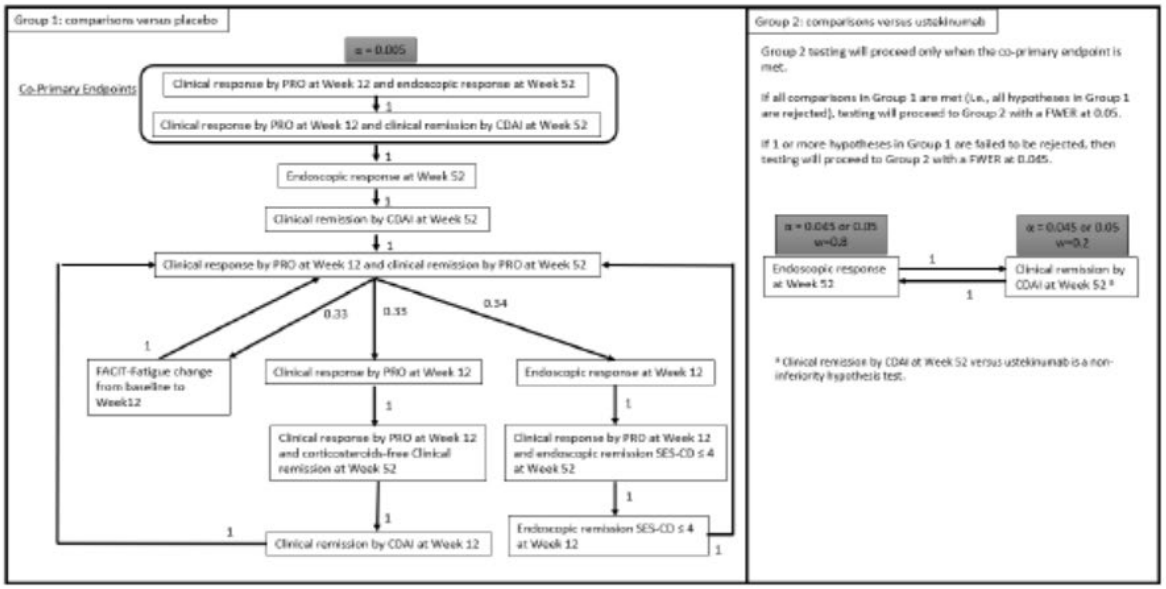
For continuous endpoints, a hybrid strategy was used. For ICEs of study intervention discontinuation and specified changes in the concomitant CD medication, the composite strategy was used such that measurements after the ICEs return to baseline. For the additional ICE where participants in the placebo group switch to mirikizumab at Week 12, a hypothetical scenario is envisaged in which these participants remained on placebo for the rest of the study and measurements after this ICE were to be imputed using MMRM methods.

Analysis Methods

The primary analysis used CMH chi-square test to compare mirikizumab to placebo adjusting for the selected stratification factors with NRI. The common risk difference and the odds ratio adjusted for the selected stratification factors with the 2-sided 99.5% CI were presented. The primary analysis was also supported with sensitivity and additional analyses using the mITT population and PAS, exclude participants impacted by crisis. A logistic regression analysis using NRI was used to analyze the two co-primary endpoints for the PAS as a sensitivity analysis. In addition, a tipping point analysis was used. Supplementary analyses included an evaluation of the impact of the additional condition of clinical response by PRO at Week 12 on clinical remission by CDAI and endoscopic response at Week 52.

Multiplicity

For testing the primary and major secondary hypotheses, a prespecified graphical scheme (Bretz et al. 2009, 2011) was implemented to control the FWER at a 2-sided alpha level of 0.05 as described below:



Abbreviations: CDAI = Crohn's Disease Activity Index; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue; PRO = patient-reported outcome; SES-CD = Simple Endoscopic Score for Crohn's Disease.

Two groups including co-primary and major secondary hypotheses were used. Group 1 will include the co-primary endpoints and all major secondary endpoints that involve comparisons versus placebo, and Group 2 included all major secondary endpoints that involved comparisons versus ustekinumab. Within each group, the graphical scheme controls the FWER at a prespecified level. For Group 1, a FWER at 0.005 was to be used. For Group 2, a FWER of 0.05 was to be used if all hypotheses in Group 1 were rejected; a FWER of 0.045 was to be used if 1 or more hypotheses in Group 1 were not rejected.

Additional and supplementary analyses were not controlled for type I error, and therefore may be considered as only supportive.

Results

- **Participant flow**

A total of 2665 participants were screened. Of these **1152** participants were randomly assigned to treatment in Study AMAM. These participants comprised the ITT population.

In the ITT population, 1105 (95.9%) participants completed Induction Period and 949 (87.1%, relative to participants entering Maintenance Period) completed Maintenance Period. The ITT population was used for disposition and demographic analyses.

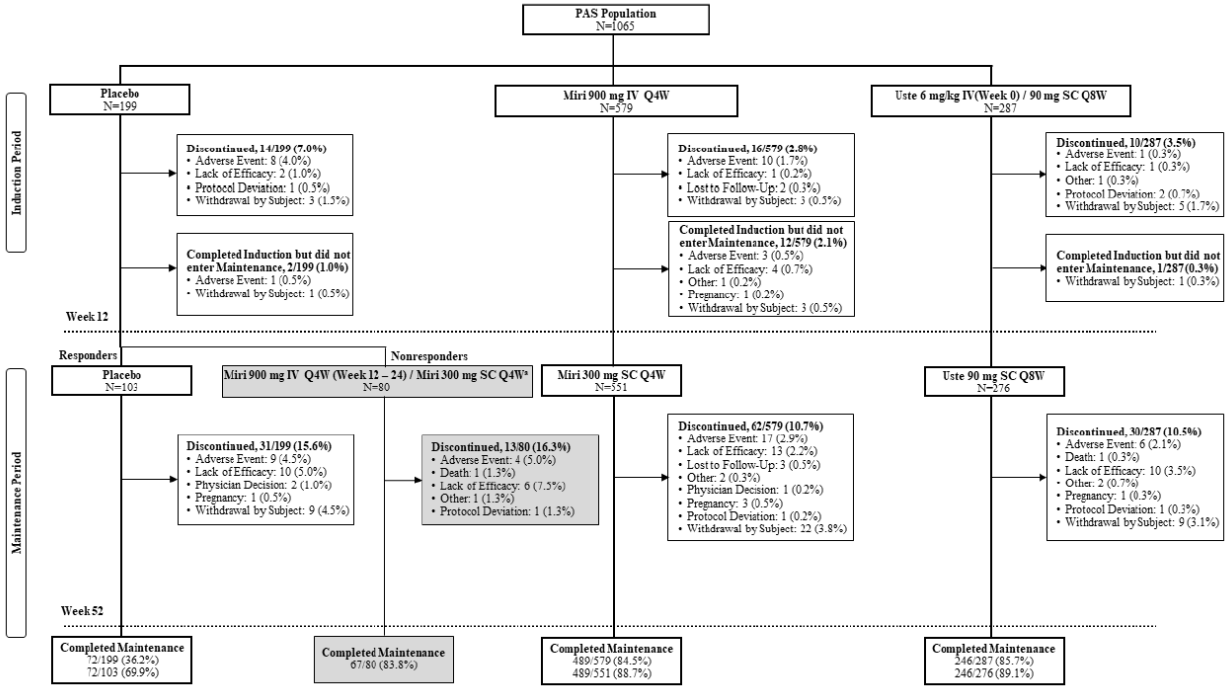
Of these 1152 ITT participants, 1150 took at least 1 dose of study treatment. These participants comprised the mITT population. The mITT population was used for sensitivity analysis for the co-primary endpoints, disposition, and demographic analyses.

Of these 1150 participants, 1065 had a baseline SES-CD of 7 or greater (4 or greater for isolated ileal disease). These participants comprised the Primary Analysis Set (PAS) population.

Of these 1065 participants randomly assigned to treatment, 1025 (96.2%) participants completed Induction Period and 874 (82.1%) completed Maintenance Period. The PAS population was used for efficacy, biomarkers, health outcomes, disposition, and demographic analyses.

No patterns were observed for reasons of discontinuation from the study in either period. The most frequently cited reasons for discontinuation in the PAS population during Induction Period were AE and withdrawal by subject, and during Maintenance Period were withdrawal by subject, lack of efficacy, and AE.

Figure: Participant flow



- **Recruitment**

Study Initiation Date: 23 July 2019 first participant first visit.

Study Completion Date: 23 August 2023 last participant last visit.

The analyses presented in this report are based on a database lock date of 04 October 2023.

- **Conduct of the study**

There were a number of amendments in the study.

Table: Protocol Amendment Summary

Milestone	Approval Date	Key Changes
I6T-MC-AMAM (Original protocol)	25 Mar 2019	N/A
Protocol Amendments		
I6T-MC-AMAM (a)	08 Apr 2020	The amendment prolonged the Screening period by 1 week, updated the inclusion and exclusion criteria, and revised the other secondary endpoints to include comparison of mirikizumab versus placebo for clinical response, endoscopic response, and clinical remission.
I6T-MC-AMAM (b)	18 Dec 2020	The primary rationale for this amendment was the addition of Appendix 12 – Provisions for Changes in Study Conduct During Exceptional Circumstances. The amendment updated Appendix 6 on Prohibited Medications. The amendment also revised restrictions on screen failures.
I6T-MC-AMAM (c)	01 Apr 2021	The amendment updated the inclusion criterion to allow up to 10% of the participant population with SES-CD score ≥3 with ulceration as a component of this total score along with other changes.
I6T-MC-AMAM (d)	07 Feb 2022	The amendment revised the co-primary and secondary objectives and endpoints in response to FDA feedback. The amendment updated co-primary endpoints from endoscopic response at Week 52 and clinical remission by PRO at Week 52 to composite co-primary endpoints of clinical response by PRO at Week 12 and endoscopic response at Week 52, and clinical response by PRO at Week 12 and clinical remission by CDAI at Week 52. The amendment was approved internally. However, it was not implemented at sites due to an error in the header.
I6T-MC-AMAM (e)	23 Feb 2022	Amendment e implemented all of the updates reflected in Amendment d. No further updates were made in Amendment e.
Protocol Addenda		
I6T-MC-AMAM (Addendum 8.2)	26 Jul 2022	This addendum allows the local labs for collection of samples in China if the laboratory samples cannot be collected and shipped to the central laboratory due to unforeseen circumstances (for example, COVID-19 government shutdowns), and allowed local laboratory tests to be utilized for data analysis.
I6T-MC-AMAM (Addendum 19)	30 Jan 2022	This addendum provides the objectives and methods associated with conducting exit interviews with AMAM participants to explore key patient-reported outcomes in terms of meaningful improvement.
I6T-MC-AMAM (Addendum 20)	15 Jun 2022	This addendum was performed in Ukraine. If the laboratory samples could not be collected and shipped to the central laboratory due to unforeseen circumstances, the sites were

Milestone	Approval Date	Key Changes
		allowed to utilize a local laboratory. The local laboratory results for hematocrit from the hematology panel were allowed to be included for data analysis.
I6T-MC-AMAM (Addendum 21)	15 Jun 2022	This addendum was performed in Russia. If the laboratory samples could not be collected and shipped to the central laboratory due to unforeseen circumstances, the sites were allowed to utilize a local laboratory. The local laboratory results for hematocrit from the hematology panel were allowed to be included for data analysis.

Abbreviations: AP = abdominal pain; CDAI = Crohn's Disease Activity Index; COVID-19 = coronavirus disease 2019; FDA = Food and Drug Administration; N/A = not applicable; PRO = 2 of the patient-reported items of the CDAI (SF and AP); SES-CD = Simple Endoscopic Score for Crohn's Disease; SF = stool frequency.

Summary of COVID-19 impact

Study AMAM had been ongoing during the global COVID-19 pandemic, which resulted in some participants being unable or unwilling to attend onsite clinic visits and have study procedures performed. Mitigations for COVID-19, consistent with the FDA guidance Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency (FDA 2020), were initially implemented as emergency measures and were subsequently incorporated into the Exceptional Circumstances Appendix added to Study AMAM on 13 January 2021. Protocol amendment (b) changed Visit 5 in Period 1 to a phone visit to avoid risk of an unnecessary visit to the site during the COVID-19 pandemic, as participants did not receive study drug at this visit and no on-site assessments were required.

Statistical Results

A total of 195 (17.0%) participants reported important protocol deviations mitigations or other study disruptions related to the COVID-19 pandemic. Among these participants, 193 (16.8%) COVID-19-related AEs and 3 COVID-related important protocol deviations/mitigations were reported. No participants died due to a COVID-19-related AE. No participants discontinued study treatment due to a COVID-19-related AE or COVID-19- related issue (for example site or travel restriction).

For the co-primary endpoints, missing data were imputed using modified nonresponder imputation as a sensitivity analysis. Missing data for reasons including the COVID-19 pandemic, were imputed by multiple imputation.

Summary of Russia-Ukraine war impact

Based upon the development of the Russia-Ukraine war the following decisions were made for Study AMAM Ukraine and Russia sites:

- 01 March 2022: At all study sites in Ukraine, participants in screening were discontinued and enrollment was closed.
- 02 March 2022: At all study sites in Russia, screening was paused.

Enrolled participants were allowed to continue in the study, provided the investigator felt it was safe and in the best interest of the participant while maintaining the scientific integrity of the trial.

Statistical Results

A total of 5 (0.4%) participants reported important protocol deviations mitigations or other study disruptions related to the Russia-Ukraine war. No participants reported having a war-related AE.

A total of 3 (0.3%) participants discontinued study treatment due to a war-related issue. Six (0.5%) war-related important protocol deviations/mitigations were reported.

For the co-primary endpoints, missing data were imputed using modified nonresponder imputation as a sensitivity analysis. Missing data for reasons including the Russia-Ukraine war were imputed by multiple imputation.

Protocol Deviations

Important protocol deviations include those that might have meaningful effects on the accuracy, completeness, or reliability of study data or those that could affect the rights, safety, or well-being of a study participant.

A total of 281 (26.4%) participants reported important protocol deviations during the Treatment Regimen Period (Periods 1 and 2) in the PAS population. The most frequently reported important protocol deviations were related to

- study procedure compliance (n=115 [10.8%]),
- informed consent (n=69 [6.5%]), and
- eligibility criteria (n=60 [5.6%]).

In the mirikizumab treatment group, there were 149 (25.7%) participants with important protocol deviations. The most frequently reported important protocol deviations were

- study procedure compliance (n=64 [11.1%]),
- informed consent (n=35 [6.0%]), and
- visit schedule criteria (n=29 [5.0%]).

In the placebo group, there were 58 (29.1%) participants with important protocol deviations. The most frequently reported important protocol deviations were

- study procedure compliance (n=21 [10.6%]),
- visit schedule criteria (n=17 [8.5%]), and
- informed consent (n=15 [7.5%]).

Similar frequencies of important protocol deviations were reported in the ustekinumab group. The Sponsor concluded that these deviations did not impact the efficacy or safety results of the study in a clinically meaningful manner.

Table: Important Protocol Deviations, Primary Analysis Set, I6T-MC-AMAM – Study Treatment Period

Data Cutoff: 25AUG2025

	placebo (N=199)	miri (N=579)	uste (N=287)	Total (N=1065)
Study Specific Deviation Term	n(%)	n(%)	n(%)	n(%)
Subjects with >=1 Important Protocol Deviation	58 (29.1)	149 (25.7)	74 (25.8)	281 (26.4)
Blinding	0 (0.0)	2 (0.3)	0 (0.0)	2 (0.2)
Concomitant Medication	4 (2.0)	4 (0.7)	3 (1.0)	11 (1.0)
Discontinuation Criteria	1 (0.5)	1 (0.2)	0 (0.0)	2 (0.2)
Eligibility Criteria	14 (7.0)	27 (4.7)	19 (6.6)	60 (5.6)
Informed Consent	15 (7.5)	35 (6.0)	19 (6.6)	69 (6.5)
Investigational Medicinal Product and/or Investigational Device	4 (2.0)	7 (1.2)	2 (0.7)	13 (1.2)
Other Protocol Deviation	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
Safety Reporting	4 (2.0)	7 (1.2)	5 (1.7)	16 (1.5)
Study Procedure Compliance	21 (10.6)	64 (11.1)	30 (10.5)	115 (10.8)
Treatment Assignment/Randomization	1 (0.5)	6 (1.0)	5 (1.7)	12 (1.1)
Visit Schedule Criteria	17 (8.5)	29 (5.0)	7 (2.4)	53 (5.0)

Abbreviations: N = number of subjects in analysis population; n = number of subjects in the specified category; miri = mirikizumab; uste = ustekinumab.
Percentages are based on the treatment column denominator, N.
Program Location: /lillyce/prd/ly3074828/i6t_mc_amam/intrm1/programs/tfl/t_c_imp_cat_pas_st.sas
Output Location: /lillyce/prd/ly3074828/i6t_mc_amam/intrm1/output/restricted/tfl/t_c_imp_cat_pas_st.rtf
Data Set Location: /lillyce/prd/ly3074828/i6t_mc_amam/intrm1/data/analysis/restricted

Serious breach

At Site 556, Participant was enrolled and randomly assigned despite meeting the following 2 exclusion criteria:

- #39: have an unstable or uncontrolled illness (…) that would potentially affect participant safety, and
- #43: are unsuitable for inclusion in the study in the opinion of the investigator or sponsor for any reason that may compromise the participant's safety or confound data interpretation.

The participant died of Cardiac arrest, which was subsequently adjudicated as cardiovascular death.

Enrolment of this participant was confirmed to be a serious breach of safety of trial participant. This site was closed after this serious breach. The participant is not included in the PAS population. The serious breach concerning this participant did not impact overall data integrity of the study.

- **Baseline data**

Demographic and Other Baseline Characteristics

In the PAS population, demographic characteristics, disease history, and baseline disease characteristics were overall well-balanced across treatment groups and consistent with a population with moderately to severely active CD. Similar demographics and baseline disease characteristics were reported in the ITT and mITT population.

The original primary endpoint of clinical remission was based on AP and SF and later updated to use CDAI, based on regulatory feedback. However, the entry criteria defining moderately to severely active disease based on AP and SF were not changed. As a result, some of the enrolled participants had baseline CDAI values outside of the usual range of 220 to 450, though they still demonstrated moderately to severely active disease based on AP and SF. A total of 116 (11.0%) participants had baseline CDAI values <220, and 79 (7.5%) participants had baseline values ≥450. Percentages of participants outside the usual range were equally distributed across treatment groups.

In the PAS population, China enrolled the largest proportion of participants (14.3%), followed by Poland (13.1%), the United States (10.1%), and Ukraine (7.9%).

Table. Summary of Selected Baseline Demographic Characteristics PAS Population

	Pbo (N = 199)	Miri (N = 579)	Uste (N = 287)
Sex, n (%)			
Female	81 (40.7)	247 (42.7)	150 (52.3)
Male	118 (59.3)	332 (57.3)	137 (47.7)
Age (years), mean (SD)	36.3 (12.71)	36.0 (13.22)	36.6 (12.72)
Age categories, n (%)			
<65 years	196 (98.5)	559 (96.5)	279 (97.2)
≥65 years	3 (1.5)	20 (3.5)	8 (2.8)
Race, n (%)			
American Indian/Alaska Native	2 (1.0)	2 (0.4)	2 (0.7)
Asian	42 (21.8)	148 (25.9)	74 (25.9)
Black/African American	5 (2.6)	10 (1.8)	8 (2.8)
White	144 (74.6)	408 (71.5)	201 (70.3)
Multiple	0	3 (0.5)	1 (0.3)
Ethnicity, n (%)[a]			
Hispanic or Latino	4 (21.1)	8 (13.3)	5 (17.2)
Not Hispanic or Latino	15 (78.9)	52 (86.7)	24 (82.8)
Geographic region, n (%)			
Asia	46 (23.1)	153 (26.4)	75 (26.1)
North America	27 (13.6)	77 (13.3)	37 (12.9)
Central/South America	9 (4.5)	30 (5.2)	20 (7.0)
Europe and ROW	117 (58.8)	319 (55.1)	155 (54.0)
Weight (kg), mean (SD)	69.55 (18.975)	68.02 (18.302)	66.86 (17.644)
BMI (kg/m^2), mean (SD)	23.766 (5.7537)	23.240 (5.4400)	23.333 (5.4631)

Abbreviations: BMI = body mass index; Miri = mirikizumab; n = number of participants in the specified category; N = number of participants in the PAS population; PAS = Primary Analysis Set; Pbo = placebo; ROW = rest of the world; SD = standard deviation; Uste = ustekinumab.

a Only includes responses from US sites.

Table. Summary of Selected Baseline Disease Characteristics PAS Population

PAS Population

	Pbo (N = 199)	Miri (N = 579)	Uste (N = 287)
Duration of CD (years), mean (SD)	7.8 (7.39)	7.4 (8.23)	7.2 (7.67)
Duration of CD ≥5 years, n (%)	107 (53.8)	274 (47.4)	144 (50.2)
Disease location, n (%)			
Ileal	19 (9.5)	65 (11.2)	29 (10.1)
Colonic	77 (38.7)	225 (38.9)	120 (41.8)
Ileal-colonic	103 (51.8)	289 (49.9)	138 (48.1)
Prior surgical bowel resection			
Yes	33 (16.6)	89 (15.4)	29 (10.1)
No	166 (83.4)	490 (84.6)	258 (89.9)
CDAI, mean (SD)	318.9 (86.15)	323.1 (85.84)	318.5 (93.18)
CDAI ≥300, n (%)	110 (56.4)	340 (59.4)	157 (55.1)
SES-CD, mean (SD)	13.1 (6.00)	13.5 (6.59)	13.9 (6.62)
SES-CD ≥12, n (%)	97 (48.7)	288 (49.7)	145 (50.5)
AP, mean (SD)	2.1 (0.57)	2.1 (0.58)	2.1 (0.64)
AP average ≥2, n (%)	151 (75.9)	452 (78.3)	206 (71.8)
SF, mean (SD)	5.8 (3.18)	5.7 (3.02)	5.7 (2.85)
SF average ≥7, n (%)	55 (27.6)	130 (22.6)	77 (26.8)
CRP (mg/L), median (range: Q1, Q3)	7.6 (2.9, 18.8)	8.5 (2.9, 25.0)	8.9 (3.4, 24.8)
Fecal calprotectin (µg/g), median (range: Q1, Q3)	1161.0 (324.0, 2170.0)	1315.0 (444.0, 2676.0)	1489.0 (519.0, 2814.0)

Abbreviations: AP = abdominal pain; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; CRP = C-reactive protein Miri = mirikizumab; n = number of patients in the specified category; N = number of patients in the PAS population; PAS = Primary analysis set; Pbo = placebo; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; SES-CD = Simple Endoscopic Score for Crohn's Disease; SF = stool frequency; Uste = ustekinumab.

Table Summary of Prior Failures of CD Therapies PAS Population

	Pbo (N = 199) n (%)	Miri (N = 579) n (%)	Uste (N = 287) n (%)
Prior corticosteroid failure	94 (47.2)	262 (45.3)	150 (52.3)
Prior immunomodulator failure	101 (50.8)	289 (49.9)	120 (41.8)
Prior biologic failure	97 (48.7)	281 (48.5)	139 (48.4)
Number of failed biologics			
1	66 (33.2)	175 (30.2)	91 (31.7)
2	25 (12.6)	82 (14.2)	42 (14.6)
>2	6 (3.0)	24 (4.1)	6 (2.1)
Prior anti-TNF failure	89 (44.7)	265 (45.8)	133 (46.3)
Prior anti-integrin failure	24 (12.1)	68 (11.7)	31 (10.8)
No prior biologic failure	102 (51.3)	298 (51.5)	148 (51.6)
Exposed but not failed	12 (6.0)	36 (6.2)	12 (4.2)
Not exposed	90 (45.2)	262 (45.3)	136 (47.4)

Abbreviations: CD = Crohn's disease; Miri = mirikizumab; n = number of participants in the specified category; N = number of participants in the PAS population; PAS = primary analysis set; Pbo = placebo; TNF = tumor necrosis factor; Uste = ustekinumab.

Note: Failure was defined as an inadequate response to, loss of response to, or intolerance to the medication.

Note: Anti-TNF alpha biologics include: infliximab, infliximab biosimilar, adalimumab, adalimumab biosimilar, and golimumab, and certolizumab pegol. Anti-integrin biologics include: natalizumab, and vedolizumab. Prior immunomodulators include: 6-mercaptopurine, azathioprine. other thiopurines and >/=25mg weekly intramuscular/subcutaneous methotrexate. Note that this is not exactly the same as the inclusion criteria defined in the protocol.

- **Numbers analysed**

Table: Analysis Populations in AMAM

Population	Description	N
Screening Population	**Definition:** All participants who signed informed consent. **Purpose:** Used for disposition analysis.	2665
PAS	**Definition:** All randomized participants who had baseline SES-CD ≥7 (or ≥4 for isolated ileal disease) and took at least 1 dose of study intervention, even if the participant did not take the assigned study intervention, did not receive the correct study intervention, or otherwise did not follow the protocol. **Purpose:** Used for efficacy, biomarkers, health outcomes, disposition and demographic.	1065
PAS, exclude participants impacted by crisis	**Definition:** All participants in PAS, excluding all affected participants at affected sites by crisis (i.e., specific to Russia-Ukraine war). **Purpose:** Used for sensitivity analysis for the co-primary endpoints and major secondary efficacy endpoints.	975
PAS, Not-Biologic-Failed Population	**Definition:** All participants in PAS who had not failed any biologic medication regardless of prior biologic exposure. **Purpose:** Used for efficacy-related analysis.	548
PAS, Biologic-Failed Population	**Definition:** All participants in PAS who had failed at least 1 biologic medication. **Purpose:** Used for efficacy-related analysis.	517
mITT Population	**Definition:** All randomized participants who took at least 1 dose of study intervention, even if the participant did not take the assigned study intervention, did not receive the correct study intervention, or otherwise did not follow the protocol. **Purpose:** Used for sensitivity analysis for the co-primary endpoints, disposition and demographics.	1150
ITT Population	**Definition:** All randomized participants, even if the participant did not take the assigned study intervention, did not receive the correct study intervention, or otherwise did not follow the protocol. **Purpose:** Used for disposition, demographics.	1152
Safety Population	**Definition:** Same as mITT Population. **Purpose:** Safety analysis for the Period 1 and for the Treatment Regimen Period was conducted on this population.	1150
All Active Treatment Safety Population	**Definition:** All randomized participants who received at least 1 dose of mirikizumab or ustekinumab, including • participants randomized to mirikizumab arm from Weeks 0 to 52 and participants randomized to placebo arm and were placebo nonresponders by PRO at Week 12 and switched to mirikizumab (from Week 12 to Week 52), and • participants randomized to ustekinumab arm from Weeks 0 to 52, and **Purpose:** Safety analysis for any active study intervention was conducted on this population.	1024

Abbreviations: AP = abdominal pain; CDAI = Clinical Disease Activity Index; ITT = intent-to-treat; mITT = modified intent-to-treat; N = number of participants in a population; PAS = Primary Analysis Set; PRO = 2 of the patient-reported items of the CDAI (SF and AP); SES-CD = Simple Endoscopic Score for Crohn's Disease; SF = stool frequency.

- **Outcomes and estimation**

Mirikizumab achieved co-primary endpoints and all major secondary endpoints compared with placebo. Mirikizumab demonstrated noninferiority to ustekinumab in Week 52 clinical remission by CDAI, while superiority over ustekinumab in Week 52 endoscopic response by SES-CD was not achieved.

Primary endpoints results

The primary objective of the study was met. A significantly greater percentage of participants achieved both co-primary endpoints at Week 52 in the mirikizumab group compared with the placebo group (p<.000001).

Supplementary analyses and sensitivity analyses showed consistent findings with the primary analyses.

Table: Co-Primary Endpoints (NRI) Treatment Regimen Period PAS Population

	Pbo (N = 199)	Miri[a] (N = 579)
Clinical Response by PRO[b] at Week 12 and Endoscopic Response by SES-CD at Week 52 (Co-Primary Endpoint)		
Response, n (%)	18 (9.0)	220 (38.0)
Common Risk Difference versus Pbo (99.5% CI), p-value		28.7 (20.6, 36.8), <.000001
Clinical Response by PRO[b] at Week 12 and Clinical Remission by CDAI at Week 52 (Co-Primary Endpoint)		
Response, n (%)	39 (19.6)	263 (45.4)
Common Risk Difference versus Pbo (99.5% CI), p-value		25.8 (15.9, 35.6), <.000001

Abbreviations: AP = abdominal pain; CDAI = Crohn's Disease Activity Index; CI = confidence interval; CMH = Cochran-Mantel-Haenzel test; IV = intravenous; Miri = mirikizumab; n = number of participants in the specified category; N = number of participants in the PAS population; NRI = nonresponder imputation; PAS = primary analysis set; Pbo = placebo; PRO = 2 of the patient-reported items of the CDAI (SF and AP); Q4W = every 4 weeks; SC = subcutaneous; SES-CD = Simple Endoscopic Score for Crohn's Disease; SF = stool frequency.

Note: Common risk difference and CMH test were adjusted by biologic-failed status (yes/no), baseline SES-CD total score (<12, ≥12), either baseline SF ≥7 and/or baseline AP ≥2.5 (yes or unknown/no).

a Mirikizumab dose regimen is 900 mg IV Q4W for 3 doses, then 300 mg SC Q4W.

b Clinical response by PRO is defined as at least a 30% decrease in SF and/or AP with neither score worse than baseline.

Supplemental analyses for co-primary endpoints

To assess the robustness of the co-primary results, 2 prespecified supplemental analyses were conducted. Results of these analyses are consistent with the results of the corresponding primary analyses.

Tipping-point analysis

The tipping-point analysis was used for endoscopic response at Week 52 and clinical remission by CDAI at Week 52 to impute Week 52 response rates of placebo Week 12 nonresponders in the hypothetical scenario where nonresponders would remain in the placebo group. Even in the most extreme case, which used observed response rates at Week 52 after participants switch to mirikizumab group, significantly higher response rates were observed in the mirikizumab group compared to the placebo group for endoscopic response at Week 52 (common risk difference = 31%; p<.000001) and clinical remission by CDAI at Week 52 (common risk difference = 17%; p= .000523).

Principal stratum

The principal stratum analysis was used to provide further context for the co-primary endpoints. By using the potential outcome framework, this analysis estimated the endoscopic response and clinical remission by CDAI rates at Week 52 among the subpopulation of participants who achieved, or hypothetically would have achieved, clinical response by PRO at Week 12 for both mirikizumab and placebo groups. In this subpopulation and under different assumptions, significantly higher response rates for endoscopic

response at Week 52 and clinical remission by CDAI at Week 52, were observed in the mirikizumab group compared to the placebo group.

Major Secondary Endpoints

Major Secondary Endpoints Comparing Mirikizumab versus Placebo

Statistically significant and clinically meaningful improvements were achieved for the mirikizumab group compared with the placebo group for all major secondary endpoints.

Table: Major Secondary Endpoints Comparing Mirikizumab versus Placebo (NRI) Treatment Regimen Period PAS Population

	Pbo (N = 199)	Miri[a] (N = 579)
Clinical Response by PRO[b] at Week 12		
Response, n (%)	103 (51.8)	409 (70.6)
Common Risk Difference versus Pbo (99.5% CI), p-value		18.9 (7.5, 30.3), p=.000001
Clinical Remission by CDAI at Week 12		
Response, n (%)	50 (25.1)	218 (37.7)
Common Risk Difference versus Pbo (99.5% CI), p-value		12.4 (2.2, 22.7), p=.001431
Endoscopic Response by SES-CD at Week 12		
Response, n (%)	25 (12.6)	188 (32.5)
Common Risk Difference versus Pbo (99.5% CI), p-value		19.7 (11.1, 28.2), <.000001
Endoscopic Remission by SES-CD at Week 12		
Response, n (%)	8 (4.0)	63 (10.9)
Common Risk Difference versus Pbo (99.5% CI), p-value		6.8 (1.6, 12.1), p=.003414
Endoscopic Remission by SES-CD at Week 12 -Alternative Definition[c]		
Response, n (%)	14 (7.0)	102 (17.6)
Common Risk Difference versus Pbo (99.5% CI), p-value		10.6 (4.1, 17.2), p=.000213
FACIT-Fatigue Change from Baseline at Week 12[d]		
LSM (SE)	2.64 (0.6)	5.86 (0.4)
LSM Difference versus Pbo (99.5% CI), p-value		3.22 (1.24, 5.19), p=.000005
Clinical Remission by CDAI at Week 52[e]		
Response, n (%)	39 (19.6)	313 (54.1)
Common Risk Difference versus Pbo (99.5% CI), p-value		34.6 (24.7, 44.4), <.000001
Endoscopic Response by SES-CD at Week 52[e]		
Response, n (%)	18 (9.0)	280 (48.4)
Common Risk Difference versus Pbo (99.5% CI), p-value		39.1 (31.0, 47.2), <.000001
Clinical Response by PRO[b] at Week 12 and Clinical Remission by PRO at Week 52		
Response, n (%)	39 (19.6)	263 (45.4)
Common Risk Difference versus Pbo (99.5% CI), p-value		25.7 (15.9, 35.6), <.000001

	Pbo (N = 199)	Miri[a] (N = 579)
Clinical Response by PRO[b] at Week 12 and Corticosteroid-Free from Week 40 to Week 52 and Clinical Remission by CDAI at Week 52		
Response, n (%)	37 (18.6)	253 (43.7)
Common Risk Difference versus Pbo (99.5% CI), p-value		25.0 (15.2, 34.7), <.000001
Clinical Response by PRO[b] at Week 12 and Endoscopic Remission by SES-CD at Week 52		
Response, n (%)	4 (2.0)	92 (15.9)
Common Risk Difference versus Pbo (99.5% CI), p-value		13.8 (8.7, 18.9), <.000001

Abbreviations: ANCOVA = analysis of covariance; AP = abdominal pain; CDAI = Crohn's Disease Activity Index; CI = confidence interval; CMH = Cochran-Mantel-Haenzel test; FACIT = Functional Assessment of Chronic Illness Therapy; IV = intravenous; LSM = least square mean; mBOCF = modified baseline observation carried forward ;Miri = mirikizumab; n = number of participants in the specified category; N = number of participants in the PAS population; NRI = nonresponder imputation; PAS = primary analysis set; Pbo = placebo; PRO = 2 of the patient-reported items of the CDAI (SF and AP); Q4W = every 4 weeks; SC = subcutaneous; SE = standard error; SES-CD = Simple Endoscopic Score for Crohn's Disease; SF = stool frequency.

Note: Common risk difference and CMH test were adjusted by biologic-failed status (yes/no), baseline SES-CD total score (<12, ≥12), either baseline SF ≥7 and/or baseline AP ≥2.5 (yes or unknown/no) for binary endpoints.

[a] Mirikizumab dose regimen is 900 mg IV Q4W for 3 doses, then 300 mg SC Q4W.

[b] Clinical response by PRO is defined as at least a 30% decrease in SF and/or AP with neither score worse than baseline.

[c] Endpoint not multiplicity-controlled.

[d] Analysis method used: ANCOVA with mBOCF.

Major Secondary Endpoints Comparing Mirikizumab versus Ustekinumab

Mirikizumab demonstrated noninferiority to ustekinumab in Week 52 clinical remission by CDAI. Superiority over ustekinumab in Week 52 endoscopic response by SES-CD was not achieved.

Table. Major Secondary Endpoints Comparing Mirikizumab versus Ustekinumab (NRI) Treatment Regimen Period PAS Population

	Miri[a] (N = 579)	Uste[b] (N = 287)
Clinical remission by CDAI at Week 52		
Response, n (%)	313 (54.1)	139 (48.4)
Common Risk Difference versus Uste (95% CI), p-value (non-inferiority)[c,d]	5.7 (-1.4, 12.8) <.0001	

	Miri[a] (N = 579)	Uste[b] (N = 287)
Endoscopic Response by SES-CD at Week 52		
Response, n (%)	280 (48.4)	133 (46.3)
Common Risk Difference versus Uste (95% CI), p-value	2.3 (-4.7, 9.3) .513623	

Abbreviations: AP = abdominal pain; CDAI = Crohn's Disease Activity Index; CI = confidence interval; CMH = Cochran-Mantel-Haenszel test; IV = intravenous; Miri = mirikizumab; n = number of participants in the specified category; N = number of participants in the PAS population; NRI = nonresponder imputation; PAS = primary analysis set; Q4W = every 4 weeks; Q8W = every 8 weeks; SC = subcutaneous; SES-CD = Simple Endoscopic Score for Crohn's Disease; SF = stool frequency; Uste = ustekinumab.

Note: Common risk difference and CMH test were adjusted by biologic-failed status (yes/no), baseline SES-CD total score (<12, ≥12), either baseline SF ≥7 and/or baseline AP ≥2.5 (yes or unknown/no).

a Mirikizumab dose regimen is 900 mg IV Q4W for 3 doses, then 300 mg SC Q4W.

b 6 mg/kg IV for one dose, then 90 mg SC Q8W starting at Week 8.

c p-value for non-inferiority is derived from the common risk difference with margin of 10%. The one-sided p-value was multiplied by 2 to be interpretable at standard alpha levels.

Sensitivity Analyses

To assess the robustness of the co-primary and major secondary efficacy results, several prespecified sensitivity analyses were conducted. Results of these analyses are consistent with the corresponding analyses from the primary analyses.

Sensitivity analyses to account for missing data and different strategies for intercurrent events (ICEs)

Sensitivity analyses

For the co-primary endpoints, missing data were imputed using modified NRI as a sensitivity analysis. Multiple imputation was used to impute missing data for reasons including

- the COVID-19 pandemic
- the Russia-Ukraine war, and
- treatment discontinuation due to lost to follow-up or pregnancy.

Sporadically missing data (that is, when a participant was still in the treatment period but data was not collected) were imputed by multiple imputation.

Additionally, the tipping point analysis was used for the co-primary endpoints to handle sporadically missing data.

For the continuous major secondary endpoint FACIT Fatigue change from baseline at Week 12, the jump to reference imputation was used to handle missing data and measurements after ICE.

For the analysis of co-primary and major secondary efficacy endpoints, sensitivity analyses were performed in the PAS population, excluding all affected participants at affected sites by crisis.

Sensitivity analyses using FDA definition for endoscopic response

The analysis of endoscopic response defined by >50% reduction from baseline in SES-CD total score was performed. The results were consistent with those for the analysis of endoscopic response defined by ≥50% reduction from baseline in SES-CD total score.

Sensitivity analysis for remission by PRO

Sensitivity analyses performed to evaluate clinical remission by PRO for mirikizumab compared to placebo using AP ≤1 combined with a range of SF thresholds (from ≤1 to ≤3) demonstrated that across the range of SF thresholds from ≤1 to ≤3 with AP ≤1 and neither score worse than baseline, mirikizumab consistently showed superiority over placebo with similar effect sizes regardless of the chosen SF remission threshold.

Table. Risk Differences for Mirikizumab versus Placebo Using Different Definitions of Remission by PRO Analysis Results (NRI),Treatment Regimen Period, PAS Population Study I6T-MC-AMAM

	Mirikizumab[a] vs Placebo Risk Difference, p-Value		
Remission Definition	**Week 12**	**Week 52[b]**	**Week 52 Composite[c] (Gated)**
AP ≤1 and SF ≤3	15.0%, p = 0.000093	34.0%, p<.000001	25.7%, p<.000001
AP ≤1 and SF ≤2.5	13.3%, p = .000396	32.8%, p<.000001	25.6%, p<.000001
AP ≤1 and SF ≤2	11.6%, p = .001483	33.2%, p<.000001	26.6%, p<.000001
AP ≤1 and SF ≤1.5	10.1%, p = .003396	30.3%, p<.000001	25.2%, p<.000001
AP ≤1 and SF ≤1	8.8%, p = .006733	27.8%, p<.000001	23.1%, p<.000001

Abbreviations: AP = abdominal pain; IV = intravenous; NRI = nonresponder imputation; PAS = primary analysis set; PRO = 2 of the patient-reported items of the CDAI (SF and AP); Q4W = every 4 weeks; SC = subcutaneous; SF = stool frequency.

a 900 mg IV Q4W for 3 doses, then 300 mg SC Q4W

b After Week 12, placebo-responders continued receiving placebo; placebo-nonresponders switched to mirikizumab, remained included in the placebo group and were imputed as nonresponders.

c Composite endpoint of clinical response by PRO (defined as at least a 30% decrease in SF and/or AP with neither score worse than baseline) and remission by PRO at Week 52.

Other secondary endpoints

Results from other, not multiplicity-controlled, secondary efficacy measures were generally consistent with and supportive of the co-primary and major secondary endpoint results, demonstrating a consistent trend of improvement during induction with sustained or continued numeric improvement of treatment effect through Week 52.

Analysis of Co-primary and Major Secondary Endpoints by Prior Biologic Failure

Biologic-failed subgroup includes all participants in PAS who had failed at least 1 biologic medication. Not-biologic-failed subgroup includes all participants in PAS who had not failed any biologic medication regardless of prior biologic exposure.

Mirikizumab showed nominally statistically significant and clinically meaningful improvements (non-multiplicity controlled) across most efficacy measures in biologic-failed and not-biologic failed subgroups compared with placebo. Response rates and treatment effect for mirikizumab compared with placebo were consistent across the biologic-failed and not-biologic-failed subgroups.

Table: Non-Multiplicity-Adjusted Co-primary Endpoints by Prior Biologic Failure (NRI) Treatment Regimen Period PAS Population

	Pbo (N = 199)	Miri[a] (N = 579)
Clinical Response by PRO[b] at Week 12 and Endoscopic Response by SES-CD at Week 52		
Biologic-Failed		
Response, n/Ns (%)	6/97 (6.2)	103/281 (36.7)
Unadjusted Risk Difference versus Pbo (95% CI), p-value[c]		30.5 (23.1, 37.9), <.000001
Not-Biologic-Failed		
Response, n/Ns (%)	12/102 (11.8)	117/298 (39.3)
Unadjusted Risk Difference versus Pbo (95% CI), p-value		27.5 (19.1, 35.9), <.000001
Clinical Response by PRO[b] at Week 12 and Clinical Remission by CDAI at Week 52		
Biologic-Failed		
Response, n/Ns (%)	12/97 (12.4)	122/281 (43.4)
Unadjusted Risk Difference versus Pbo (95% CI), p-value		31.0 (22.3, 39.8), <.000001
Not-Biologic-Failed		
Response, n/Ns (%)	27/102 (26.5)	141/298 (47.3)
Unadjusted Risk Difference versus Pbo (95% CI), p-value		20.8 (10.6, 31.1), .000289

Abbreviations: AP = abdominal pain; CDAI = Crohn's Disease Activity Index; CI = confidence interval; IV = intravenous; Miri = mirikizumab; n = number of participants in the specified category; N = number of participants in the PAS population; NRI = nonresponder imputation; Ns = number of patients in each subgroup; PAS = primary analysis set; Pbo = placebo; PRO = 2 of the patient-reported items of the CDAI (SF and AP); Q4W = every 4 weeks; SC = subcutaneous; SES-CD = Simple Endoscopic Score for Crohn's Disease; SF = stool frequency.

a Mirikizumab dose regimen is 900 mg IV Q4W for 3 doses, then 300 mg SC Q4W.

b Clinical response by PRO is defined as at least a 30% decrease in SF and/or AP with neither score worse than baseline.

c Fisher's exact test was used.

Note: Two of the participants could not be defined as having an inadequate response to, loss of response to, or intolerance to corticosteroids or immunomodulators.

Durability of Response

Durability of response to treatment for participants in the mirikizumab treatment group compared to placebo was demonstrated at Week 52 by endpoint analyses, including

- durability of endoscopic response defined as percentage of participants achieving endoscopic response at Week 12 and Week 52, and
- stability of clinical remission by CDAI defined as percentage of participants achieving clinical remission by CDAI for at least 80% of the visits from Week 12 to Week 52.

Table. Results of Other Secondary Endpoints Supporting Durability of Mirikizumab Efficacy (NRI) PAS Population Study I6T-MC-AMAM

	Pbo (N = 199)	Miri[a] (N = 579)	Common Risk Difference[b] Miri versus Pbo (95% CI), p-Value
Endoscopic Response at Week 12 and Week 52			
Response[c], n (%)	7 (3.5)	139 (24.0)	20.3 (16.0, 24.6), p<.000001
Response for composite endpoint with Clinical Response (PRO)[d] at Week 12, n (%)	7 (3.5)	110 (19.0)	15.3 (11.2, 19.4), p<.000001
Clinical Remission by CDAI at 80% or more of visits			
Response[c], n (%)	25 (12.6)	210 (36.3)	23.7 (17.6, 29.8), p<.000001
Response for composite endpoint with Clinical Response (PRO)[d] at Week 12, n (%)	25 (12.6)	195 (33.7)	21.0 (15.0, 27.1), p<.000001

Abbreviations: AP = abdominal pain; CDAI = Crohn's Disease Activity Index; CI = confidence interval; IV = intravenous; Miri = mirikizumab; n = number of participants in the specified category; N = number of participants in the PAS population; NRI = nonresponder imputation; PAS = primary analysis set; Pbo = placebo; PRO = 2 of the patient-reported items of the CDAI (SF and AP); Q4W = every 4 weeks; SC = subcutaneous; SES-CD = Simple Endoscopic Score for Crohn's Disease; SF = stool frequency.

a 900 mg IV Q4W for 3 doses, then 300 mg SC Q4W.

b Common risk difference and Cochran-Mantel-Haenszel test were adjusted by biologic-failed status (yes / no), baseline SES-CD total score (<12, ≥12), either baseline SF ≥7 and/or baseline AP ≥2.5 (yes or unknown/no).

c After Week 12, placebo-responders continued receiving placebo; placebo-nonresponders switched to mirikizumab, remained included in the placebo group, and were imputed as nonresponders.

d Clinical response by PRO is defined as at least a 30% decrease in SF and/or AP with neither score worse than baseline.

Composite Endpoints of Clinical Remission and Endoscopic Response or Remission

Endoscopic Response and Clinical Response by CDAI

A significantly greater percentage of participants achieving endoscopic response and clinical response by CDAI was observed in mirikizumab-treatment group compared with the placebo group at Week 12 (common risk difference=14.7%; p=.000004) and Week 52 (common risk difference= 35.1%; p<.000001).

Endoscopic Response and Clinical Remission by CDAI

A significantly greater percentage of participants achieving endoscopic response and clinical remission by CDAI was observed in the mirikizumab-treatment group compared with the placebo group at Week 12 (common risk difference=9.4%; p=.000396) and Week 52 (common risk difference=28.2%; p<.000001).

Table: Mirikizumab Compared to Placebo in Composite Endpoint Endoscopic Response and Clinical Remission Rates by CDAI (NRI) Treatment Regimen Period PAS Population Study I6T-MC-AMAM (Week 12)

Parameter: Endo. resp. and clin. rem. by CDAI

	placebo (N=199)	miri (N=579)	uste (N=287)	Total (N=1065)
Week 12 (Observed)				
Nx	162	502	248	912
Response, n (%) *a	10 (6.2)	85 (16.9)	42 (16.9)	137 (15.0)
95% CI *b	(2.5, 9.9)	(13.7, 20.2)	(12.3, 21.6)	(12.7, 17.3)
Week 12 (NRI)				
Response, n (%)	10 (5.0)	85 (14.7)	42 (14.6)	137 (12.9)
95% CI *b	(2.0, 8.1)	(11.8, 17.6)	(10.5, 18.7)	(10.9, 14.9)
Common Risk Difference (95% CI) vs. placebo		9.4 (5.2, 13.6)	9.4 (4.4, 14.5)	
Common Relative Risk (95% CI) vs. placebo		2.85 (1.52, 5.36)	2.83 (1.48, 5.39)	
Odds Ratio (95% CI) vs. placebo *c		3.22 (1.63, 6.36)	3.32 (1.60, 6.92)	
p-value vs. placebo *c		0.000396	0.000792	
Common Risk Difference (95% CI) vs. uste	-9.4 (-14.5, -4.4)	0.1 (-4.8, 5.1)		
Common Relative Risk (95% CI) vs. uste	0.35 (0.19, 0.67)	1.01 (0.72, 1.42)		
Odds Ratio (95% CI) vs. uste *c	0.30 (0.14, 0.63)	1.01 (0.68, 1.51)		
p-value vs. uste *c	0.000792	0.956322		

Abbreviations: miri = mirikizumab; uste = ustekinumab; CI = confidence interval; N = number of patients in the analysis population; n = number of patients in the specified category; NRI = nonresponder imputation; Nx = number of patients with non-missing values.

Endoscopic Remission and Clinical Remission by CDAI

A significantly greater percentage of participants achieving endoscopic remission and clinical remission by CDAI was observed in the mirikizumab-treatment group compared with the placebo group at Week 12 (common risk difference=3.3%: p=.052262) and at Week 52 (common risk difference=13.5%; p<.000001).

A significantly greater percentage of participants achieving clinical response by PRO at Week 12, and endoscopic response and clinical remission by CDAI was observed in the mirikizumab-treatment group compared with the placebo group (common risk difference=23.6%; p<.000001).

A significantly greater percentage of participants achieving clinical response by PRO at Week 12 and endoscopic remission and clinical remission by CDAI was observed in the mirikizumab-treatment group compared with the placebo group (common risk difference=12.1%; p<.000001).

Table: Mirikizumab Compared to Placebo in Composite Endpoints (NRI) Treatment Regimen Period PAS Population Study I6T-MC-AMAM

	Pbo (N = 199)	Miri[a] (N = 579)	Common Risk Difference[b] Miri versus Pbo (95% CI), p-Value
Endoscopic Response[c] and Clinical Remission by CDAI[d] at Week 52			
Response[e], n (%)	12 (6.0)	199 (34.4)	28.2 (23.2, 33.3), p<.000001
Response for Composite Endpoint with Clinical Response (PRO)[f] at Week 12, n (%)	12 (6.0)	173 (29.9)	23.6 (18.7, 28.6), p<.000001
Endoscopic Remission[g] and Clinical Remission by CDAI[d] at Week 52			
Response[e], n (%)	2 (1.0)	84 (14.5)	13.5 (10.3, 16.7), p<.000001
Response for Composite Endpoint with Clinical Response (PRO)[f] at Week 12, n (%)	2 (1.0)	76 (13.1)	12.1 (9.0, 15.1), p<.000001
Alternative Endoscopic Remission[h] and Clinical Remission by CDAI[d] at Week 52			
Response[e], n (%)	4 (2.0)	122 (21.1)	19.1 (15.2, 22.9), p<.000001
Response for Composite Endpoint with Clinical Response (PRO)[f] at Week 12, n (%)	4 (2.0)	108 (18.7)	16.5 (12.8, 20.3), p<.000001

Abbreviations: AP = abdominal pain; CI = confidence interval; CDAI = Crohn's Disease Activity Index; IV = intravenous; Miri = mirikizumab; n = number of participants in the specified category; N = number of participants in the PAS population; NRI = nonresponder imputation; PAS = primary analysis set; Pbo = placebo; PRO = 2 of the patient-reported items of the CDAI (SF and AP); Q4W = every 4 weeks; SC = subcutaneous; SES-CD = Simple Endoscopic Score for Crohn's Disease; SF = stool frequency.

a 900 mg IV Q4W for 3 doses, then 300 mg SC Q4W.

b Common risk difference and Cochran-Mantel-Haenszel test were adjusted by biologic-failed status (yes or no), baseline SES-CD total score (<12, ≥12), either baseline SF ≥7 and/or baseline AP ≥2.5 (yes or unknown / no).

c Endoscopic response is defined as ≥50% reduction from baseline in SES-CD total score.

d Clinical remission by CDAI is defined as CDAI total score <150.

e After Week 12, placebo-responders continued receiving placebo; placebo-nonresponders switched to mirikizumab, remained included in the placebo group, and were imputed as nonresponders.

f Clinical response by PRO is defined as at least a 30% decrease in SF and/or AP with neither score worse than baseline.

g SES-CD ≤4 and 2-point or greater reduction from baseline, and no subscore >1, defined as no segmental subscore (*sum of the 4 individual variable scores in a given bowel segment)* >1.

h SES-CD ≤4 and 2-point or greater reduction from baseline, and no subscore >1, defined as no subscore >1 in any

Symptomatic Endpoints of Fatigue and Urgency

Fatigue and bowel urgency are two of the most bothersome symptoms of CD, and improvement in these symptoms is critical to help patients continue in their daily activities and maintain a good quality of life. In Study AMAM, mirikizumab improved symptoms of fatigue and bowel urgency after induction, with continued improvement through Week 52.

Fatigue

Change from baseline at Week 52

Participants in Study AMAM had mean (SD) FACIT-Fatigue total baseline scores of 32.3 (11.1) for those in the placebo group and 31.5 (11.6) for those in the mirikizumab treatment group, indicating greater fatigue than the general population. Participants treated with mirikizumab reported greater mean change (improvement) from baseline in FACIT-Fatigue score versus placebo in the PAS Population, and in biologic-failed and not-biologic-failed subgroups at Week 12.

This improvement in FACIT-Fatigue was maintained in mirikizumab-treated participants in these populations at Week 52, with mean change from baseline FACIT-Fatigue scores of

- 7.47 (SE = 0.361) in the PAS Population
- 7.12 (SE = 0.510) in the biologic-failed subgroup, and
- 7.83 (SE = 0.518) in the not-biologic-failed subgroup.

Bowel urgency

Participants in Study AMAM had mean (SD) Urgency NRS total baseline scores of 6.6 (2.07) for those in the placebo group and 6.6 (2.14) for those in the mirikizumab treatment group.

Participants treated with mirikizumab reported greater mean change (improvement) from baseline in Urgency NRS score compared to placebo at Week 12, with a mean improvement of 2.4 points (SE = 0.1) for those in the mirikizumab group and 1.6 points (SE = 0.2) for the placebo group (p-value = .000011)

This improvement in Urgency NRS continued in mirikizumab-treated participants at Week 52, with a mean change from baseline Urgency NRS score of 3.2 (SE = 0.1)

Clinical and Symptomatic Relief Over Time

With mirikizumab treatment, there is an early onset of clinical remission and symptomatic improvement that is maintained or further improved with continued treatment through Week 52.

These results demonstrate internal consistency among study endpoints and support the robust effect of mirikizumab in treatment of CD.

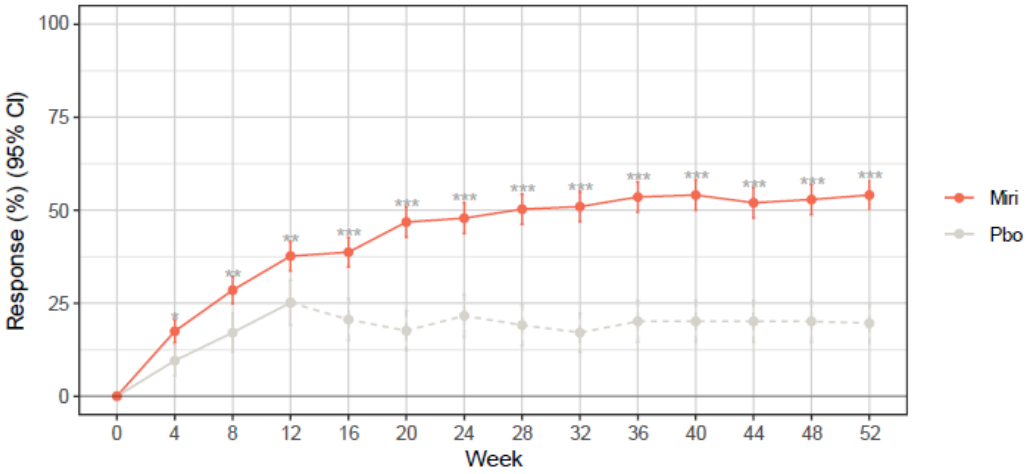
Early onset of efficacy

Early onset of efficacy was observed in clinical remission by CDAI, with differentiation between mirikizumab and placebo groups as early as Week 4. Early symptomatic relief was also demonstrated as the mirikizumab treatment group showed nominally significantly greater mean reductions compared to placebo in AP as early as Week 4, and in bowel urgency and SF as early as Week 6.

Sustained efficacy

Clinical remission by CDAI showed further improvement in response rates through Week 12 and Week 24 and sustained response rates through Week 52. A nominally significantly greater percentage of mirikizumab-treated participants achieved this outcome at all reported timepoints between Week 12 and Week 52, compared to placebo. Nominally significantly greater improvements in AP SF and bowel urgency were also observed at Week 12 and through Week 52 in the mirikizumab treatment group compared with the placebo group.

Figure. Proportion of participants with clinical remission by CDAI by visit (PAS and NRI).

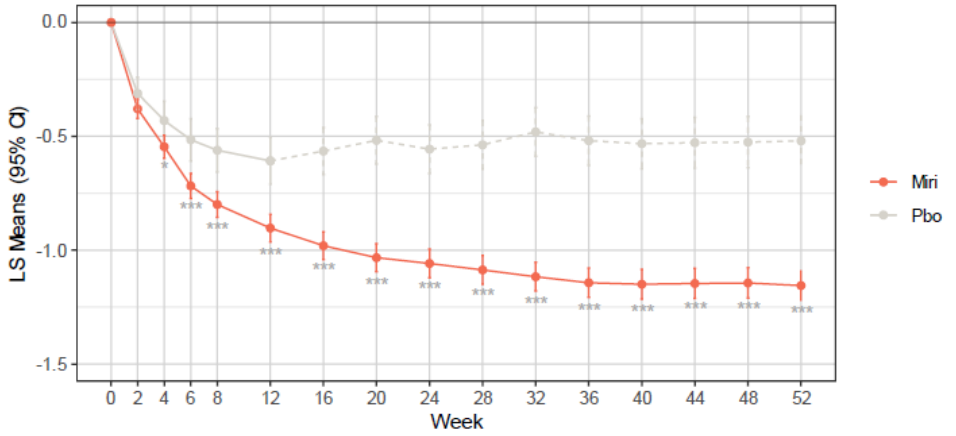


Abbreviations: CDAI = Crohn's Disease Activity Index; CI = confidence interval; IV = intravenous; Miri = mirikizumab; NRI = nonresponder imputation; PAS = primary analysis set; Pbo = placebo; Q4W = every 4 weeks; SC = subcutaneous; vs = versus.
vs Pbo: *p<.05, **p<.01, and ***p<.001.
Notes:

- Mirikizumab dose regimen is 900 mg IV Q4W for 3 doses, then 300 mg SC Q4W.
- After Week 12, placebo-responders continued receiving placebo; placebo-nonresponders switched to mirikizumab, remained included in the placebo group and were imputed as nonresponders.

Source: Table AMAM.8.66.

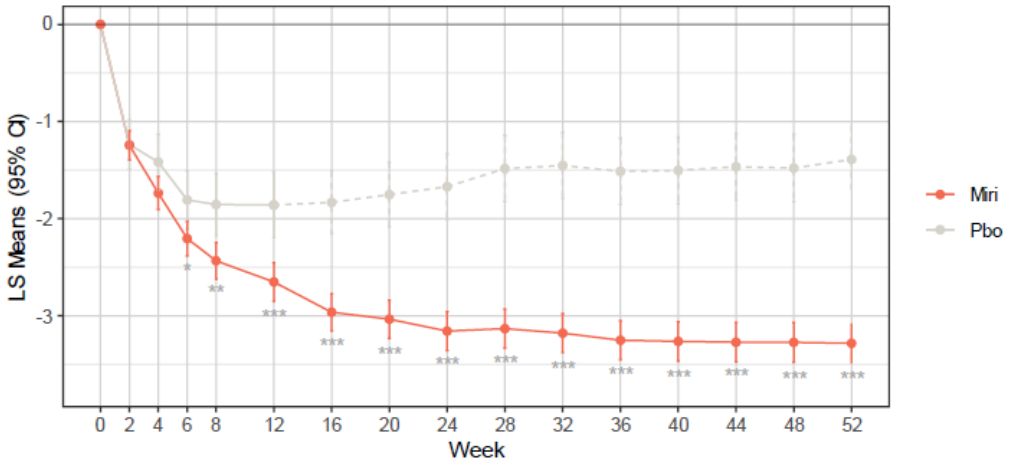
Figure. AP change from baseline by visit (PAS and ANCOVA with mBOCF).



Abbreviations: ANCOVA = analysis of covariance; AP = abdominal pain; CI = confidence interval; IV = intravenous; LS = least squares; mBOCF = modified baseline observation carried forward; Miri = mirikizumab; NRI = nonresponder imputation; PAS = primary analysis set; Pbo = placebo; Q4W = every 4 weeks; SC = subcutaneous; vs = versus.
vs Pbo: *p<.05 and ***p<.001.
Notes:

- Mirikizumab dose regimen is 900 mg IV Q4W for 3 doses, then 300 mg SC Q4W.
- After Week 12, placebo-responders continued receiving placebo; placebo-nonresponders switched to mirikizumab, remained included in the placebo group and were imputed as baseline observation carried forward.

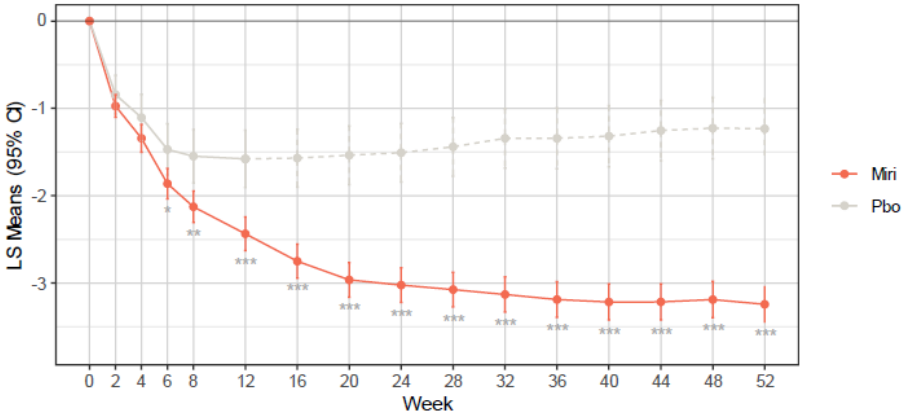
Figure. SF change from baseline by visit (PAS and ANCOVA with mBOCF).



Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; IV = intravenous; LS = least squares; mBOCF = modified baseline observation carried forward; Miri = mirikizumab; NRI = nonresponder imputation; PAS = primary analysis set; Pbo = placebo; Q4W = every 4 weeks; SC = subcutaneous; SF = stool frequency; vs = versus.
vs Pbo: *p<.05, **p<.01, and ***p<.001.
Notes:

- Mirikizumab dose regimen is 900 mg IV Q4W for 3 doses, then 300 mg SC Q4W.
- After Week 12, placebo-responders continued receiving placebo; placebo-nonresponders switched to mirikizumab, remained included in the placebo group and were imputed as baseline observation carried forward.

Figure. Urgency NRS change from baseline by visit (PAS and ANCOVA with mBOCF).



Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; IV = intravenous; LS = least squares; mBOCF = modified baseline observation carried forward; Miri = mirikizumab; NRI = nonresponder imputation; NRS = numeric rating scale; PAS = primary analysis set; Pbo = placebo; Q4W = every 4 weeks; SC = subcutaneous; vs = versus.
vs Pbo: *p<.05, **p<.01, and ***p<.001.
Notes:

- Mirikizumab dose regimen is 900 mg IV Q4W for 3 doses, then 300 mg SC Q4W.
- After Week 12, placebo-responders continued receiving placebo; placebo-nonresponders switched to mirikizumab, remained included in the placebo group and were imputed as baseline observation carried forward.

Source: Table AMAM.8.79.

- **Ancillary analyses**

Subgroup analyses

Efficacy subgroup analyses were conducted in the study for the co-primary endpoints and most major secondary endpoints in the PAS.

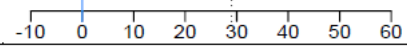
The subgroups analysed included:

- demographic characteristics: age, sex, body mass index, region
- baseline disease characteristics: duration of CD, baseline disease location, baseline fecal calprotectin, baseline CRP, baseline SES-CD total score, prior CD therapy, prior biologic failure, prior anti-TNF failure, baseline CD therapy, baseline corticosteroid use, baseline immunomodulator use.

For the subgroup analyses, p-values were not adjusted for multiplicity and were based on Fisher exact test. The risk difference was not adjusted for covariates.

Table: Clinical Response by PRO at Week 12 and Endoscopic Response at Week 52. Subgroup Analysis by Baseline Demographics, PAS Population, Study I6T-MC-AMAM

	Risk Difference % (95% CI)	Pbo n (%)	Miri n (%)	Diff %
All participants		18 (9.0)	220 (38.0)	29.0
Age				
<40 years		12 (9.7)	151 (39.1)	29.4
≥40 years		6 (8.0)	69 (35.8)	27.8
Sex				
Male		11 (9.3)	122 (36.7)	27.4
Female		7 (8.6)	98 (39.7)	31.0
BMI				
Underweight (<18.5 kg/m^2)		3 (7.9)	35 (32.1)	24.2
Normal (≥18.5 and <25 kg/m^2)		11 (11.7)	118 (40.8)	29.1
Overweight (≥25 and <30 kg/m^2)		1 (3.2)	47 (40.9)	37.6
Obese (≥30 and <40 kg/m^2)		3 (8.8)	17 (28.3)	19.5
Extreme obese (≥40 kg/m^2)[a]		0 (0.0)	3 (50.0)	
Region				
Asia		3 (6.5)	57 (37.3)	30.7
North America		2 (7.4)	28 (36.4)	29.0
Central America / South America[a]		2 (22.2)	13 (43.3)	
Europe and ROW		11 (9.4)	122 (38.2)	28.8



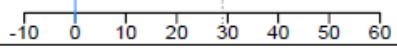
Abbreviations: AP = abdominal pain; BMI = body mass index; CDAI = Crohn's Disease Activity Index; CI = confidence interval; Diff = Unadjusted risk difference; Miri = mirikizumab; n = number of patients in the specified category; PAS = primary analysis set; Pbo = placebo; PRO = 2 of the patient-reported items of the CDAI (SF and AP); ROW = rest of world; SF = stool frequency.

Note: Risk differences greater than 0 (blue line) favor mirikizumab. The dotted line is the overall unadjusted estimated risk difference for all participants.

[a] Plot not presented due to small subgroup size (<10% of the PAS).

Table. Clinical Response by PRO at Week 12 and Endoscopic Response at Week 52 Subgroup Analysis by Baseline Disease Characteristics PAS Population, Study I6T-MC-AMAM

	Risk Difference % (95% CI)	Pbo n (%)	Miri n (%)	Diff %
All participants		18 (9.0)	220 (38.0)	29.0
Prior biologic failure				
Ever		6 (6.2)	103 (36.7)	30.5
Never		12 (11.8)	117 (39.3)	27.5
Prior anti-TNF failure				
Ever		6 (6.7)	100 (37.7)	31.0
Never		12 (10.9)	120 (38.2)	27.3
Baseline corticosteroid use				
Yes		7 (12.1)	70 (39.5)	27.5
No		11 (7.8)	150 (37.3)	29.5
Baseline immunomodulator use				
Yes		8 (13.8)	63 (43.2)	29.4
No		10 (7.1)	157 (36.3)	29.2
Duration of CD				
<1 year		0 (0.0)	33 (37.5)	37.5
≥1 to <5 years		9 (12.5)	93 (43.1)	30.6
≥5 years		9 (8.4)	94 (34.3)	25.9
Baseline disease location				
Ileal		2 (10.5)	14 (21.5)	11.0
Colonic		8 (10.4)	93 (41.3)	30.9
Ileal-colonic		8 (7.8)	113 (39.1)	31.3
Baseline fecal calprotectin				
≤250 ug/g		5 (15.2)	20 (26.7)	11.5
>250 ug/g		10 (8.5)	159 (41.0)	32.5
Baseline CRP				
≤10 mg/L		10 (8.5)	110 (34.5)	25.9
>10 mg/L		8 (9.8)	110 (42.3)	32.6
Baseline SES-CD total score				
<12		8 (7.8)	82 (28.2)	20.3
≥12		10 (10.3)	138 (47.9)	37.6

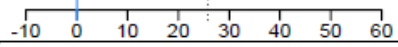


Abbreviations: AP = abdominal pain; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; CI = confidence interval; CRP = C-reactive protein; Diff = Unadjusted risk difference; Miri = mirikizumab; n = number of patients in the specified category; PAS = primary analysis set; Pbo = placebo; PRO = 2 of the patient-reported items of the CDAI (SF and AP); SES-CD = Simple Endoscopic Score for Crohn's Disease; SF = stool frequency; TNF = tumor necrosis factor.

Note: Risk differences greater than 0 (blue line) favor mirikizumab. Dotted line is the overall unadjusted estimated risk difference for all participants.

Table: Clinical Response by PRO at Week 12 and Clinical Remission by CDAI at Week 52 Subgroup Analysis by Baseline Demographics, PAS Population, Study I6T-MC-AMAM

	Risk Difference % (95% CI)	Pbo n (%)	Miri n (%)	Diff %
All participants		39 (19.6)	263 (45.4)	25.8
Age				
<40 years		23 (18.5)	180 (46.6)	28.1
≥40 years		16 (21.3)	83 (43.0)	21.7
Sex				
Male		21 (17.8)	152 (45.8)	28.0
Female		18 (22.2)	111 (44.9)	22.7
BMI				
Underweight (<18.5 kg/m^2)		2 (5.3)	41 (37.6)	32.4
Normal (≥18.5 and <25 kg/m^2)		20 (21.3)	142 (49.1)	27.9
Overweight (≥25 and <30 kg/m^2)		7 (22.6)	55 (47.8)	25.2
Obese (≥30 and <40 kg/m^2)		10 (29.4)	21 (35.0)	5.6
Extreme obese (≥40 kg/m^2)[a]		0 (0.0)	4 (66.7)	
Region				
Asia		6 (13.0)	71 (46.4)	33.4
North America		5 (18.5)	27 (35.1)	16.5
Central America/South America[a]		3 (33.3)	15 (50.0)	
Europe and ROW		25 (21.4)	150 (47.0)	25.7

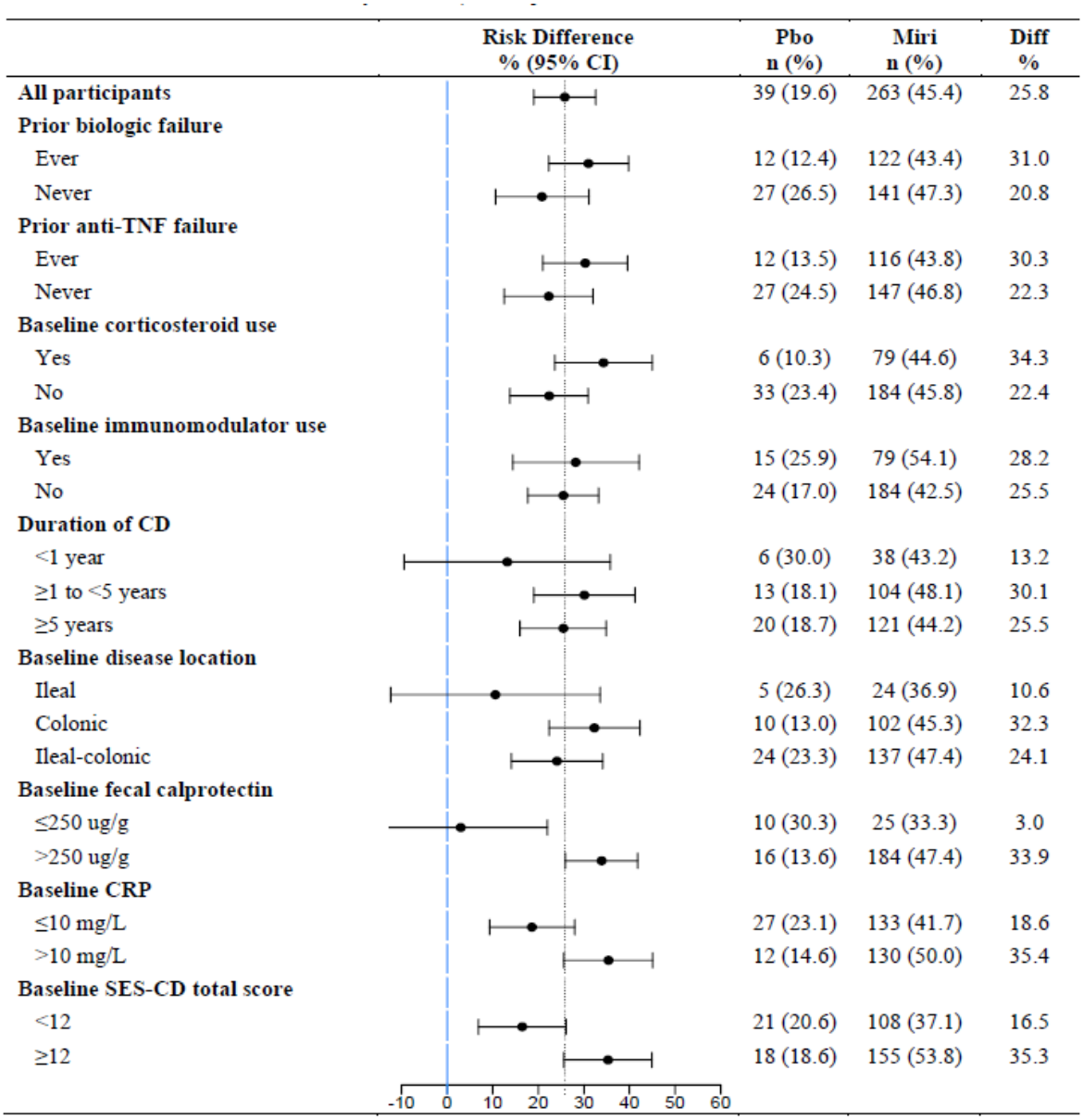


Abbreviations: AP = abdominal pain; BMI = body mass index; CDAI = Crohn's Disease Activity Index; CI = confidence interval; Diff = Unadjusted risk difference; Miri = mirikizumab; n = number of patients in the specified category; PAS = primary analysis set; Pbo = placebo; PRO = 2 of the patient-reported items of the CDAI (SF and AP); ROW = rest of world; SF = stool frequency.

Note: Risk differences greater than 0 (blue line) favor mirikizumab. Dotted line is the overall unadjusted estimated risk difference for all participants.

[a] Plot not presented due to small subgroup size (<10% of the PAS).

Table. Clinical Response by PRO at Week 12 and Clinical Remission by CDAI at Week 52 Subgroup Analysis by Baseline Disease Characteristics PAS Population, Study I6T-MC-AMAM



Abbreviations: AP = abdominal pain; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; CI = confidence interval; CRP = C-reactive protein; Diff = Unadjusted risk difference; Miri = mirikizumab; n = number of patients in specified category; PAS = primary analysis set; Pbo = placebo; PRO = 2 of the patient-reported items of the CDAI (SF and AP); SES-CD = Simple Endoscopic Score for Crohn's Disease; SF = stool frequency; TNF = tumor necrosis factor.

Note: Risk differences greater than 0 (blue line) favor mirikizumab. Dotted line is the overall unadjusted estimated risk difference for all participants.

Results depending on baseline CDAI, SF and AP score

The applicant also performed the subgroup analysis depending on baseline CDAI score, baseline SF score (average: <7, >=7), and baseline AP score (average <2, >=2). In general, the results for these subgroups were consistent with the results for the overall population.

Table: Clinical Remission by PRO at week 12, Subgroup: Baseline CDAI Group >=220 and <450

Parameter: Clinical Remission by PRO
Subgroup: Baseline CDAI Group 2: <150, >=150 and <220, >=220 and <450, >=450

	placebo (N=199)	miri (N=579)	uste (N=287)	Total (N=1065)
Baseline CDAI Group 2: >=220 and <450 (Ns)	158	475	224	857
Response at Week 12 (NRI) [2]	35 (22.2)	184 (38.7)	76 (33.9)	295 (34.4)
95% CI [3]	(15.7, 28.6)	(34.4, 43.1)	(27.7, 40.1)	(31.2, 37.6)
Difference (95% CI) vs. placebo [3]		16.6 (8.8, 24.4)	11.8 (2.8, 20.7)	
p-value vs. placebo [4]		0.000154	0.016061	
Difference (95% CI) vs. uste [3]		4.8 (-2.8, 12.4)		
p-value vs. uste [4]		0.240673		

Table: Clinical Remission by PRO at week 52, Subgroup: Baseline CDAI Group >=220 and <450

Parameter: Clinical Remission by PRO
Subgroup: Baseline CDAI Group 2: <150, >=150 and <220, >=220 and <450, >=450

	placebo (N=199)	miri (N=579)	uste (N=287)	Total (N=1065)
Baseline CDAI Group 2: >=220 and <450 (Ns)	158	475	224	857
Response at Week 52 (NRI) [2]	31 (19.6)	267 (56.2)	106 (47.3)	404 (47.1)
95% CI [3]	(13.4, 25.8)	(51.7, 60.7)	(40.8, 53.9)	(43.8, 50.5)
Difference (95% CI) vs. placebo [3]		36.6 (29.0, 44.2)	27.7 (18.7, 36.7)	
p-value vs. placebo [4]		<0.000001	<0.000001	
Difference (95% CI) vs. uste [3]		8.9 (1.0, 16.8)		
p-value vs. uste [4]		0.028638		

Table: Endoscopic Remission SES-CD <=4 at week 12, Subgroup: Baseline CDAI Group >=220 and <450

Parameter: Endoscopic Remission
Subgroup: Baseline CDAI Group 2: <150, >=150 and <220, >=220 and <450, >=450

	placebo (N=199)	miri (N=579)	uste (N=287)	Total (N=1065)
Baseline CDAI Group 2: >=220 and <450 (Ns)	158	475	224	857
Response at Week 12 (NRI) [2]	6 (3.8)	52 (10.9)	18 (8.0)	76 (8.9)
95% CI [3]	(0.8, 6.8)	(8.1, 13.8)	(4.5, 11.6)	(7.0, 10.8)
Difference (95% CI) vs. placebo [3]		7.1 (3.1, 11.2)	4.2 (-0.4, 8.9)	
p-value vs. placebo [4]		0.006267	0.132657	
Difference (95% CI) vs. uste [3]		2.9 (-1.6, 7.4)		
p-value vs. uste [4]		0.280207		

Table: Endoscopic Remission SES-CD <=4 at week 12, Subgroup: Baseline CDAI Group >=220 and <450

	placebo (N=199)	miri (N=579)	uste (N=287)	Total (N=1065)
Baseline CDAI Group 2: >=220 and <450 (Ns)	158	475	224	857
Response at Week 52 (NRI) [2]	3 (1.9)	97 (20.4)	41 (18.3)	141 (16.5)
95% CI [3]	(0.0, 4.0)	(16.8, 24.0)	(13.2, 23.4)	(14.0, 18.9)
Difference (95% CI) vs. placebo [3]		18.5 (14.3, 22.7)	16.4 (10.9, 21.9)	
p-value vs. placebo [4]		<0.000001	<0.000001	
Difference (95% CI) vs. uste [3]		2.1 (-4.1, 8.3)		
p-value vs. uste [4]		0.542498		

Table: Endoscopic Response Rates, Week 12, Prior anti-integrin failure subgroup

Parameter: Endoscopic Response
Subgroup: Prior anti-integrin failure: Ever, Never

	placebo (N=199)	miri (N=579)	uste (N=287)	Total (N=1065)
Prior anti-integrin failure: Ever (Ns)	24	68	31	123
Response at Week 12 (NRI) [2]	4 (16.7)	18 (26.5)	7 (22.6)	29 (23.6)
95% CI [3]	(1.8, 31.6)	(16.0, 37.0)	(7.9, 37.3)	(16.1, 31.1)
Difference (95% CI) vs. placebo [3]		9.8 (-8.4, 28.0)	5.9 (-15.0, 26.9)	
p-value vs. placebo [4]		0.412873	0.738454	
Difference (95% CI) vs. uste [3]		3.9 (-14.2, 22.0)		
p-value vs. uste [4]		0.805041		
Prior anti-integrin failure: Never (Ns)	175	511	256	942
Response at Week 12 (NRI) [2]	21 (12.0)	170 (33.3)	85 (33.2)	276 (29.3)
95% CI [3]	(7.2, 16.8)	(29.2, 37.4)	(27.4, 39.0)	(26.4, 32.2)
Difference (95% CI) vs. placebo [3]		21.3 (15.0, 27.6)	21.2 (13.7, 28.7)	
p-value vs. placebo [4]		<0.000001	<0.000001	
Difference (95% CI) vs. uste [3]		0.1 (-7.0, 7.1)		
p-value vs. uste [4]		>0.999999		

Abbreviations: mirikizumab; uste = ustekinumab; CI = confidence interval; N = number of patients in the analysis population; n =

Table: Endoscopic Response Rates, Week 52, Prior anti-integrin failure subgroup

Subgroup: Prior anti-integrin failure: Ever, Never

	placebo (N=199)	miri (N=579)	uste (N=287)	Total (N=1065)
Prior anti-integrin failure: Ever (Ns)	24	68	31	123
Response at Week 52 (NRI) [2]	0 (0.0)	27 (39.7)	13 (41.9)	40 (32.5)
95% CI [3]	(0.0, 0.0)	(28.1, 51.3)	(24.6, 59.3)	(24.2, 40.8)
Difference (95% CI) vs. placebo [3]		39.7 (28.1, 51.3)	41.9 (24.6, 59.3)	
p-value vs. placebo [4]		0.000058	0.000202	
Difference (95% CI) vs. uste [3]		-2.2 (-23.1, 18.7)		
p-value vs. uste [4]		0.829420		
Prior anti-integrin failure: Never (Ns)	175	511	256	942
Response at Week 52 (NRI) [2]	18 (10.3)	253 (49.5)	120 (46.9)	391 (41.5)
95% CI [3]	(5.8, 14.8)	(45.2, 53.8)	(40.8, 53.0)	(38.4, 44.7)
Difference (95% CI) vs. placebo [3]		39.2 (33.0, 45.5)	36.6 (29.0, 44.2)	
p-value vs. placebo [4]		<0.000001	<0.000001	
Difference (95% CI) vs. uste [3]		2.6 (-4.9, 10.1)		
p-value vs. uste [4]		0.540050		

Abbreviations: mirikizumab; uste = ustekinumab; CI = confidence interval; N = number of patients in the analysis population; n = number of patients in the specified category; NRI = nonresponder imputation; Ns = number of patients in each subgroup.

Table: Clinical Remission by CDAI, Week 12, Prior anti-integrin failure subgroup

Parameter: Clinical Remission by CDAI
Subgroup: Prior anti-integrin failure: Ever, Never

	placebo (N=199)	miri (N=579)	uste (N=287)	Total (N=1065)
Prior anti-integrin failure: Ever (Ns)	24	68	31	123
Response at Week 12 (NRI) [2]	3 (12.5)	26 (38.2)	9 (29.0)	38 (30.9)
95% CI [3]	(0.0, 25.7)	(26.7, 49.8)	(13.1, 45.0)	(22.7, 39.1)
Difference (95% CI) vs. placebo [3]		25.7 (8.2, 43.3)	16.5 (-4.2, 37.3)	
p-value vs. placebo [4]		0.022149	0.194264	
Difference (95% CI) vs. uste [3]		9.2 (-10.5, 28.9)		
p-value vs. uste [4]		0.497230		
Prior anti-integrin failure: Never (Ns)	175	511	256	942
Response at Week 12 (NRI) [2]	47 (26.9)	192 (37.6)	98 (38.3)	337 (35.8)
95% CI [3]	(20.3, 33.4)	(33.4, 41.8)	(32.3, 44.2)	(32.7, 38.8)
Difference (95% CI) vs. placebo [3]		10.7 (2.9, 18.5)	11.4 (2.6, 20.3)	
p-value vs. placebo [4]		0.010165	0.016829	
Difference (95% CI) vs. uste [3]		-0.7 (-8.0, 6.6)		
p-value vs. uste [4]		0.874650		

Abbreviations: mirikizumab; uste = ustekinumab; CI = confidence interval; N = number of patients in the analysis population; n = number of patients in the specified category; NRI = nonresponder imputation; Ns = number of patients in each subgroup.

Table: Clinical Remission by CDAI, Week 12, Prior anti-integrin failure subgroup

Parameter: Clinical Remission by CDAI
Subgroup: Prior anti-integrin failure: Ever, Never

	placebo (N=199)	miri (N=579)	uste (N=287)	Total (N=1065)
Prior anti-integrin failure: Ever (Ns)	24	68	31	123
Response at Week 52 (NRI) [2]	3 (12.5)	36 (52.9)	14 (45.2)	53 (43.1)
95% CI [3]	(0.0, 25.7)	(41.1, 64.8)	(27.6, 62.7)	(34.3, 51.8)
Difference (95% CI) vs. placebo [3]		40.4 (22.7, 58.2)	32.7 (10.7, 54.6)	
p-value vs. placebo [4]		0.000609	0.017211	
Difference (95% CI) vs. uste [3]		7.8 (-13.4, 28.9)		
p-value vs. uste [4]		0.520516		
Prior anti-integrin failure: Never (Ns)	175	511	256	942
Response at Week 52 (NRI) [2]	36 (20.6)	277 (54.2)	125 (48.8)	438 (46.5)
95% CI [3]	(14.6, 26.6)	(49.9, 58.5)	(42.7, 55.0)	(43.3, 49.7)
Difference (95% CI) vs. placebo [3]		33.6 (26.3, 41.0)	28.3 (19.7, 36.8)	
p-value vs. placebo [4]		<0.000001	<0.000001	
Difference (95% CI) vs. uste [3]		5.4 (-2.1, 12.9)		
p-value vs. uste [4]		0.168076		

Abbreviations: mirikizumab; uste = ustekinumab; CI = confidence interval; N = number of patients in the analysis population; n = number of patients in the specified category; NRI = nonresponder imputation; Ns = number of patients in each subgroup.

Effect of immunogenicity on efficacy

Neither the presence of TE ADA nor the titer levels demonstrated an impact on efficacy measures associated with mirikizumab.

- **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-AMAM

Title: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo- and Active-Controlled, Treat-Through Study to Evaluate the Efficacy and Safety of Mirikizumab in Patients with Moderately to Severely Active Crohn's Disease	
Study identifier	I6T-MC-AMAM

Design	Phase 3, multicenter, randomised, double-blind, placebo- and active-controlled treat-through study		
	Duration of main phase (induction and maintenance treatment periods combined)		52 weeks
Hypothesis	Superiority		
Treatment groups	Mirikizumab		900 mg IV Q4W for 3 doses, then 300 mg SC Q4W Number randomised in PAS = 579
	Ustekinumab		~6 mg/kg IV for one dose, then 90 mg SC every 8 weeks Number randomised in PAS = 287
	Placebo		IV or SC At Week 12: • Responders continued to receive placebo • Nonresponders switched to mirikizumab as described above Number randomised in PAS = 199
Endpoints and definitions	Co-Primary endpoints	To evaluate if the efficacy of mirikizumab is superior to placebo as assessed by • clinical response by PRO at Week 12 and endoscopic response at Week 52	• Proportion of participants achieving clinical response by PRO[a] at Week 12 and endoscopic response[b] by SES-CD at Week 52
		• clinical response by PRO at Week 12 and clinical remission by CDAI at Week 52	• Proportion of participants achieving clinical response by PRO[a] at Week 12 and clinical remission by CDAI[c] at Week 52
	Major secondary endpoint	To evaluate if the efficacy of mirikizumab is superior to placebo at Week 12 as assessed by • clinical response by PRO	• Proportion of participants achieving clinical response by PRO[a] at Week 12
		• clinical remission by CDAI	• Proportion of participants achieving clinical remission by CDAI[c] at Week 12
		• endoscopic response	• Proportion of participants achieving endoscopic response[b] at Week 12
		• endoscopic remission	• Proportion of participants achieving endoscopic remission by SES-CD[d,e] at Week 12

		• FACIT-Fatigue scores	• Change from baseline in FACIT-Fatigue scores at Week 12
	Major secondary endpoint	To evaluate if the efficacy of mirikizumab is superior to placebo at Week 52 as assessed by • clinical remission by CDAI	• Proportion of participants achieving clinical remission by CDAI[c] at Week 52
		• endoscopic response	• Proportion of participants achieving endoscopic response[b] at Week 52
	Major secondary endpoint	To evaluate if the efficacy of mirikizumab is superior to placebo as assessed by both clinical response by PRO at Week 12 and each below, individually: • clinical remission by PRO at Week 52	Proportion of participants achieving clinical response by PRO[a] at Week 12 and each below, individually: • Clinical remission by PRO[f] at Week 52
		• corticosteroid-free clinical remission by CDAI	• Corticosteroid-free from Week 40 to Week 52 and clinical remission by CDAI[c] at Week 52
		• endoscopic remission at Week 52	• Endoscopic remission by SES-CD[d,e] at Week 52
	Major secondary endpoint	To evaluate the efficacy of mirikizumab in comparison to ustekinumab at Week 52 as assessed by • endoscopic response (superior)	Proportion of participants achieving • Endoscopic response[b] at Week 52
		• clinical remission by CDAI (non-inferior)	• Clinical remission by CDAI[c] at Week 52
Database lock	04 Oct 2023		
Results and analysis			
Analysis description	**Co-Primary analysis:** To evaluate if the efficacy of mirikizumab is superior to placebo as assessed by • clinical response by PRO[a] at Week 12 and endoscopic response[b] at Week 52 • clinical response by PRO[a] at Week 12 and clinical remission by CDAI[c] at Week 52		
Analysis population,	PAS		

time point description, and statistical model	Weeks 12 and 52 CMH test with NRI			
Descriptive statistics and estimate variability	Treatment group		Placebo	Mirikizumab
	Number of patients		199	579
	Clinical response by PRO at Week 12 and endoscopic response at Week 52, n (%)		18 (9.0)	220 (38.0)
Effect estimate per comparison	Co-Primary endpoint: Clinical response by PRO at Week 12 and endoscopic response at Week 52	Comparison groups	Mirikizumab versus placebo	
		Common risk difference (99.5% CI)	28.7 (20.6, 36.8)	
		p-value	<.000001	
Descriptive statistics and estimate variability	Treatment group		Placebo	Mirikizumab
	Number of patients		199	579
	Clinical response by PRO at Week 12 and clinical remission by CDAI at Week 52, n (%)		39 (19.6)	263 (45.4)
Effect estimate per comparison	Co-Primary endpoint: Clinical Response by PRO at Week 12 and Clinical Remission by CDAI at Week 52	Comparison groups	Mirikizumab versus placebo	
		Common risk difference (99.5% CI)	25.8 (15.9, 35.6)	
		p-value	<.000001	
Results and analysis				
Analysis description	**Major secondary analysis:** Clinical Response by PRO[a] at Week 12			
Analysis population, time point description, and statistical model	PAS Week 12 CMH test with NRI			
Descriptive statistics and estimate variability	Treatment group		Placebo	Mirikizumab
	Number of patients		199	579
	Clinical Response by PRO at Week 12, n (%)		103 (51.8)	409 (70.6)
Effect estimate per comparison	Major secondary endpoint: Clinical Response by PRO at Week 12	Comparison groups	Mirikizumab versus placebo	
		Common risk difference (99.5% CI)	18.9 (7.5, 30.3)	
		p-value	0.000001	
Results and analysis				

Analysis description	**Major secondary analysis:** Clinical Remission by CDAI[c] at Week 12			
Analysis population, time point description, and statistical model	PAS Week 12 CMH test with NRI			
Descriptive statistics and estimate variability	Treatment group		Placebo	Mirikizumab
	Number of patients		199	579
	Clinical Remission by CDAI at Week 12, n (%)		50 (25.1)	218 (37.7)
Effect estimate per comparison	Major secondary endpoint:	Comparison groups	Mirikizumab versus placebo	
	Clinical Remission by CDAI at Week 12	Common risk difference (99.5% CI)	12.4 (2.2, 22.7)	
		p-value	0.001431	
Results and analysis				
Analysis description	**Major secondary analysis:** Endoscopic Response by SES-CD[b] at Week 12			
Analysis population, time point description, and statistical model	PAS Week 12 CMH test with NRI			
Descriptive statistics and estimate variability	Treatment group		Placebo	Mirikizumab
	Number of patients		199	579
	Endoscopic Response by SES-CD at Week 12, n (%)		25 (12.6)	188 (32.5)
Effect estimate per comparison	Major secondary endpoint: Endoscopic Response by SES-CD at Week 12	Comparison groups	Mirikizumab versus placebo	
		Common risk difference (99.5% CI)	19.7 (11.1, 28.2)	
		p-value	<.000001	
Results and analysis				
Analysis description	**Major secondary analysis:** Endoscopic Remission by SES-CD[d] at Week 12			
Analysis population, time point description, and statistical model	PAS Week 12 CMH test with NRI			

Descriptive statistics and estimate variability	Treatment group		Placebo	Mirikizumab
	Number of patients		199	579
	Endoscopic Remission by SES-CD at Week 12, n (%)		8 (4.0)	63 (10.9)
Effect estimate per comparison	Major secondary endpoint: Endoscopic Remission by SES-CD at Week 12	Comparison groups	Mirikizumab versus placebo	
		Common risk difference (99.5% CI)	6.8 (1.6, 12.1)	
		p-value	0.003414	
Results and analysis				
Analysis description	**Secondary analysis:** Endoscopic Remission by SES-CD at Week 12 - Alternative Definition[e]			
Analysis population, time point description, and statistical model	PAS Week 12 CMH test with NRI			
Descriptive statistics and estimate variability	Treatment group		Placebo	Mirikizumab
	Number of patients		199	579
	Endoscopic Remission by SES-CD at Week 12 - Alternative Definition, n (%)		14 (7.0)	102 (17.6)
Effect estimate per comparison	Secondary endpoint: Endoscopic Remission by SES-CD at Week 12 - Alternative Definition	Comparison groups	Mirikizumab versus placebo	
		Common risk difference (99.5% CI)	10.6 (4.1, 17.2)	
		p-value	0.000213	
Results and analysis				
Analysis description	**Major secondary analysis:** FACIT-Fatigue Change from Baseline at Week 12			
Analysis population, time point description, and statistical model	PAS Week 12 CMH test, ANCOVA with mBOCF			
Descriptive statistics and estimate variability	Treatment group		Placebo	Mirikizumab
	Number of patients		199	579
	FACIT-Fatigue Change from Baseline at Week 12, LSM (SE)		2.64 (0.606)	5.86 (0.358)
Effect estimate	Major secondary endpoint:	Comparison groups	Mirikizumab versus placebo	

per comparison	FACIT-Fatigue Change from Baseline at Week 12	Common risk difference (99.5% CI)	3.22 (1.24, 5.19)
		p-value	0.000005
Results and analysis			
Analysis description	**Major secondary analysis:** Clinical Remission by CDAI[c] at Week 52[g]		
Analysis population, time point description, and statistical model	PAS		
	Week 52 CMH test with NRI		
Descriptive statistics and estimate variability	Treatment group	Placebo	Mirikizumab
	Number of patients	199	579
	Clinical Remission by CDAI at Week 52, n (%)	39 (19.6)	313 (54.1)
Effect estimate per comparison	Major secondary endpoint: Clinical Remission by CDAI at Week 52	Comparison groups	Mirikizumab versus placebo
		Common risk difference (99.5% CI)	34.6 (24.7, 44.4)
		p-value	<.000001
Results and analysis			
Analysis description	**Major secondary analysis:** Endoscopic Response by SES-CD[b] at Week 52[g]		
Analysis population, time point description, and statistical model	PAS Week 52 CMH test with NRI		
Descriptive statistics and estimate variability	Treatment group	Placebo	Mirikizumab
	Number of patients	199	579
	Endoscopic Response by SES-CD at Week 52, n (%)	18 (9.0)	280 (48.4)
Effect estimate per comparison	Major secondary endpoint: Endoscopic Response by SES-CD at Week 52	Comparison groups	Mirikizumab versus placebo
		Common risk difference (99.5% CI)	39.1 (31.0, 47.2)
		p-value	<.000001
Results and analysis			
Analysis description	**Major secondary analysis:** Clinical Response by PRO[a] at Week 12 and Clinical Remission by PRO[f] at Week 52		

Analysis population, time point description, and statistical model	PAS Weeks 12 and 52 CMH test with NRI			
Descriptive statistics and estimate variability	Treatment group		Placebo	Mirikizumab
	Number of patients		199	579
	Clinical Response by PRO at Week 12 and Clinical Remission by PRO at Week 52, n (%)		39 (19.6)	263 (45.4)
Effect estimate per comparison	Major secondary endpoint: Clinical Response by PRO at Week 12 and Clinical Remission by PRO at Week 52	Comparison groups	Mirikizumab versus placebo	
		Common risk difference (99.5% CI)	25.7 (15.9, 35.6)	
		p-value	<.000001	
Results and analysis				
Analysis description	**Major secondary analysis:** Clinical Response by PRO[a] at Week 12 and Corticosteroid-Free from Week 40 to Week 52 and Clinical Remission by CDAI[c] at Week 52			
Analysis population, time point description, and statistical model	PAS Weeks 12 and 52 CMH test with NRI			
Descriptive statistics and estimate variability	Treatment group		Placebo	Mirikizumab
	Number of patients		199	579
	Clinical Response by PRO at Week 12 and Corticosteroid-Free from Week 40 to Week 52 and Clinical Remission by CDAI at Week 52, n (%)		37 (18.6)	253 (43.7)
Effect estimate per comparison	Major secondary endpoint: Clinical Response by PRO at Week 12 and Corticosteroid-Free from Week 40 to Week 52 and Clinical Remission by CDAI at Week 52	Comparison groups	Mirikizumab versus placebo	
		Common risk difference (99.5% CI)	25.0 (15.2, 34.7)	
		p-value	<.000001	
Results and analysis				
Analysis description	**Major secondary analysis:** Clinical Response by PRO[a] at Week 12 and Endoscopic Remission by SES-CD[d] at Week 52			

Analysis population, time point description, and statistical model	PAS Weeks 12 and 52 CMH test with NRI			
Descriptive statistics and estimate variability	Treatment group		Placebo	Mirikizumab
	Number of patients		199	579
	Clinical Response by PRO at Week 12 and Endoscopic Remission by SES-CD at Week 52, n (%)		4 (2.0)	92 (15.9)
Effect estimate per comparison	Major secondary endpoint: Clinical Response by PRO at Week 12 and Endoscopic Remission by SES-CD at Week 52	Comparison groups	Mirikizumab versus placebo	
		Common risk difference (99.5% CI)	13.8 (8.7, 18.9)	
		p-value	<.000001	
Results and analysis				
Analysis description	**Secondary analysis:** Clinical Response by PRO[a] at Week 12 and Endoscopic Remission by SES-CD at Week 52 - Alternative Definition[e]			
Analysis population, time point description, and statistical model	PAS Weeks 12 and 52 CMH test with NRI			
Descriptive statistics and estimate variability	Treatment group		Placebo	Mirikizumab
	Number of patients		199	579
	Clinical Response by PRO at Week 12 and Endoscopic Remission by SES-CD at Week 52 - Alternative Definition, n (%)		8 (4.0)	136 (23.5)
Effect estimate per comparison	Secondary endpoint: Clinical Response by PRO at Week 12 and Endoscopic Remission by SES-CD at Week 52 - Alternative Definition	Comparison groups	Mirikizumab versus placebo	
		Common risk difference (99.5% CI)	19.4 (13.1, 25.7)	
		p-value	<.000001	
Results and analysis				
Analysis description	**Major secondary analysis:** Clinical remission by CDAI[c] at Week 52 – Mirikizumab in comparison to ustekinumab			

Analysis population, time point description, and statistical model	PAS Week 52 CMH test with NRI			
Descriptive statistics and estimate variability	Treatment group		Ustekinumab	Mirikizumab
	Number of patients		287	579
	Clinical Remission by CDAI at Week 52 – Mirikizumab in comparison to ustekinumab, n (%)		139 (48.4)	313 (54.1)
Effect estimate per comparison	Major secondary endpoint: Clinical Remission by CDAI at Week 52	Comparison groups	Mirikizumab versus Ustekinumab	
		Common risk difference[h] (95% CI)	5.7 (-1.4, 12.8)	
		Non-inferiority test, p-value	<.0001	
Results and analysis				
Major secondary analysis: Endoscopic response by SES-CD[b] at Week 52 – Mirikizumab in comparison to Ustekinumab				
Analysis population, time point description, and statistical model	PAS Week 52 CMH test with NRI			
Descriptive statistics and estimate variability	Treatment group		Ustekinumab	Mirikizumab
	Number of patients		287	579
	Endoscopic response by SES-CD at Week 52, n (%)		133 (46.3)	280 (48.4)
Effect estimate per comparison	Major secondary endpoint: Endoscopic response by SES-CD at Week 52	Comparison groups	Mirikizumab versus Ustekinumab	
		Common risk difference[h] (95% CI)	2.3 (-4.7, 9.3)	
		Superiority test, p-value	.513623	

Abbreviations: ANCOVA = analysis of covariance; AP = abdominal pain; CDAI = Crohn's Disease Activity Index; CI = confidence interval; CMH = Cochran-Mantel-Haenzel; FACIT = Functional Assessment of Chronic Illness Therapy; IV = intravenous; LSM = least squares mean; mBOCF = modified baseline observation carried forward; n = number of patients in the specified category; NRI = nonresponder imputation; PAS = primary analysis set; PRO = two of the patient-reported items of the CDAI (SF and AP); Q4W = every 4 weeks; SC = subcutaneous; SE = standard error; SES-CD = Simple Endoscopic Score for Crohn's Disease; SF = stool frequency

a Clinical response by PRO is defined as at least a 30% decrease in SF or AP or both, with neither score worse than baseline.
b Endoscopic response by SES-CD is defined as ≥50% reduction from baseline in SES-CD total score.
c Clinical remission by CDAI is defined as CDAI total score <150.
d Endoscopic remission by SES-CD:
- SES-CD ≤4
- ≥2-point reduction from baseline, and
- no subscore >1, defined as no segmental subscore (sum of the 4 individual variable scores in a given bowel segment) >1.

e Endoscopic remission by SES-CD – alternative definition is a non-major secondary endpoint, and is not multiplicity-controlled:
- SES-CD ≤4
- ≥2-point reduction from baseline, and
- no subscore >1, defined as no subscore >1 in any individual variable.

f Clinical remission by PRO is defined as unweighted daily average SF≤3 and not worse than baseline (as per Bristol Stool Scale Category 6 or 7) and unweighted daily average AP ≤1 and not worse than baseline.
g After Week 12, placebo-responders continued receiving placebo; placebo-nonresponders switched to mirikizumab, remained included in the placebo group and were imputed as nonresponders.
h Common risk difference and Cochran-Mantel-Haenszel test were adjusted by biologic-failed status (yes / no), baseline SES-CD total score (<12 and ≥12), either baseline SF ≥7 and/or baseline AP ≥2.5 (yes or unknown /no).
i p-Value for non-inferiority is derived from the common risk difference with a margin of 10%. The 1-sided p-value was multiplied by 2 to be interpretable at standard alpha levels

2.6.5.3. Clinical studies in special populations

Adolescents

Study AMAM had an "adolescent addendum" to which 6 patients enrolled, before the study was concluded as part of a PIP amendment (EMEA-002208-PIP02-17-M02 from 11 March 2022).

Elderly

The dose finding study included patients between 18 and 75 years of age, whereas the pivotal study included patients ≥18 and ≤80 years of age. No differences in efficacy depending on the age of participants was noted. In relation to Elderly, the following statement is included in the SmPC:

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

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable

2.6.5.6. Supportive study(ies)

The long term efficacy and safety of Mirikizumab in patients with CD is being investigated in Phase 3, Multicenter, Open-Label, Long-Term Extension Study to Evaluate the Long-Term Efficacy and Safety of Mirikizumab in Patients with Crohn's Disease. Study AMAX is ongoing, and final results for this study will be submitted in a CSR, expected to be available in 2027. No efficacy data from this study were provided with this submission.

2.6.6. Discussion on clinical efficacy

The MAH submitted one pivotal Phase 3 study (Study I6T-MC-AMAM [AMAM]) and one dose finding study (Phase 2 study (Study I6T-MC-AMAG [AMAG])) in support of this extension of indication application.

The long-term extension Phase 3 study (Study I6T-MC-AMAX [AMAX]) is still ongoing and only safety data from this study were provided.

The proposed indication is:

Crohn's disease

Omvoh is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic treatment.

Dose finding study

Induction dose

In the AMAG study, three induction doses were tested: 200 mg IV Q4W, 600 mg IV Q4W, and 1000 mg Q4W. The two highest doses (600 mg and 1000 mg) showed superiority in comparison to placebo for all endpoints investigated. A model-based analysis of the relationship between individual subject mirikizumab systemic exposures and Week 12 endoscopic response revealed a significant relationship, with higher mirikizumab exposures associated with higher rates of endoscopic response. Hence, 900 mg IV induction dose was selected for the pivotal phase III study since it is expected to produce near-maximal effect based on this exposure-response analysis.

Maintenance doses

In the AMAG study, four maintenance doses were investigated: 200 mg IV Q4W, 600 mg IV Q4W, 1000 mg IV Q4W and 300 mg SC Q4W. The Week 52 endoscopic response and PRO remission rates were similar across the maintenance treatment groups and did not appear to have any relationship to dose or mirikizumab exposure as evaluated in Study AMAG. Based on these data, a mirikizumab maintenance dose of 300 mg SC Q4W was selected to be investigated in the phase III study. This is agreed by the CHMP.

Design and conduct of clinical studies

Main study

The study AMAM, was a Phase 3, multicenter, randomized, double-blind, double-dummy, parallel group, active- and placebo-controlled, treat-through study, designed to evaluate the efficacy and safety of mirikizumab in participants with moderately to severely active CD.

In this study, there was an induction period (Period 1, Weeks 0 to 12) and a maintenance period (Period 2, Weeks 12 to 52). During the induction period, patients were randomized in a 6:3:2 ratio to receive mirikizumab, ustekinumab, or placebo. The dose of mirikizumab was 900 mg IV Q4W (Weeks 0, 4, and

8). The dose of Ustekinumab was ~6 mg/kg IV at Week 0 and 90 mg SC Q8W starting at Week 8. During the maintenance period, patients originally assigned mirikizumab continue to receive this treatment but subcutaneously at the dose of 300mg Q4W. Patients originally assigned ustekinumab continue to receive 90 mg SC dose of ustekinumab Q8W. Only responders to placebo continued to receive placebo in the maintenance period.

The AMAM study had a treat-through design, i.e. patients were treated continuously without rerandomization. As indicated in the Guideline on the development of new medicinal products for the treatment of Crohn's Disease (CPMP/EWP/2284/99 Rev. 2), studies without re-randomisation are acceptable, especially when a general claim "treatment of CD" is being sought.

A total duration of the study was 52 weeks, which is acceptable to the CHMP.

Study population

In line with the CHMP guideline (CPMP/EWP/2284/99 Rev. 2), patients enrolled to CD studies should have clinically relevant symptoms as well as signs of mucosal inflammation. The study included patients with moderate to severe CD as defined by an unweighted daily average SF ≥4 (loose and watery stools defined as Bristol Stool Scale Category 6 or 7), AND/OR an unweighted daily average AP ≥2 at baseline. In relation to signs of mucosal inflammation patients had to have a SES-CD score ≥7 in participants with ileal-colonic or ≥4 in participants with isolated ileal disease within 21 days before randomization. Of note, CDAI score values were not specified for enrolment. A diagnosis of CD had to be established at least 3 months prior to enrolment, which is acceptable to the CHMP and in line with the CHMP guideline (CPMP/EWP/2284/99 Rev. 2).

There were some concerns whether all enrolled patients in the study had moderate to severe CD. As indicated in the CHMP guideline (CPMP/EWP/2284/99 Rev. 2), the inclusion criteria of moderate to severe CD population of patients may use the CDAI score (e.g. at least 220) or alternatively PROs based on symptom sub-scores of the CDAI, (e.g. the "PRO2" of at least 14). However, these requirements were not fulfilled in the study (please see also below).

The study enrolled patients with a history of an inadequate response to, loss of response to, or intolerance to other CD treatments, this is in line with the intended indication of "patients who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic treatment".

The prior medications failure criteria used to define the study population are acceptable to the CHMP.

Placebo

Placebo was selected as the primary comparator for the study AMAM. As stated in the CHMP CD guideline (CPMP/EWP/2284/99 Rev. 2), for a second line indication (after failure or intolerance to primary therapy), placebo is an acceptable comparator (especially as add-on to established therapy). Hence, this is agreed by the CHMP. Of note, only responders to placebo continued to received placebo in Period 2 of the study, whereas non-responders to placebo at week 12 received a blinded mirikizumab therapy.

Comparator

Ustekinumab was selected as an active comparator. A single IV induction dose of approximately 6 mg/kg (based on the weight tiers described in labelling), which is the approved induction dose for participants with CD, was given to patients at week 0. Subsequently, at week 8, patients received 90 mg of ustekinumab subcutaneously. The ustekinumab Q8W dose regimen (and not Q12W dose regimen) was chosen for the maintenance treatment, which is acceptable as both options are listed in the SmPC for ustekinumab. The main comparison of mirikizumab to ustekinumab was conducted based on the Week 52 results.

Concomitant CD treatment

Patients in the study could also receive conventional concomitant CD treatment (such as oral 5-ASAs, oral corticosteroids (prednisone ≤30mg/day or equivalent, or budesonide≤9 mg/day), immunomodulators (for example, AZA, 6-MP, or MTX) or antibiotics (for treatment of CD). Biological therapy for CD was prohibited while on the study.

Doses of CD concomitant medications were to be kept stable unless modifications were needed due to AEs or for appropriate medical management. Corticosteroid doses were required to be stable until Week 12. At Week 12, participants who were receiving corticosteroids and who achieved clinical response, as assessed by PRO, initiated corticosteroid tapering as instructed in the protocol.

Primary endpoint

The primary hypothesis tested in this study was that mirikizumab is superior to placebo with regards to the co-primary endpoints:

- clinical response by PRO at Week 12 and endoscopic response at Week 52
- clinical response by PRO at Week 12 and clinical remission by CDAI at Week 52

Clinical response by PRO was defined as at least a 30% decrease in SF and/or AP with neither score worse than baseline, endoscopic response was defined as ≥50% reduction from baseline in SES-CD Total Score and clinical remission by CDAI was defined as CDAI total score <150. These definitions are acceptable, and they were used previously in other CD development programs.

For testing the primary and major secondary hypotheses, a prespecified graphical scheme (Bretz et al. 2009, 2011) was implemented to control the FWER at a 2-sided alpha level of 0.05.

These co-primary endpoints were introduced while the study was ongoing through the protocol amendment on 23 Feb 2022 (Study Initiation Date (first patient visit) was 23 July 2019) and were based on, as indicated by the MAH, recommendation from the FDA. The original primary endpoint was to evaluate whether treatment with mirikizumab is superior to placebo as assessed by endoscopic response at Week 52 and clinical remission by PRO at Week 52.

It is also noted that the primary endpoint chosen differs from the endpoints currently recommended in the CHMP CD guideline (CPMP/EWP/2284/99 Rev. 2) stating that *"The primary endpoint in studies in luminal CD should be the co-primary evaluation of symptomatic remission and endoscopic remission. Consequently, co-primary endpoints of treatment should concern:*

1) The proportion of patients with symptomatic remission, and

2) The proportion of patients with endoscopic remission.

Therefore, the main difference is that the primary endpoint used in the AMAM study, contains endoscopic response and not endoscopic remission, as recommended by the guideline. However, it is noted that in the AMAM study, endoscopic remission is investigated in secondary endpoints including those under multiplicity adjustment (such as the endpoint clinical response by PRO at Week 12 and endoscopic remission at Week 52).

Another difference is that symptoms in the primary endpoint were evaluated by CDAI and not by PRO2, which is recommended in the guideline. However, again, there are many secondary endpoints assessing improvement of symptoms by PRO.

In conclusion, taking also into consideration the ranked multiplicity-controlled secondary endpoints, the primary endpoint as used in the study are acceptable to the CHMP.

The primary endpoint used for the AMAM study also differs from pivotal endpoints used in other CD development programmes which analysed results for the induction period and maintenance period separately. Instead, this application focuses on the week 52 results in a subgroup of patients who also showed a clinical response in week 12. However, the applicant investigated several endpoints which resemble endpoints used in other development at the end of the induction studies (i.e endoscopic response and clinical remission by CDAI/PRO at week 12) and at the end of the maintenance period (clinical response by PRO response by PRO at Week 12, and endoscopic response and clinical remission by CDAI at week 52 or clinical response by PRO at Week 12, and endoscopic remission and clinical remission by CDAI at week 52).

Secondary endpoints

There were several secondary endpoints in the study which investigated the efficacy results at the end of the induction period (at week 12) as well as at the end of the maintenance period (week 52). Composite endpoints combining results from week 12 and week 52 were also present. Clinical response and remission by PRO and CDAI and endoscopic response and remission were the most important outcome measures investigated. As discussed, definitions of these outcome measure as used by the MAH are acceptable to the CHMP.

Main secondary endpoints

Major secondary endpoints that involve comparisons versus placebo include proportion of participants achieving

endoscopic responded at Week 52, proportion of participants achieving clinical remission by CDAIe at Week 52, proportion of participants achieving endoscopic responded at Week 12, proportion of participants achieving endoscopic remission SES-CD ≤4i at Week 12, proportion of participants achieving clinical response by PROc at Week 12, proportion of participants achieving clinical remission by CDAIe at Week 12, change from baseline in FACIT-Fatigue scores at Week 12, clinical remission by PROf at Week 52, endoscopic remission SES-CD ≤4i at Week 52 and corticosteroid-free from Week 40 to Week 52 and clinical remission by CDAIe at Week 52

Comparison to ustekinumab

There were also two main secondary endpoints and several other secondary endpoints comparing the efficacy of mirikizumab with ustekinumab.

Endoscopic response (for superiority) and clinical remission by CDAI (for non-inferiority), both assessed at week 52, were compared between treatments. These endpoints were under multiplicity adjustment. A 10% difference as NI margin was selected. As indicated by the MAH, there is no universally accepted value for what is considered a clinically unimportant difference between 2 CD treatments based on CDAI remission. However, in a survey of International Organization for the Study of Inflammatory Bowel Diseases (IOIBD) members, a majority of the 46 respondents considered 10% or higher to be an adequate margin in NI trials for biologic-naïve and biologic-experienced patients (Olivera et al. 2018).

Of note, sensitivity analysis with lower NI margins of 8% and 5% also demonstrated non-inferiority to ustekinumab.

Efficacy in not-biologic-failed and biologic-failed subgroups

The pivotal study included patients who failed previous therapy (conventional or biological). To investigate whether the treatment benefit is observed in not-biologic-failed as well as in biologic-failed group of patients, subgroup analyses were performed. These subgroups analyses, including analysis of the co-primary endpoints and major secondary endpoints were without multiplicity adjustment.

Symptomatic Relief Over Time

Onset of action of the treatment is important for patients and prescribers. In the study, this was investigated through the assessment of proportion of participants with clinical remission (by CDAI) by visit and through the assessment of AP or SF change from baseline (by visit).

Fatigue and bowel urgency

Fatigue and bowel urgency are bothersome symptoms of CD. Change from baseline in FACIT-Fatigue Score at week 12 is one of main secondary endpoints in the study. Change from baseline at Week 52 is assessed as another secondary endpoint. FACIT-Fatigue Score has been accepted previously by the CHMP as a secondary endpoint for other products.

Bowel urgency was assessed using the Urgency Numeric Rating Scale (NRS). Urgency NRS was developed and previously validated for UC (Dubinsky et al. 2022), and its validation for CD was performed using AMAM data.

Efficacy data and additional analyses

Results

In total, 1152 patients were randomly assigned to the treatment in the study AMAM and 1150 took at least 1 dose of study treatment. Of these 1150 participants, 1065 had a baseline SES-CD of 7 or greater (4 or greater for isolated ileal disease). These participants comprised the primary analysis set (PAS) population. The majority of patients receiving active treatment (mirikizumab or ustekinumab) completed the induction period (95% and 96% respectively) and the maintenance period (84.5% and 85% respectively). In relation to patients on placebo only 52% responded to placebo at week 12 and continued to receive placebo during the maintenance period. 36% of patients originally assigned to placebo completed the study on placebo.

Baseline characteristics

CD presents most commonly in adolescence and early adulthood, but it may occur at any age. The mean age of enrolled patients was 36.2 (ranging from 17 to 76) and this is line with the age distribution as described in the literature. Although CD has been reported to occur more frequently in females, in this study slightly more men (55.1%) were enrolled. Of note, similar overrepresentation of men was seen in pivotal studies for other development programs. In relation to race, the majority of patients were white (71.1%) or Asian (25%). The mean BMI was 23.363 kg/m^2, and weight ranged from 21.1 kg to 155.0 kg.

As highlighted by the applicant, the original primary endpoint of clinical remission was based on AP and SF and it was later updated to CDAI, based on regulatory feedback from the US FDA. However, the entry criteria defining moderately to severely active disease based on AP and SF were not changed. In the study, moderate to severe CD was defined by an unweighted daily average SF $\geq$4 (loose and watery stools defined as Bristol Stool Scale Category 6 or 7), AND/OR an unweighted daily average AP $\geq$2 at baseline and this represents a moderately to severe population.

At baseline the mean AP was 2.1 (ranging from 0 to 3) and the mean SF was 5.7 (ranging from 0 to 31).

At baseline, the mean CDAI was 321.1 (ranging from 71.5 to 726.3). Some of the enrolled participants had baseline CDAI values outside of the range of 220 to 450, used to define moderate to severe CD. A total of 116 (11.0%) participants had baseline CDAI values <220, and 79 (7.5%) participants had baseline values $\geq$450.

In line with the inclusion criteria, all patients enrolled to the study had to have an inadequate response to, loss of response to, or intolerance to at least 1 of the medications (conventional or biological) used for treatment of CD.

As clarified by the MAH, the majority but not all enrolled patients (i.e. 77.7%) reported a prior conventional treatment failure whereas a prior biologic failure was reported in 517 (48.5%) participants.

ECCO guidelines (Gomollón et al. 2017; Adamina et al. 2020) traditionally recommended that CD patients need to have "failed, proven intolerant to, or have contraindications to 'conventional' therapy" before being started on a biologic treatment. However, these guidelines also include recommendations for early therapy with an anti-TNF drug for multiple subpopulations of high-risk CD patients. Therefore, the inclusion of a small proposition of patients who failed biologic treatment only could be justified taking into consideration the above guidelines.

In relation to the biologic-failed subgroup, only patients not responding or intolerant to anti-TNF or anti-integrin were enrolled to the study including 487 patients (46%) who failed anti-TNFs and 123 patients (11.5%) who failed anti-integrin antibodies. Information on the proportion of patients with prior TNFa failure/intolerance and prior vedolizumab failure/intolerance is included in section 5.1 of the SmPC**.**

Primary endpoint results

The primary objective of the study was met. The data showed that 38% of patients on mirikizumab achieved clinical response by patient-reported outcomes (PRO) at week 12 and endoscopic response at week 52, compared to 9% patients in the placebo cohort (RD 28.7 (99.5% CI:20.6, 36.8; p-value <.000001). In addition, 45.4% of patients on mirikizumab achieved clinical response by patient-reported outcomes (PRO) at week 12 and clinical remission by CDAI at week 52, compared to 19.6% patients on placebo (RD 25.8 (99.5% CI:15.9, 35.6; p-value <.000001). Supplementary analyses and sensitivity analyses showed consistent findings with the primary analyses.

Secondary endpoints results

All main secondary endpoints investigated in the study in comparison to placebo were met, including the most stringent such as Clinical Remission by CDAI at Week 12 (RD 12.4 (99.5% CI: (2.2, 22.7); p- value =.001431) and Endoscopic Remission by SES-CD at Week 12 (RD 6.8 (99.5% CI: (1.6, 12.1); p value =.003414). The percentage of patients with clinical remission by CDAI as compared to placebo increased at week 52 with RD 34.6 (99.5% CI 24.7, 44.4), p-value <.000001. At week 12, there was an improvement in Fatigue as measured by FACIT-Fatigue score. LSM Difference versus placebo was 3.22 (99.5% CI 1.24, 5.19, p=.000005).

Mirikizumab was also superior as compared to placebo in composite endpoints which resemble endpoints used in other development programs at the end of the induction period and at the end of the maintenance period. For endoscopic response and clinical remission by CDAI at week 12, OR versus placebo was 3.22 (95%CI 1.63;6.36). For clinical response by PRO at Week 12, and endoscopic response and clinical remission by CDAI at week 52 RD was 23.6% (95% CI 18.7, 28.6). For the secondary endpoint which resemble EMA guideline-stipulated endpoints: Endoscopic Remission rate and Clinical Remission Rate by CDAI at week 52, OR versus placebo was 16.98 (95% CI 4.12, 69.9)

Early onset of efficacy was observed in clinical remission by CDAI, with differentiation between mirikizumab and placebo groups at Week 4. Mirikizumab treatment group also showed nominally significantly greater mean reductions compared to placebo in AP at Week 4, and in SF at Week 6.

Mirikizumab showed statistically significant improvements (non-multiplicity controlled) across most efficacy measures in biologic-failed and not-biologic failed subgroups compared with placebo. For the co-primary Endpoints by Prior Biologic Failure the risk difference versus placebo ranged from 20.8% to 27.5% for the not-biologic failed group and ranged from 30.5% to 31.0 % for the biologic failed group.

Mirikizumab demonstrated noninferiority to ustekinumab in Week 52 clinical remission by CDAI. Superiority over ustekinumab in Week 52 endoscopic response by SES-CD was not achieved. Participants treated with mirikizumab reported greater mean change (improvement) from baseline in Urgency NRS score compared to placebo at Week 12, with a mean improvement of 2.4 points (SE = 0.1) for those in the mirikizumab group and 1.6 points (SE = 0.2) for the placebo group (p-value = .000011).

The results reported across the subgroups analyzed were in general consistent with the results for the overall population. The point estimates for all subgroups favoured mirikizumab, 95% confidence interval contains the value of zero only for few smaller subgroups, i.e. patients with baseline Fecal Calprotectin <=250 ug/g, with Ileal disease location, obese and in patients with a short history of the disease.

The MAH also performed the subgroup analysis depending on baseline CDAI score, baseline SF score (average: <7, >=7), and baseline AP score (average <2, >=2). In general, the results for these subgroups were consistent with the results for the overall population.

In the subgroup of patients with baseline CDAI score >=220 and <450 (used to define moderate to severe disease), mirikizumab was superior in comparison to placebo for clinical remission and endoscopic remission at week 12 and 52.

Not all patients responded to treatment by the end of the induction period. At week 12 a clinical response by PRObb was reported in 204/281 (72.6%) patients. However, the percentage of patients who responded to treatment increased further with plateau achieved around week 24. Therefore, consideration should be given to discontinuing treatment in patients who have shown no evidence of therapeutic benefit by week 24.

One pivotal study

The MAH provided one pivotal study. For one pivotal study as per the guideline ((CPMP/EWP/2330/99 Rev.2) the following criteria need to be fulfilled:

- The internal validity. There should be no indications of a potential bias.
- The external validity. The study population should be suitable for extrapolation to the population to be treated.
- Clinical relevance. The estimated size of treatment benefit must be large enough to be clinically valuable.
- The degree of statistical significance
- Data quality.
- Internal consistency. Similar effects demonstrated in different pre-specified sub-populations. All-important endpoints showing similar findings.
- Centre effects. None of the study centres should dominate the overall result, neither in terms of number of subjects nor in terms of magnitude of effect.
- The plausibility of the hypothesis tested.

The criteria as listed above are fulfilled. Mirikizumab is a drug with known mechanism of action, and it is already approved in a related indication (i.e. ulcerative colitis). Other anti IL23 inhibitors are approved for the same indication. A higher degree of statistical significance was applied in the study and there is no objection to the quality of the data. Similar effects were demonstrated in all pre-specified sub-populations and all-important endpoints showed similar findings. For the primary endpoints and most other secondary endpoints the difference could be considered as not only statistically significant but also

clinically relevant. Therefore, the CHMP concludes that efficacy is demonstrated in the intended population.

2.6.7. Conclusions on the clinical efficacy

The clinical efficacy of mirikizumab in adult patients with moderately to severely active Crohn's disease who have had an inadequate response, lost response to, or were intolerant to either conventional therapy or a biologic treatment has been demonstrated.

2.6.8. Clinical safety

Mirikizumab (LY3074828) is a humanized immunoglobulin G4 isotype monoclonal antibody that binds with high affinity and specificity to the p19 subunit of IL-23, a naturally occurring proinflammatory cytokine, and inhibits its interaction with the IL-23 receptor. The IL-23 pathway has been clinically demonstrated to play a central role in the pathogenesis of multiple immune-mediated and chronic inflammatory diseases, including CD. Following approval of Mirikizumab for treatment of UC in 2023, the MAH is now seeking a new indication in patients with CD, which is the focus of this assessment.

The primary source of safety data supporting this MAA come from the Phase 3 pivotal study in adults with moderate to severely active CD:

- Phase 3 Study I6T-MC-AMAM (AMAM).

Supportive safety data is provided from two other studies in adults with moderate to severely active CD:

- Phase 2 Study I6T-MC-AMAG (AMAG), and
- Phase 3 LTE Study I6T-MC-AMAX (AMAX)

In addition to the safety data from the above 3 trials for moderately to severely active CD, additional supportive safety data is provided from adult participants with UC and psoriasis from:

4 studies in participants with moderately to severely active UC, including

- Phase 2 Study I6T-MC-AMAC (AMAC)
- Phase 3 Study I6T-MC-AMAN (AMAN)
- Phase 3 Study I6T-MC-AMBG (AMBG), and
- Phase 3 LTE Study I6T-MC-AMAP (AMAP), and

5 studies in participants with moderate-to-severe plaque psoriasis, including

- I6T-MC-AMBP (AMBP)
- I6T-MC-AMAF (AMAF)
- I6T-MC-AMAK (AMAK)
- I6T-MC-AMAJ (AMAJ), and
- I6T-MC-AMAH (AMAH).

The MAH has also provided blinded listings from the ongoing double-blind studies and study periods (Studies AMAN and AMBG China Maximized Extended Enrollment) as well as the available safety data from paediatric studies separately. These data were not included in the integrated safety database.

Analysis sets

Six analysis sets are used to assess safety. There are 3 CD analysis sets, 2 IBD analysis sets (CD and UC) and 1 all-disease- state analysis set (CD, UC and psoriasis).

The focus of the safety assessment is on the first two CD analysis sets from the pivotal study AMAM:

- CD Induction Placebo and Active- Controlled Analysis Set (Week 0 through Week 12)
- CD Treatment Regimen Placebo- and Active- Controlled Analysis Set (Week 0 through Week 52)

The safety population included all randomized participants who took at least 1 dose of study intervention, even if the participant did not take the assigned study intervention, did not receive the correct study intervention, or otherwise did not follow the protocol.

The IBD Randomized Induction Integrated Analysis Set was used to provide additional randomized placebo-controlled data for the ADR determination.

Table Safety Analysis Sets: Controlled

Analysis Set (Controlled?)	Studies Included I6T-MC-	Treatment Period	Analysis Population	Treatment Groups	Treatment Comparisons	Purpose
CD						
CD Induction Placebo- and Active-Controlled Analysis Set (Yes)	AMAM	Induction (Weeks 0 to 12)	CD safety population	• Miri 900 mg Q4W IV • Pbo, and • Uste ~6 mg/kg IV for 1 dose, then 90 mg SC at Week 8	• Miri 900 mg Q4W IV vs pbo • Miri 900 mg Q4W IV vs uste ~6 mg/kg IV for 1 dose, then 90 mg SC at Week 8[a]	To evaluate safety of miri 900 mg Q4W IV compared with pbo over a 12-week Induction Period. This is the main analysis used for ADR determination.[a]
CD Treatment Regimen Placebo- and Active-Controlled Analysis Set[b] (Yes)	AMAM	Treatment Period (Weeks 0 to 52)	CD safety population	• Miri 900 mg Q4W IV followed by miri 300 mg Q4W SC • Pbo • Uste ~6 mg/kg IV for 1 dose, then 90 mg SC Q8W.	• Miri 900 mg Q4W IV followed by miri 300 mg Q4W SC vs pbo[b] • Miri 900 mg Q4W IV, miri 300 mg Q4W SC vs uste ~6 mg/kg IV for 1 dose, then 90 mg SC Q8W[a]	To evaluate the safety of the entire miri treatment scheme (induction followed by maintenance) through the 52-week period.[a]

Analysis Set (Controlled?)	Studies Included I6T-MC-	Treatment Period	Analysis Population	Treatment Groups	Treatment Comparisons	Purpose
IBD (CD and UC)						
IBD Randomized Induction Integrated Analysis Set (Yes)	AMAM and AMAN	• All treatment periods where participants are randomly assigned to either miri or pbo for induction treatment	IBD miri exposures safety population to include CD and UC induction safety populations	• Miri 900 mg Q4W IV (CD induction) and • Miri 300 mg Q4W IV (UC induction) • Pbo (dose cohorts)	Pooled miri 900 mg Q4W IV (CD induction) and miri 300 mg Q4W IV (UC induction) vs pbo	To provide additional randomized placebo-controlled data for the ADR determination.

Table Safety Analysis Sets: Uncontrolled

Analysis Set (Controlled?)	Studies Included I6T-MC-	Treatment Period	Analysis Population	Treatment Groups	Treatment Comparisons	Purpose
CD Mirikizumab Exposures Integrated Analysis Set[c] (No)	AMAG, AMAM, and AMAX	• All treatment periods where miri is administered • All treatment periods where miri is administered plus off miri/post-treatment follow-up time	CD miri exposures safety population	Miri (all doses and routes)	N/A	To facilitate identification of rarer adverse events or those with a delayed onset that might require longer observation periods and further evaluation.
IBD Integrated Analysis Set[d] (No)	AMAG, AMAM, AMAX, AMAC, AMAN, AMBG, and AMAP	• All treatment periods where miri is administered. • All treatment periods where miri is administered plus off miri/post-treatment follow-up time.	IBD miri exposures safety population	Miri (all doses and routes)	N/A	To provide supportive information for some sections of the SCS where the totality of evidence is presented as needed.
All disease states (CD, UC, and psoriasis)						
All Miri Exposures Integrated Analysis Set (No)	AMAG, AMAM, AMAX, AMAC, AMAN, AMBG, AMAP, AMBP, AMAF, AMAK, AMAJ, and AMAH.	• All treatment periods where miri is administered. • All treatment periods where miri is administered plus off miri/post-treatment follow-up time.	All miri exposures safety population	Miri (all doses and routes)	N/A	To provide supportive information for some sections of the SCS where the totality of evidence is presented as needed.

Abbreviations: ADR = adverse drug reaction; CD = Crohn's disease; IBD = inflammatory bowel disease; IV = intravenous; miri = mirikizumab; N/A = not applicable; pbo = placebo; PSAP = program safety analysis plan; Q4W = every 4 weeks; Q8W = every 8 weeks; SC = subcutaneous; SCS = Summary of Clinical Safety; UC = ulcerative colitis; uste = ustekinumab; vs = versus.

[a] The main comparisons are made against pbo, but supportive comparisons against uste are used to complement the safety analysis. Data are presented for pbo group participants, uste treatment participants, and miri treatment participants. However, discussions of uste data are included only when relevant.

Comparisons between treatment groups are based on

- raw frequencies (%) for the CD Induction Placebo- and Active-Controlled and IBD Randomized Induction Integrated Analysis Sets, and
- EAIRs (per 100 PYE) for the:
  - CD Treatment Regimen Placebo- and Active-Controlled Analysis Set to account for the differences in exposure length between placebo group participants compared with mirikizumab-treated participants, and
  - CD Mirikizumab Exposures Integrated Analysis Sets, to account for the differences in exposure length between Study AMAM mirikizumab treatment participants and mirikizumab treatment participants with longer exposures.

2.6.8.1. Patient exposure

Study AMAM – Pivotal CD Study

In the Study AMAM Induction Period, the Safety Population included 1150 participants, including

- 211 placebo group participants

- 309 ustekinumab treatment participants, 1 dose IV then SC Q8W, and
- 630 mirikizumab treatment participants, IV Q4W

In Study AMAM, 1005 participants were eligible to continue on their randomly assigned treatment during maintenance, which included

- 109 placebo group participants who remained on placebo
- 296 ustekinumab treatment participants, and
- 600 mirikizumab treatment participants

Table: Total Exposure to Mirikizumab CD Treatment Regimen Placebo- and Active-Controlled, CD Mirikizumab Exposures Integrated, IBD Randomized Induction Integrated, IBD Integrated, and All Mirikizumab Exposures Integrated Analysis Sets

	CD Treatment Regimen			CD Miri Integrated[b]	IBD Induction Integrated		IBD Integrated	All Miri Integrated
	Pbo[a] N = 211	Miri N = 630	Uste N = 309	Miri N = 1178	Pbo N = 532	Miri N = 1588	Miri N = 2632	Miri N = 4802
Patient-weeks of exposure, mean (SD)	29.6 (19.7)	49.2 (11.5)	49.5 (11.2)	88.8 (69.4)	12.6 (2.6)	13.0 (1.9)	111.1 (83.0)	119.6 (71.5)
Weeks of exposure, n (%)								
>0	211 (100.0)	630 (100.0)	309 (100.0)	1178 (100)	532 (100)	1588 (100)	2632 (100)	4802 (100)
≥4	207 (98.1)	629 (99.8)	306 (99.0)	1154 (98.0)	521 (97.9)	1580 (99.5)	2598 (98.7)	4751 (98.9)
≥8	200 (94.8)	621 (98.6)	303 (98.1)	1131 (96.0)	500 (94.0)	1556 (98.0)	2553 (97.0)	4696 (97.8)
≥12	185 (87.7)	611 (97.0)	298 (96.4)	1099 (93.3)	469 (88.2)	1468 (92.4)	2489 (94.6)	4617 (96.1)
≥16	110 (52.1)	598 (94.9)	296 (95.8)	1070 (90.8)	–	–	2359 (89.6)	4475 (93.2)
≥24 (approximately 6 months)	97 (46.0)	581 (92.2)	292 (94.5)	1019 (86.5)	–	–	2264 (86.0)	4325 (90.1)
≥32	88 (41.7)	570 (90.5)	282 (91.3)	976 (82.9)	–	–	2053 (78.0)	4077 (84.9)
≥40	85 (40.3)	559 (88.7)	275 (89.0)	–	–	–	–	–
≥48	81 (38.4)	545 (86.5)	271 (87.7)	–	–	–	–	–
≥52 (approximately 1 year)	–	–	–	810 (68.8)	–	–	1840 (69.9)	3799 (79.1)
≥104 (approximately 2 years)	–	–	–	354 (30.1)	–	–	1238 (47.0)	2815 (58.6)
Total patient-years[c]	119.5	593.6	293.3	2004.2	128.0	394.5	5605.4	11003.1

Abbreviations: CD = Crohn's disease; IBD = inflammatory bowel disease; Miri = mirikizumab; n = number of participants in the specified category; N = number of participants in the safety analysis set; Pbo = placebo; SD = standard deviation; Uste = ustekinumab.

[a] The CD Treatment Regimen Placebo- and Active-Controlled Analysis Set includes all participants who were randomly assigned to pbo (that is, not limited to pbo responders). Participants who were randomly assigned to pbo and were nonresponders at Week 12 switched to miri treatment, and data from these participants after Week 12 are not included in the CD Treatment Regimen Placebo- and Active-Controlled Analysis Set.

[b] The CD Mirikizumab Exposures Integrated Analysis Set includes data from 85 Study AMAM participants who were randomly assigned to pbo at the start of Study AMAM and who were subsequently pbo nonresponders and switched to miri.

[c] Overall exposure in total patient-years is calculated as the sum of duration exposure in days for all participants in the dosing regimen divided by 365.25.

2.6.8.2. Adverse events

In the CD Induction Placebo- and Active-Controlled Analysis Set, the overall frequencies of TEAEs, SAEs, and discontinuations due to AEs were higher in placebo group participants compared with mirikizumab treatment participants.

Similarly, in the CD Treatment Regimen Placebo- and Active-Controlled Analysis Set, the overall EAIRs for TEAEs, SAEs, and discontinuations due to AEs were higher in placebo group participants compared with mirikizumab treatment participants.

Three deaths were reported in Study AMAM:

- 1 in a placebo group participant.
- 1 in an ustekinumab group participant.

- 1 in a placebo group nonresponder participant who switched to mirikizumab after Week 12.

Therefore, data from this participant are not included in the CD Treatment Regimen Analysis Set but are included in the CD Mirikizumab Exposures Integrated Analysis Set.

After the Study AMAX data cutoff date (15 June 2023), two additional deaths were reported in the LTE Study AMAX. These 2 participants were mirikizumab treatment participants in both Studies AMAM and AMAX. The number of deaths in the active- and placebo-controlled Study AMAM was low and balanced across groups. None were considered related to the study drug

In the CD Mirikizumab Exposures Integrated Analysis Set, which includes the LTE Study AMAX, the EAIRs of TEAEs, SAEs, and discontinuations from study treatment due to AEs were lower than the EAIRs in the CD Treatment Regimen Placebo- and Active-Controlled Analysis Set, indicating no increase in EAIRs with an increased exposure.

The overall safety profile of mirikizumab in the CD development program is consistent with the known safety profile of mirikizumab and no new ADRs are proposed.

Regarding ustekinumab comparisons, in the CD Induction Placebo- and Active-Controlled Analysis Set, the overall TEAEs and SAEs were less frequently reported in Ustekinumab treatment participants compared with mirikizumab treatment participants. This imbalance was not observed in the CD Treatment Regimen Placebo- and Active-Controlled Analysis Set, where the overall EAIRs for TEAEs and SAEs were similar between the groups. Discontinuations of study treatment due to AEs were less frequently reported in ustekinumab treatment participants compared with mirikizumab treatment participants in both the CD Induction Placebo- and Active-Controlled and CD Treatment Regimen Placebo- and Active-Controlled Analysis Sets.

Table **Overview of AEs CD Induction Placebo- and Active-Controlled, CD Treatment Regimen Placebo- and Active-Controlled, and CD Mirikizumab Exposures Integrated Analysis Sets**

Event, n (%) [EAIR]	CD Induction			CD Treatment Regimen			CD Miri Integrated[a]
	Pbo N = 211 PYE = 49	Miri N = 630 PYE = 150.4	Uste N = 309 PYE = 73.7	Pbo[b] N = 211 PYE = 119.5	Miri N = 630 PYE = 593.6	Uste N = 309 PYE = 293.3	Miri N = 1178 PYE = 2004.2
Participants with at least 1 TEAE	119 (56.4) [358.3]	326 (51.7) [317.4]	134 (43.4) [253.9]	154 (73.0) [291.8]	495 (78.6) [201.9]	239 (77.3) [180.4]	939 (79.7) [159.2]
Deaths	1 (0.5) [2.0]	0	0	1 (0.5) [0.8]	0	1 (0.3) [0.3]	1 (0.1) [0.0][c]
SAEs	19 (9.0) [40.0]	37 (5.9) [25.3]	11 (3.6) [15.4]	36 (17.1) [32.5]	65 (10.3) [11.5]	33 (10.7) [11.8]	158 (13.4) [8.5]
Discontinuations from study treatment due to AE	10 (4.7) [20.6][d]	15 (2.4) [10.0][d]	1 (0.3) [1.4]	20 (9.5) [17.1]	32 (5.1) [5.4]	8 (2.6) [2.7]	81 (6.9) [4.1]

Abbreviations: AE = adverse event; CD = Crohn's disease; EAIR = exposure-adjusted incidence rate; Miri = mirikizumab; n = number of participants in the specified category; N = number of participants in the safety analysis set; PYE = patient-years of exposure; SAE = serious adverse event; TEAE = treatment-emergent adverse event; Uste = ustekinumab.

[a] The CD Mirikizumab Exposures Integrated Analysis Set includes data from 85 Study AMAM participants who were randomly assigned to pbo at the start of Study AMAM and who were subsequently pbo nonresponders and switched to miri.

[b] The CD Treatment Regimen Placebo- and Active-Controlled Analysis Set includes all participants who were randomly assigned to pbo (that is, not limited to pbo responders). Participants who were randomly assigned to pbo and were nonresponders at Week 12 switched to miri treatment, and data from these participants after Week 12 are not included in the CD Treatment Regimen Placebo- and Active-Controlled Analysis Set.

[c] The death of a pbo group participant who was a pbo nonresponder who switched to miri after Week 12 is not included in the CD Treatment Regimen Placebo- and Active-Controlled Analysis Set but is included in the CD Mirikizumab Exposures Integrated Analysis Set.

[d] Two participants randomly assigned to pbo and 2 randomly assigned to miri reported AEs during the Induction Period (Weeks 0 to 12) but were not discontinued until the Maintenance Period (Weeks 12 to 52).

Source: Table AMAM.8.120, Table AMAM.8.122, and Table APP.2.7.4.18

Treatment-Emergent Adverse Events by System Organ Class

In both the CD Induction Placebo- and Active-Controlled and CD Treatment Regimen Placebo and Active-Controlled Analysis Sets, the SOCs with TEAEs reported by more than 10% of the participants in any treatment group were Infections and infestations and Gastrointestinal disorders**.**

Table SOCs Reported by At Least 10% of Mirikizumab Treatment Participants, by Decreasing Frequency in the CD Treatment Regimen Placebo- and Active-Controlled Analysis Set CD Induction Placebo- and Active-Controlled and CD Treatment Regimen Placebo- and Active-Controlled Analysis Sets

SOC, n (%) [EAIR]	CD Induction			CD Treatment Regimen		
	Pbo N = 211 PYE = 49	Miri N = 630 PYE = 150.4	Uste N = 309 PYE = 73.7	Pbo[a] N = 211 PYE = 119.5	Miri N = 630 PYE = 593.6	Uste N = 309 PYE = 293.3
Participants with at least 1 TEAE	119 (56.4) [358.3]	326 (51.7) [317.4]	134 (43.4) [253.9]	154 (73.0) [291.8]	495 (78.6) [201.9]	239 (77.3) [180.4]
Infections and infestations	33 (15.6) [72.7]	127 (20.2) [94.6]	42 (13.6) [61.1]	73 (34.6) [81.3]	261 (41.4) [59.7]	130 (42.1) [58.1]
Gastrointestinal disorders	45 (21.3) [101.6]	103 (16.3) [75.2]	42 (13.6) [61.8]	83 (39.3) [90.1]	203 (32.2) [42.7]	95 (30.7) [39.3]
General disorders and administration site conditions	15 (7.1) [31.7]	36 (5.7) [24.8]	10 (3.2) [13.8]	30 (14.2) [28.5]	124 (19.7) [23.9]	45 (14.6) [16.6]
Investigations	15 (7.1) [31.8]	47 (7.5) [32.5]	15 (4.9) [20.9]	27 (12.8) [24.8]	99 (15.7) [18.6]	42 (13.6) [15.6]
Musculoskeletal and connective tissue disorders	15 (7.1) [31.7]	46 (7.3) [31.9]	9 (2.9) [12.4]	24 (11.4) [22.1]	98 (15.6) [18.4]	29 (9.4) [10.5]
Skin and subcutaneous tissue disorders	11 (5.2) [23.0]	41 (6.5) [28.4]	17 (5.5) [23.9]	20 (9.5) [18.1]	97 (15.4) [18.1]	35 (11.3) [13.1]
Blood and lymphatic system disorders	17 (8.1) [36.2]	41 (6.5) [28.3]	17 (5.5) [23.9]	26 (12.3) [24.0]	76 (12.1) [14.0]	34 (11.0) [12.6]
Nervous system disorders	8 (3.8) [16.8]	30 (4.8) [20.5]	13 (4.2) [18.1]	14 (6.6) [12.3]	71 (11.3) [12.9]	28 (9.1) [10.2]

CD Induction Placebo- and Active-Controlled Analysis Set

Infections and infestations

In the Infections and infestations SOC, the frequency of participants who reported a TEAE was higher in mirikizumab treatment participants compared with placebo group participants. In the CD Treatment Regimen Placebo- and Active-Controlled Analysis Set, this imbalance was not observed, as the EAIR was higher in placebo group participants compared with mirikizumab treatment participants. In mirikizumab treatment participants, the most frequently reported TEAEs within the Infections and infestations SOC were COVID-19, URTI, and Nasopharyngitis.

Gastrointestinal disorders

In the Gastrointestinal disorders SOC, the frequency of participants who reported a TEAE was lower in mirikizumab treatment participants compared with placebo group participants. The most frequently reported TEAE in the Gastrointestinal disorders SOC was CD. Notably, a higher frequency of placebo group participants reported a TEAE of CD compared with mirikizumab treatment participants, clinically indicative of a lack of improvement of CD in placebo group participants.

In the remaining SOCs, no other frequency differences greater than 1.5% were observed in mirikizumab treatment participants compared with placebo group participants.

Skin and subcutaneous tissue disorders

In the CD Induction Placebo- and Active-Controlled Analysis Set, a higher frequency of mirikizumab treatment participants reported a TEAE in the Skin and subcutaneous tissue disorders SOC compared with placebo group participants. This difference is mainly due to higher frequencies of TEAEs within the Rash cluster, which was previously identified as an ADR for mirikizumab.

In the CD Treatment Regimen Placebo- and Active-Controlled Analysis Set, this imbalance was not observed.

CD Treatment Regimen Placebo- and Active-Controlled Analysis Set

In the SOCs reported by more than 10% of the participants in any treatment group, the SOC EAIRs were lower in mirikizumab treatment participants compared with placebo group participants except for

- Skin and subcutaneous tissue disorders – where the EAIRs were the same, and
- Nervous system disorders – where the EAIRs were similar.

Table SOCs Reported by At least 10% of Mirikizumab Treatment Participants, by Decreasing Frequency in the CD Teatment Regimen Placebo-And Active-Controlled Analysis Set CD induction Placebo-and Active-Controlled and CT Treatment Regimen Placebo- and Active-Controlled Analysis Sets

SOC, n (%) [EAIR]	CD Induction			CD Treatment Regimen		
	Pbo N = 211 PYE = 49	Miri N = 630 PYE = 150.4	Uste N = 309 PYE = 73.7	Pbo[a] N = 211 PYE = 119.5	Miri N = 630 PYE = 593.6	Uste N = 309 PYE = 293.3
Participants with at least 1 TEAE	119 (56.4) [358.3]	326 (51.7) [317.4]	134 (43.4) [253.9]	154 (73.0) [291.8]	495 (78.6) [201.9]	239 (77.3) [180.4]
Infections and infestations	33 (15.6) [72.7]	127 (20.2) [94.6]	42 (13.6) [61.1]	73 (34.6) [81.3]	261 (41.4) [59.7]	130 (42.1) [58.1]
Gastrointestinal disorders	45 (21.3) [101.6]	103 (16.3) [75.2]	42 (13.6) [61.8]	83 (39.3) [90.1]	203 (32.2) [42.7]	95 (30.7) [39.3]
General disorders and administration site conditions	15 (7.1) [31.7]	36 (5.7) [24.8]	10 (3.2) [13.8]	30 (14.2) [28.5]	124 (19.7) [23.9]	45 (14.6) [16.6]
Investigations	15 (7.1) [31.8]	47 (7.5) [32.5]	15 (4.9) [20.9]	27 (12.8) [24.8]	99 (15.7) [18.6]	42 (13.6) [15.6]
Musculoskeletal and connective tissue disorders	15 (7.1) [31.7]	46 (7.3) [31.9]	9 (2.9) [12.4]	24 (11.4) [22.1]	98 (15.6) [18.4]	29 (9.4) [10.5]
Skin and subcutaneous tissue disorders	11 (5.2) [23.0]	41 (6.5) [28.4]	17 (5.5) [23.9]	20 (9.5) [18.1]	97 (15.4) [18.1]	35 (11.3) [13.1]
Blood and lymphatic system disorders	17 (8.1) [36.2]	41 (6.5) [28.3]	17 (5.5) [23.9]	26 (12.3) [24.0]	76 (12.1) [14.0]	34 (11.0) [12.6]
Nervous system disorders	8 (3.8) [16.8]	30 (4.8) [20.5]	13 (4.2) [18.1]	14 (6.6) [12.3]	71 (11.3) [12.9]	28 (9.1) [10.2]

Common TEAEs

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

The most common TEAEs reported in the mirikizumab treatment participants were COVID-19, Nasopharyngitis, and URTI. These TEAEs are included in the URTI including COVID-19 (cluster), which is proposed as an ADR.

The following table summarizes only the results for TEAEs occurring in at least 2% of mirikizumab treatment participants in the 3 CD analysis sets.

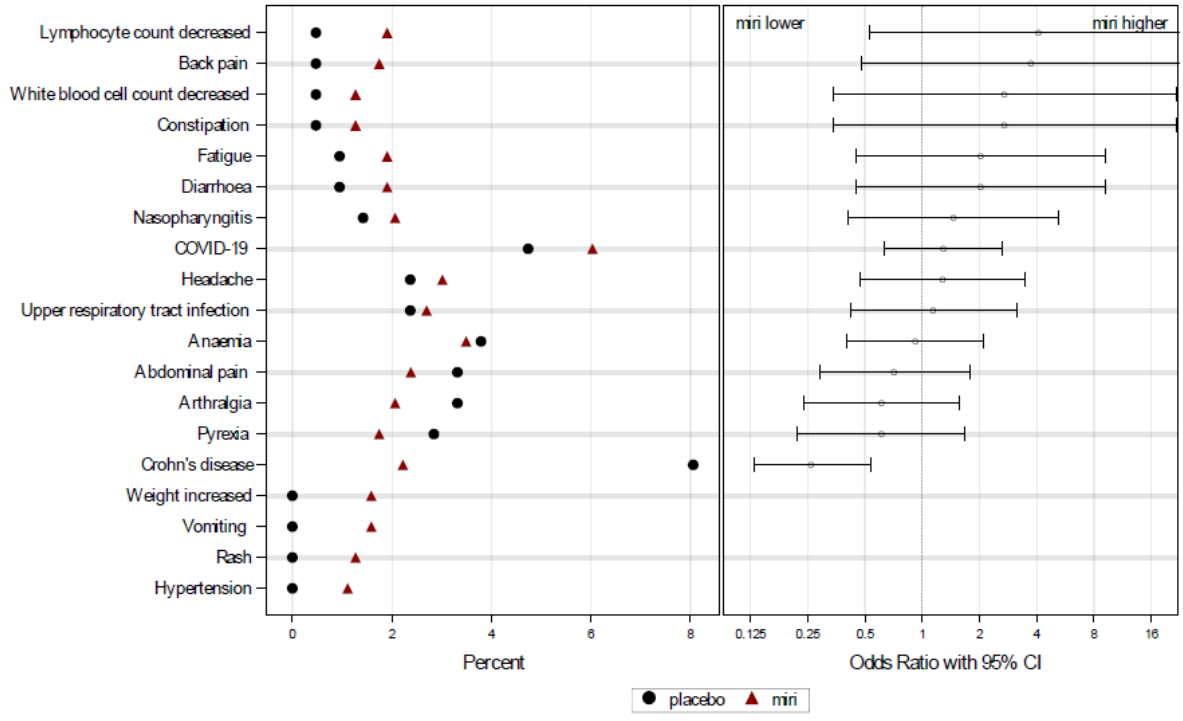
Table TEAEs occurring in at least 2% of mirikizumab treatment participants in the 3 CD analysis sets.

PT, n (%) [EAIR]	CD Induction			CD Treatment Regimen			CD Miri Integrated[a]
	Pbo N = 211 PYE = 49	Miri N = 630 PYE = 150.4	Uste N = 309 PYE = 73.7	Pbo[b] N = 211 PYE = 119.5	Miri N = 630 PYE = 593.6	Uste N = 309 PYE = 293.3	Miri N = 1178 PYE = 2004.2
Participants with at least 1 TEAE	119 (56.4) [358.3]	326 (51.7) [317.4]	134 (43.4) [253.9]	154 (73.0) [291.8]	495 (78.6) [201.9]	239 (77.3) [180.4]	939 (79.7) [159.2]
COVID-19	10 (4.7) [20.9]	38 (6.0) [26.0]	10 (3.2) [13.8]	29 (13.7) [26.4]	104 (16.5) [19.3]	47 (15.2) [17.3]	242 (20.5) [13.7]
Nasopharyngitis	3 (1.4) [6.1]	13 (2.1) [8.8]	6 (1.9) [8.2]	9 (4.3) [7.7]	36 (5.7) [6.3]	19 (6.1) [6.7]	113 (9.6) [6.2]
Upper respiratory tract infection	5 (2.4) [10.3]	17 (2.7) [11.5]	7 (2.3) [9.6]	9 (4.3) [7.8]	38 (6.0) [6.7]	22 (7.1) [7.8]	105 (8.9) [5.7]
Arthralgia	7 (3.3) [14.5]	13 (2.1) [8.8]	2 (0.6) [2.7]	11 (5.2) [9.6]	41 (6.5) [7.2]	8 (2.6) [2.8]	100 (8.5) [5.5]
Headache	5 (2.4) [10.4]	19 (3.0) [12.9]	6 (1.9) [8.3]	9 (4.3) [7.8]	41 (6.5) [7.2]	15 (4.9) [5.3]	96 (8.1) [5.3]
Anaemia	8 (3.8) [16.7]	22 (3.5) [14.9]	7 (2.3) [9.6]	14 (6.6) [12.2]	42 (6.7) [7.4]	15 (4.9) [5.3]	97 (8.2) [5.2]
Abdominal pain	7 (3.3) [14.5]	15 (2.4) [10.1]	4 (1.3) [5.5]	13 (6.2) [11.2]	28 (4.4) [4.8]	10 (3.2) [3.5]	75 (6.4) [4.0]
Crohn's disease	17 (8.1) [36.0]	14 (2.2) [9.4]	4 (1.3) [5.5]	33 (15.6) [30.2]	26 (4.1) [4.4]	19 (6.1) [6.6]	73 (6.2) [3.7]
Pyrexia	6 (2.8) [12.4]	11 (1.7) [7.4]	1 (0.3) [1.4]	8 (3.8) [6.8]	25 (4.0) [4.3]	8 (2.6) [2.8]	68 (5.8) [3.6]
Diarrhoea	2 (0.9) [4.1]	12 (1.9) [8.1]	4 (1.3) [5.5]	10 (4.7) [8.6]	35 (5.6) [6.1]	12 (3.9) [4.2]	67 (5.7) [3.5]
Injection site reaction	0	1 (0.2) [0.7]	0	0	24 (3.8) [4.1]	4 (1.3) [1.4]	58 (4.9) [3.1]

PT, n (%) [EAIR]	CD Induction			CD Treatment Regimen			CD Miri Integrated[a]
	Pbo N = 211 PYE = 49	Miri N = 630 PYE = 150.4	Uste N = 309 PYE = 73.7	Pbo[b] N = 211 PYE = 119.5	Miri N = 630 PYE = 593.6	Uste N = 309 PYE = 293.3	Miri N = 1178 PYE = 2004.2
Hypertension	0	7 (1.1) [4.7]	2 (0.6) [2.7]	3 (1.4) [2.5]	19 (3.0) [3.3]	3 (1.0) [1.0]	56 (4.8) [2.9]
Back pain	1 (0.5) [2.0]	11 (1.7) [7.4]	1 (0.3) [1.4]	2 (0.9) [1.7]	20 (3.2) [3.5]	3 (1.0) [1.0]	51 (4.3) [2.6]
Vomiting	0	10 (1.6) [6.7]	1 (0.3) [1.4]	1 (0.5) [0.8]	23 (3.7) [4.0]	6 (1.9) [2.1]	47 (4.0) [2.4]
Fatigue	2 (0.9) [4.1]	12 (1.9) [8.1]	0	10 (4.7) [8.7]	23 (3.7) [4.0]	7 (2.3) [2.4]	45 (3.8) [2.3]
Nausea	1 (0.5) [2.0]	6 (1.0) [4.0]	4 (1.3) [5.5]	4 (1.9) [3.4]	15 (2.4) [2.6]	7 (2.3) [2.4]	42 (3.6) [2.2]
Rash	0	8 (1.3) [5.4]	1 (0.3) [1.4]	3 (1.4) [2.6]	19 (3.0) [3.3]	1 (0.3) [0.3]	41 (3.5) [2.1]
Blood creatine phosphokinase increased	0	4 (0.6) [2.7]	3 (1.0) [4.1]	2 (0.9) [1.7]	15 (2.4) [2.6]	7 (2.3) [2.4]	38 (3.2) [2.0]
Weight increased	0	10 (1.6) [6.7]	2 (0.6) [2.7]	1 (0.5) [0.8]	17 (2.7) [2.9]	4 (1.3) [1.4]	37 (3.1) [1.9]
Injection site pain	1 (0.5) [2.0]	3 (0.5) [2.0]	1 (0.3) [1.4]	8 (3.8) [7.0]	20 (3.2) [3.4]	11 (3.6) [3.8]	36 (3.1) [1.9]
Influenza	1 (0.5) [2.0]	2 (0.3) [1.3]	1 (0.3) [1.4]	4 (1.9) [3.4]	10 (1.6) [1.7]	6 (1.9) [2.1]	35 (3.0) [1.8]
Constipation	1 (0.5) [2.0]	8 (1.3) [5.4]	2 (0.6) [2.7]	2 (0.9) [1.7]	17 (2.7) [2.9]	6 (1.9) [2.1]	34 (2.9) [1.7]
Alanine aminotransferase increased	1 (0.5) [2.0]	6 (1.0) [4.0]	1 (0.3) [1.4]	1 (0.5) [0.8]	17 (2.7) [2.9]	2 (0.6) [0.7]	34 (2.9) [1.7]
Urinary tract infection	1 (0.5) [2.0]	5 (0.8) [3.3]	1 (0.3) [1.4]	3 (1.4) [2.5]	13 (2.1) [2.2]	4 (1.3) [1.4]	33 (2.8) [1.7]
Abdominal pain upper	2 (0.9) [4.1]	5 (0.8) [3.3]	5 (1.6) [6.8]	3 (1.4) [2.5]	15 (2.4) [2.6]	8 (2.6) [2.8]	33 (2.8) [1.7]
Sinusitis	1 (0.5) [2.0]	4 (0.6) [2.7]	0	2 (0.9) [1.7]	9 (1.4) [1.5]	5 (1.6) [1.7]	32 (2.7) [1.6]

PT, n (%) [EAIR]	CD Induction			CD Treatment Regimen			CD Miri Integrated[a]
	Pbo N = 211 PYE = 49	Miri N = 630 PYE = 150.4	Uste N = 309 PYE = 73.7	Pbo[b] N = 211 PYE = 119.5	Miri N = 630 PYE = 593.6	Uste N = 309 PYE = 293.3	Miri N = 1178 PYE = 2004.2
Gastroenteritis	0	6 (1.0) [4.0]	3 (1.0) [4.1]	5 (2.4) [4.3]	15 (2.4) [2.6]	8 (2.6) [2.8]	32 (2.7) [1.6]
Oropharyngeal pain	1 (0.5) [2.0]	2 (0.3) [1.3]	1 (0.3) [1.4]	1 (0.5) [0.8]	10 (1.6) [1.7]	4 (1.3) [1.4]	30 (2.5) [1.5]
Pharyngitis	2 (0.9) [4.1]	4 (0.6) [2.7]	1 (0.3) [1.4]	3 (1.4) [2.5]	9 (1.4) [1.5]	5 (1.6) [1.7]	28 (2.4) [1.4]
Cough	1 (0.5) [2.0]	3 (0.5) [2.0]	1 (0.3) [1.4]	3 (1.4) [2.5]	10 (1.6) [1.7]	5 (1.6) [1.7]	28 (2.4) [1.4]
Aspartate aminotransferase increased	0	2 (0.3) [1.3]	2 (0.6) [2.7]	1 (0.5) [0.8]	11 (1.7) [1.9]	4 (1.3) [1.4]	25 (2.1) [1.3]
Injection site erythema	0	0	0	0	13 (2.1) [2.2]	1 (0.3) [0.3]	23 (2.0) [1.2]
Lymphocyte count decreased	1 (0.5) [2.0]	12 (1.9) [8.1]	3 (1.0) [4.1]	4 (1.9) [3.4]	15 (2.4) [2.6]	5 (1.6) [1.7]	23 (2.0) [1.2]
White blood cell count decreased	1 (0.5) [2.0]	8 (1.3) [5.4]	1 (0.3) [1.4]	1 (0.5) [0.8]	15 (2.4) [2.6]	5 (1.6) [1.7]	23 (2.0) [1.2]

Figure **TEAEs occurring in at least 1% of mirikizumab treatment participants sorted by odds ratio CD Induction Placebo- and Active-Controlled Analysis Set**



The figure above shows the OR for TEAEs occurring in at least 1% of mirikizumab treatment participants in the CD Induction Placebo- and Active-Controlled Analysis Set.

The TEAEs that were identified for further evaluation from each analysis set were:

Infusion related hypersensitivity reaction

In the CD Induction Placebo- and Active-Controlled Analysis Set, Infusion related hypersensitivity reaction was reported at a low frequency in mirikizumab treatment participants (n = 3, 0.5%). One event was reported as moderate and 2 were reported as severe. None were reported as serious. All 3 events led to study treatment discontinuation and were considered related to study drug by the investigator.

The time-to-onset pattern was after the second or third infusion and on the same day of the infusion.

One placebo group participant reported a moderate Infusion related hypersensitivity reaction during the second infusion that did not lead to discontinuation.

Although none were serious and uncommonly observed, Infusion related hypersensitivity reaction events that occurred in mirikizumab treatment participants had a specific time-to-onset pattern, were all considered related to study drug by the investigators and led to discontinuation in all cases. Infusion related hypersensitivity reaction is considered an ADR for mirikizumab for the UC indication, and it will remain as an ADR.

Rash

In the CD Induction Placebo- and Active-Controlled Analysis Set, rash was reported more frequently in mirikizumab treatment participants compared with placebo group participants. In mirikizumab treatment participants, all 8 Rash events were reported as mild or moderate in severity. None were reported as serious or led to study treatment discontinuation. Of the 8 mirikizumab treatment participants who reported Rash, all remained on mirikizumab and 5 were considered related to study drug by the investigator. No pattern in the time-to-onset, duration of the events, or common underlying etiology was observed. The Rash cluster, which includes Rash (PT), is considered a mirikizumab ADR for the UC indication, and will remain as an ADR.

Injection site reaction

In the CD Treatment Regimen Placebo- and Active-Controlled Analysis Set, Injection site reaction was reported at a higher incidence in mirikizumab treatment participants compared with placebo group participants. In mirikizumab treatment participants, all events were reported as mild or moderate in severity. None were serious or led to treatment discontinuation. Most events occurred on the day of an SC injection and resolved within 48 hours. All events were considered related to study drug by the investigator.

Treatment period:

The injection site reaction (HLT) was reported in 65 participants (EAIR = 15.3 per 100 PYE) in the mirikizumab group, 7 participants (EAIR = 10.4 per 100 PYE) in the placebo group, and 17 participants (EAIR = 7.1 per 100 PYE) in the ustekinumab group.

- Injection site reaction
    - 0 participant (EAIR = 0 per 100 PYE) in the placebo group
    - 4 participants (EAIR = 1.6 per 100 PYE) in the ustekinumab group, and
    - 24 participants (EAIR = 5.5 per 100 PYE) in the mirikizumab group.

One participant (PT: Injection site pain) in the mirikizumab group discontinued study treatment due to injection site reactions (HLT) during the Treatment Regimen Period.

Injection site reaction (HLT), which includes the Injection site reaction (PT), is considered a mirikizumab ADR cluster for the UC indication and will remain within this ADR cluster.

Injection site erythema

In the CD Treatment Regimen Placebo- and Active-Controlled Analysis Set, Injection site erythema was reported at a higher incidence in mirikizumab treatment participants compared with placebo group participants. In mirikizumab treatment participants, all 13 events were reported as mild or moderate in severity. None were reported as serious or led to study treatment discontinuation. Most events had onset on the day of an SC injection and lasted 2 days. No common underlying etiology was observed. Of the 13 mirikizumab treatment participants who reported Injection site erythema, all remained on mirikizumab, and 12 cases were considered related to study drug by the investigator.

Injection site reaction (HLT), which includes the Injection site erythema (PT), is considered a mirikizumab ADR cluster for the UC indication, and will remain within this ADR cluster.

COVID-19

In the CD Induction Placebo- and Active-Controlled Analysis Set, COVID-19 was reported more frequently in mirikizumab treatment participants (6.0%) compared with placebo group participants (4.7%). In mirikizumab treatment participants, all 38 events were reported as mild or moderate in severity. One event was reported as serious) No deaths or discontinuations were reported. No pattern in the time-to-onset was observed. All participants recovered without sequela. One event was considered related to study drug by the investigator.

In the CD Treatment Regimen Placebo- and Active-Controlled Analysis Set, this imbalance was not observed, as the EAIR was higher in placebo group participants compared with mirikizumab treatment participants.

The mirikizumab CD clinical program was conducted during the COVID-19 pandemic. However, most participants were enrolled after 2021, when vaccines were already available. This might explain the mild profile of COVID-19 events, more similar to classical URTIs in the CD clinical program. Therefore, COVID-19 is being proposed to be included under the URTI cluster list. The URTI cluster is considered a mirikizumab ADR for the UC indication, and it will remain as an ADR.

Back pain

In the CD Induction Placebo- and Active-Controlled and CD Treatment Regimen Placebo- and Active-Controlled Analysis Sets, Back pain was reported at a higher frequency and EAIR in mirikizumab treatment participants compared with placebo group participants.

Overall, the frequency of was low, the OR crossed 1, and the 95% CI was wide. The observed imbalance is not unexpected, given the overall low incidence rate.

In mirikizumab treatment participants, all 20 events were reported as mild or moderate in severity. 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. Of mirikizumab treatment participants who reported back pain, all remained on mirikizumab and most recovered while on mirikizumab treatment. One case was considered related to study drug by the investigator.

Different underlying etiologies were observed, such as

- a medical history of back pain

- a medical history of vertebral conditions, such as
    - intervertebral disc operation
    - intervertebral disc protrusion
    - intervertebral disc degeneration
    - lumbar vertebral fracture
    - arthralgia
    - back pain
    - muscle spasms, or
    - scoliosis

- evidence of chronic pain, including
    - medical history of fibromyalgia or
    - chronic use of tramadol, pregabalin, or duloxetine, or
- concomitant AE of fall (reported in 1 case).

A review of all individual cases showed that the Back pain reported in these participants was probably related to multiple different underlying causes and unlikely related to study drug.

No known biologic plausibility for an association between mirikizumab administration and the occurrence of back pain exists.

As per the applicant, the worldwide prevalence of nonspecific back pain is estimated at 30.8% (Maher et al. 2017), and up to 4% of patients with CD have spondyloarthritis (Amarnani et al. 2022). Back pain incidence reported in the CD analysis sets was within the back pain background rate. Therefore, back pain is not proposed as an ADR for mirikizumab.

Vomiting

In the CD Induction Placebo- and Active-Controlled and CD Treatment Regimen Placebo- and Active-Controlled Analysis Sets, Vomiting was reported at a higher frequency and EAIR in mirikizumab treatment participants compared with placebo group participants.

Overall, the numbers and frequencies of TEAEs were low. The observed imbalances are not unexpected, given the overall low incidence rate. In mirikizumab treatment participants, most events (22 out of 23) were reported as mild or moderate in severity. None were reported as serious or led to study treatment discontinuation. Most events were transitory, lasting no more than 2 days. No pattern in the time-to-onset was observed. Different underlying aetiologies were observed, such as

- CD-activity-related symptoms
- gastrointestinal obstructions
- infections, and
- concomitant medications such as antibiotics.

Most mirikizumab treatment participants who reported Vomiting remained on mirikizumab and recovered or were recovering while on mirikizumab treatment. Among a total of 23 events reported, only 2 were considered possibly related to mirikizumab by the investigator.

Vomiting is a common symptom of gastroduodenal involvement, which can be noted in approximately 20% of patients with CD (Horjus Talabur Horje et al. 2016). Therefore, vomiting is not proposed as an ADR for mirikizumab.

TEAEs by PT and by decreasing frequency within cluster

Table **Event Clusters by Decreasing Frequency in Mirikizumab Treatment Participants in the CD Treatment Regimen Placebo- and Active-Controlled Analysis Set CD Induction Placebo- and Active-Controlled and CD Treatment Regimen Placebo- and Active-Controlled Analysis Sets**

	CD Induction			CD Treatment Regimen		
Cluster, n (%) [EAIR]	**Pbo[a] N = 211 PYE = 49**	**Miri N = 630 PYE = 150.4**	**Uste N = 309 PYE = 73.7**	**Pbo[a] N = 211 PYE = 119.5**	**Miri N = 630 PYE = 593.6**	**Uste N = 309 PYE = 293.3**
Upper respiratory tract infection including COVID-19[b]	21 (10.0) [44.8]	76 (12.1) [54.0]	27 (8.7) [38.3]	48 (22.7) [47.7]	187 (29.7) [38.4]	97 (31.4) [39.6]
Abdominal pain	11 (5.2) [23.1]	21 (3.3) [14.2]	9 (2.9) [12.4]	18 (8.5) [15.7]	47 (7.5) [8.3]	16 (5.2) [5.6]
Headache	5 (2.4) [10.4]	19 (3.0) [12.9]	6 (1.9) [8.3]	9 (4.3) [7.8]	41 (6.5) [7.2]	15 (4.9) [5.3]
Diarrhea	3 (1.4) [6.2]	13 (2.1) [8.8]	5 (1.6) [6.8]	11 (5.2) [9.5]	36 (5.7) [6.3]	14 (4.5) [4.9]
Fatigue	4 (1.9) [8.2]	13 (2.1) [8.8]	0	13 (6.2) [11.4]	32 (5.1) [5.6]	12 (3.9) [4.2]
Leukopenia	1 (0.5) [2.0]	14 (2.2) [9.4]	2 (0.6) [2.7]	1 (0.5) [0.8]	24 (3.8) [4.2]	8 (2.6) [2.8]
Rash	1 (0.5) [2.0]	10 (1.6) [6.7]	2 (0.6) [2.7]	5 (2.4) [4.3]	24 (3.8) [4.1]	4 (1.3) [1.4]
Hypertension	1 (0.5) [2.0]	7 (1.1) [4.7]	3 (1.0) [4.1]	4 (1.9) [3.4]	21 (3.3) [3.6]	4 (1.3) [1.4]
Gastroenteritis	0	6 (1.0) [4.0]	3 (1.0) [4.1]	5 (2.4) [4.3]	18 (2.9) [3.1]	9 (2.9) [3.1]
Neutropenia	1 (0.5) [2.0]	4 (0.6) [2.7]	2 (0.6) [2.7]	1 (0.5) [0.8]	11 (1.7) [1.9]	7 (2.3) [2.4]
Herpes simplex or herpes zoster infection	1 (0.5) [2.0]	5 (0.8) [3.3]	1 (0.3) [1.4]	2 (0.9) [1.7]	9 (1.4) [1.5]	6 (1.9) [2.1]
Herpes simplex infection	1 (0.5) [2.0]	2 (0.3) [1.3]	1 (0.3) [1.4]	2 (0.9) [1.7]	4 (0.6) [0.7]	5 (1.6) [1.7]
Tinea infection	1 (0.5) [2.0]	1 (0.2) [0.7]	0	1 (0.5) [0.8]	3 (0.5) [0.5]	0
Hypertriglyceridemia	0	0	0	0	2 (0.3) [0.3]	1 (0.3) [0.3]

TEAEs by PT and by maximum severity

Table TEAEs by Maximum Severity CD Induction Placebo- and Active-Controlled and CD Treatment Regimen Placebo- and Active-Controlled Analysis Sets

	CD Induction			CD Treatment Regimen		
Severity, n (%)	Pbo N = 211	Miri N = 630	Uste N = 309	Pbo[a] N = 211	Miri N = 630	Uste N = 309
Participants with at least 1 TEAE	119 (56.4)	326 (51.7)	134 (43.4)	154 (73.0)	495 (78.6)	239 (77.3)
Mild	59 (28.0)	188 (29.8)	76 (24.6)	60 (28.4)	233 (37.0)	121 (39.2)
Moderate	45 (21.3)	104 (16.5)	52 (16.8)	62 (29.4)	204 (32.4)	94 (30.4)
Severe	15 (7.1)	34 (5.4)	6 (1.9)	32 (15.2)	58 (9.2)	24 (7.8)

CD Induction Placebo- and Active-Controlled and CD Treatment Regimen Placebo- and Active-Controlled Analysis Sets

In the CD Induction Placebo- and Active-Controlled and CD Treatment Regimen Placebo- and Active-Controlled Analysis Sets, the frequency of participants who reported a severe TEAE was lower in mirikizumab treatment participants compared with placebo group participants.

The Gastrointestinal disorders SOC had the highest frequency of severe events reported:

- CD Induction Placebo- and Active-Controlled Analysis Set:
  - 11 (5.2%) placebo group participants
  - 3 (1.0%) ustekinumab treatment participants, and
  - 18 (2.9%) mirikizumab treatment participants.

- CD Treatment Regimen Placebo- and Active-Controlled Analysis Set:
  - 20 (9.5%) placebo group participants
  - 9 (2.9%) ustekinumab treatment participants, and
  - 25 (4.0%) mirikizumab treatment participants.

Of the severe TEAEs reported within the Gastrointestinal disorders SOC, the highest frequency of severe events reported among mirikizumab treatment participants was CD:

- CD Induction Placebo- and Active-Controlled Analysis Set:
  - 6 (2.8%) placebo group participants
  - 1 (0.3%) ustekinumab treatment participants, and
  - 8 (1.3%) mirikizumab treatment participants.

- CD Treatment Regimen Placebo- and Active-Controlled Analysis Set
  - 9 (4.3%) placebo group participants
  - 4 (1.3%) ustekinumab treatment participants, and

- 11 (1.7%) mirikizumab treatment participants.

2.6.8.3. Serious adverse event/deaths/other significant events

Adverse drug reactions

Based on review of summary- and participant-level data of common TEAEs reported in the CD placebo-controlled analysis sets for both induction and/or treatment regimen period, the following TEAEs were considered notable and were recommended to remain as ADRs, as previously identified in the UC clinical program (see above for further details):

- Infusion related hypersensitivity reaction (isolated PT)
- Rash (within the Rash cluster)
- Injection site reaction (within the Injection site reaction HLT)
- Injection site erythema (within the Injection site reaction HLT), and
- COVID-19 (within the URTI cluster)

Table Frequency of Adverse Reactions in Mirikizumab-Treated Adults with Ulcerative Colitis and Crohn's Disease Indications

Table 2.5.5.5. Frequency of Adverse Reactions in Mirikizumab-Treated Adults with Ulcerative Colitis and Crohn's Disease Indications

System Organ Class PT, HLT or Lilly-defined cluster	Very Common ≥10%	Common ≥1% and <10%	Uncommon ≥0.1% and <1%	Rare ≥0.01% and <0.1%	Very Rare <0.01%
General disorders and administrative site conditions					
Injection site reactions (HLT)[a]	X				
Immune system disorders					
Infusion related hypersensitivity reaction			X		
Infections and infestations					
Upper respiratory tract infections (cluster)[b,c]		X			
Investigations					
Alanine aminotransferase increased			X		
Aspartate aminotransferase increased			X		
Nervous system disorders					
Headache[d]		X			
Skin and subcutaneous tissue disorders					
Rash (cluster)[e]		X			

Adverse events of special interest (AESI) for mirikizumab include:

- Hepatic safety

- Malignancies
- Depression and suicidal ideation or behaviour
- Hypersensitivity reactions
- Infusion and injection site reactions
- Infections including opportunistic and serious infection
- Cerebrovascular events

Hepatic safety

The potential for hepatic enzyme elevations is currently captured in sections 4.4 and 4.8 of the SmPC based on the ulcerative colitis population.

Section 4.4 currently states:

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

There are accepted hepatic manifestations of Crohn's disease including:
- NAFLD
- primary sclerosing cholangitis
- autoimmune hepatitis, and
- cholelithiasis

Table Literature Discussing Crohn's Disease and Hepatic Disorders

Table 2.7.4.29. Literature Discussing Crohn's Disease and Hepatic Disorders

	Reference	Incidence (%)	IR/100 PY
Common hepatobiliary manifestations among patients with CD and IBD			
CD			
NAFLD	Kodali et al. 2023	10.95-53.80	–
PSC	Restellini et al. 2017 and Burisch et al. 2019	1.2-3.4	0.065
AIH	Silva et al. 2019	0.7	–
Cholelithiasis	Restellini et al. 2017, Chen et al. 2018, and Gizard et al. 2014	11-34	0.71-1.44
IBD			
PSC	Mazza et al. 2021 and Burisch et al. 2019	2-8	0.094
AIH	Saubermann et al. 2017	0.3-1.6	–
Cholelithiasis	Chen et al. 2018	3.73	0.52
Incidence of elevated liver enzymes among patients with CD			
Liver enzyme			
ALT ≥ ULN	Wewer et al. 1991 and Voss et al. 2021	7.8-8.0	–
ALT ≥2x ULN		0.99-2.4	–
AST ≥ ULN		2.4-6.3	–
AST ≥2x ULN		0.31-0.80	–
Bilirubin ≥ ULN	Wewer et al. 1991	2.4	–
GGT ≥ ULN	Voss et al. 2021	21.1	–
GGT ≥2x ULN		5.6	–
GGT >5x ULN		0.99	–
ALP ≥ ULN	Wewer et al. 1991 and Voss et al. 2021	16.8-19.8	–
ALP >2x ULN		0.68-1.6	–

Table Hepatic TEAEs Occurring in More Than 1 Mirikizumab Treatment Participant in the CD Mirikizumab Exposures Integrated Analysis Set CD Induction Placebo- and Active-Controlled, CD Treatment Regimen Placebo-and Active-Controlled, CD Treatment Regimen Placebo-and Active-Controlled, CD Mirikizumab Exposures Integrated, and IBD Integrated Analysis Sets.

Event, n (%) [EAIR]	CD Induction			CD Treatment Regimen			CD Miri Integrated[a]	IBD Integrated
	Pbo N = 211 PYE = 49	Miri N = 630 PYE = 150.4	Uste N = 309 PYE = 73.7	Pbo[b] N = 211 PYE = 119.5	Miri N = 630 PYE = 593.6	Uste N = 309 PYE = 293.3	Miri N = 1178 PYE = 2004.2	Miri N = 2632 PYE = 5475.3
Participant with at least 1 reported narrow scope TEAE	6 (2.8) [12.4]	12 (1.9) [8.1]	2 (0.6) [2.7]	9 (4.3) [7.8]	39 (6.2) [6.8]	8 (2.6) [2.8]	89 (7.6) [4.7]	171 (6.5) [3.3]
Alanine aminotransferase increased	1 (0.5) [2.0]	6 (1.0) [4.0]	1 (0.3) [1.4]	1 (0.5) [0.8]	17 (2.7) [2.9]	2 (0.6) [0.7]	34 (2.9) [1.7]	59 (2.2) [1.1]
Aspartate aminotransferase increased	0	2 (0.3) [1.3]	2 (0.6) [2.7]	1 (0.5) [0.8]	11 (1.7) [1.9]	4 (1.3) [1.4]	25 (2.1) [1.3]	46 (1.7) [0.9]
Blood bilirubin increased	0	2 (0.3) [1.3]	0	0	5 (0.8) [0.8]	0	8 (0.7) [0.4]	16 (0.6) [0.3]
Gamma-glutamyltransferase increased	2 (0.9) [4.1]	2 (0.3) [1.3]	0	2 (0.9) [1.7]	8 (1.3) [1.4]	1 (0.3) [0.3]	16 (1.4) [0.8]	40 (1.5) [0.7]
Hepatic enzyme increased	0	1 (0.2) [0.7]	0	0	1 (0.2) [0.2]	1 (0.3) [0.3]	7 (0.6) [0.4]	13 (0.5) [0.2]
Hepatic function abnormal	0	1 (0.2) [0.7]	0	0	2 (0.3) [0.3]	0	4 (0.3) [0.2]	8 (0.3) [0.1]
Liver function test increased	0	0	0	0	2 (0.3) [0.3]	0	5 (0.4) [0.3]	11 (0.4) [0.2]
Transaminases increased	1 (0.5) [2.0]	1 (0.2) [0.7]	0	1 (0.5) [0.8]	1 (0.2) [0.2]	0	4 (0.3) [0.2]	7 (0.3) [0.1]
Ascites	0	1 (0.2) [0.7]	0	0	1 (0.2) [0.2]	0	2 (0.2) [0.1]	2 (0.1) [0.0]
Hepatic steatosis	0	0	0	1 (0.5) [0.8]	3 (0.5) [0.5]	2 (0.6) [0.7]	9 (0.8) [0.5]	22 (0.8) [0.4]
Liver injury	0	0	0	0	1 (0.2) [0.2]	0	2 (0.2) [0.1]	2 (0.1) [0.0]

In the CD Induction Placebo- and Active-Controlled Analysis Set, the most frequently reported TE hepatic disorder was ALT increased in

- 1 (0.5%) placebo group participant
- 1 (0.3%) ustekinumab treatment participant, and
- 6 (1.0%) mirikizumab treatment participants.

In the CD Treatment Regimen Placebo- and Active-Controlled Analysis Set, the most frequently reported TE hepatic disorder was ALT increased in

- 1 [EAIR = 0.8 per 100 PYE] placebo group participant
- 2 [EAIR = 0.7 per 100 PYE] ustekinumab treatment participants, and
- 17 [EAIR = 2.9 per 100 PYE] mirikizumab treatment participants.

In mirikizumab treatment participants, no reports of ALT increased were serious or led to treatment discontinuation. No pattern in the time-to-onset, duration of the events, or common underlying etiology were observed. Of the 17 cases, 2 cases were considered related to study drug by the investigator.

AST increased was also identified for further evaluation, as it was reported at a higher incidence in mirikizumab treatment participants [n = 11; EAIR = 1.9 per 100 PYE] compared with placebo group participants [n = 1; EAIR = 0.8 per 100 PYE]. 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 etiology was observed. Of the 11 cases, 1 was considered related to study drug by the investigator.

In a mirikizumab treatment participant, 1 non-serious case of DILI (PT) was reported during the Maintenance Period.

In the CD Treatment Regimen Placebo- and Active-Controlled Analysis Set, there was low incidence of ALT and AST at least 5-fold ULN. There was a numerically higher EAIR in mirikizumab treatment participants (ALT 0.5 and AST 0.3 per 100 PYE) compared with placebo group participants, but at a low incidence.

During Treatment Regimen Period, a maximum ALT postbaseline to ≥3xULN was reported in

- 0 participant (EAIR = 0 per 100 PYE) in the placebo group
- 6 participants (EAIR=2.0 per 100 PYE) in the ustekinumab group, and
- 12 participants (EAIR=2.0 per 100 PYE) in the mirikizumab group.

A maximum postbaseline shift to ≥5xULN was reported in

- 0 participant (EAIR = 0 per 100 PYE) in the placebo group
- 1 participant (EAIR=0.3 per 100 PYE) in the ustekinumab group, and
- 3 participants (EAIR=0.5 per 100 PYE) in the mirikizumab group.

No ALT shifts ≥10xULN were reported in the mirikizumab treatment or placebo groups. One participant (EAIR = 0.3 per 100 PYE) in the ustekinumab group reported ALT shifts ≥10xULN.

AST

During Treatment Regimen Period, a maximum AST postbaseline shift to ≥3xULN was reported In

- 2 participants (EAIR = 1.7 per 100 PYE) in the placebo group
- 7 participants (EAIR = 2.4 per 100 PYE) in the ustekinumab group, and
- 9 participants (EAIR = 1.5 per 100 PYE) in the mirikizumab group.

A maximum postbaseline ≥5xULN was reported in

- 0 participant (EAIR = 0 per 100 PYE) in the placebo group
- 4 participants (EAIR = 1.4 per 100 PYE) in the ustekinumab group, and
- 2 participants (EAIR = 0.3 per 100 PYE) in the mirikizumab group.

No Hy's Law cases, serious liver injuries, or cases of ALT or AST higher than 10-fold ULN were reported in the CD developmental program.

Overall, one participant each from the placebo (PT: Hepatitis cholestatic), mirikizumab (PT: Non-alcoholic fatty liver), and ustekinumab (PT: Alanine aminotransferase increased) groups discontinued treatment due to hepatic-related TEAEs during the Treatment Regimen Period.

Table Treatment Emergent Increases in ALT, ALP and TB

CD Induction Placebo- and Active-Controlled, CD Treatment Regimen Placebo-and Active-Controlled, CD Treatment Regimen Placebo-and Active-Controlled, CD Mirikizumab Exposures Integrated, and IBD Integrated Analysis Sets.

Maximum Postbaseline Category, n (%) [EAIR]	CD Induction			CD Treatment Regimen			CD Miri Integrated[a]	IBD Integrated
	Pbo N = 211 PYE = 49	Miri N = 630 PYE = 150.4	Uste N = 309 PYE = 73.7	Pbo[b] N = 211 PYE = 119.5	Miri N = 630 PYE = 593.6	Uste N = 309 PYE = 293.3	Miri N = 1178 PYE = 2004.2	Miri N = 2632 PYE = 5605.4
ALT	Nx = 207	Nx = 627	Nx = 303	Nx =207	Nx =627	Nx = 304	Nx = 1156	Nx =2599
≥3xULN	0	3 (0.5) [2.0]	3 (1.0) [4.1]	0	12 (1.9) [2.0]	6 (2.0) [2.0]	26 (2.2) [1.3]	60 (2.3) [1.1]
≥5xULN	0	1 (0.2) [0.7]	0	0	3 (0.5) [0.5]	1 (0.3) [0.3]	5 (0.4) [0.2]	17 (0.7) [0.3]
≥10xULN	0	0	0	0	0	1 (0.3) [0.3]	0	4 (0.2) [0.1]
AST	Nx = 207	Nx = 627	Nx = 303	Nx = 207	Nx = 627	Nx = 304	Nx = 1155	Nx = 2598
≥3xULN	1 (0.5) [2.1]	1 (0.2) [0.7]	2 (0.7) [2.7]	2 (1.0) [1.7]	9 (1.4) [1.5]	7 (2.3) [2.4]	19 (1.6) [0.9]	56 (2.2) [1.0]
≥5xULN	0	0	1 (0.3) [1.4]	0	2 (0.3) [0.3]	4 (1.3) [1.4]	4 (0.3) [0.2]	22 (0.8) [0.4]
≥10xULN	0	0	1 (0.3) [1.4]	0	0	2 (0.7) [0.7]	0	3 (0.1) [0.1]
ALP	Nx = 207	Nx = 627	Nx = 303	Nx =207	Nx =627	Nx = 304	Nx = 1156	Nx = 2599
≥2xULN	1 (0.5) [2.1]	2 (0.3) [1.3]	0	2 (1.0) [1.7]	7 (1.1) [1.2]	0	12 (1.0) [0.6]	25 (1.0) [0.5]
TB	Nx = 207	Nx = 627	Nx = 303	Nx =207	Nx =627	Nx = 304	Nx = 1156	Nx = 2599
≥2xULN	0	3 (0.5) [2.0]	1 (0.3) [1.4]	0	6 (1.0) [1.0]	5 (1.6) [1.7]	13 (1.1) [0.6]	34 (1.3) [0.6]

Malignancy

No participant in the Induction Period reported malignancies.

During Treatment Regimen Period, malignancies meeting the AESI criteria were reported in 1 participant (EAIR=0.8 per 100 PYE) in the placebo group (PT: Basal cell carcinoma), 2 participants (EAIR=0.3 per 100 PYE) in the mirikizumab group (PT: Basal cell carcinoma [n = 1] and Breast cancer [n = 1]).

One mirikizumab treatment participant reported a serious malignancy of Breast cancer in the CD Treatment Regimen Placebo- and Active-Controlled Analysis Set. This led to discontinuation but was unrelated to study treatment.

Table Malignancy TEAEs

CD Induction Placebo- and Active-Controlled, CD Treatment Regimen Placebo-and Active-Controlled, CD Treatment Regimen Placebo-and Active-Controlled, CD Mirikizumab Exposures Integrated, and IBD Integrated Analysis Sets.

Event, n (%) [EAIR]	CD Induction			CD Treatment Regimen			CD Miri Integrated[a]	IBD Integrated
	Pbo N = 211 PYE = 49	Miri N = 630 PYE = 150.4	Uste N = 309 PYE = 73.7	Pbo[b] N = 211 PYE = 119.5	Miri N = 630 PYE = 593.6	Uste N = 309 PYE = 293.3	Miri N = 1178 PYE = 2004.2	Miri N = 2632 PYE = 5475.3
Participants with at least 1 TE malignancy	0	0	0	1 (0.5) [0.8]	2 (0.3) [0.3]	0	4 (0.3) [0.2]	25 (0.9) [0.5]
Participants with at least 1 TE NMSC malignancy	0	0	0	1 (0.5) [0.8]	1 (0.2) [0.2]	0	1 (0.1) [0.0]	5 (0.2) [0.1]
Basal cell carcinoma	0	0	0	1 (0.5) [0.8]	1 (0.2) [0.2]	0	1 (0.1) [0.0]	2 (0.1) [0.0]
Squamous cell carcinoma of skin	0	0	0	0	0	0	0	3 (0.1) [0.1]
Participants with at least 1 TE malignancy other than NMSC	0	0	0	0	1 (0.2) [0.2]	0	3 (0.3) [0.1]	20 (0.8) [0.4]
Adenocarcinoma of colon	0	0	0	0	0	0	0	4 (0.2) [0.1]
Breast cancer	0	0	0	0	1 (0.2) [0.2]	0	1 (0.1) [0.0]	1 (0.0) [0.0]
Prostate cancer	0	0	0	0	0	0	0	1 (0.1) [0.0]
Colon cancer	0	0	0	0	0	0	1 (0.1) [0.0]	1 (0.0) [0.0]
Rectal cancer	0	0	0	0	0	0	0	3 (0.1) [0.1]
Cervix carcinoma stage III	0	0	0	0	0	0	1 (0.2) [0.1]	1 (0.1) [0.0]
Acute myeloid leukaemia	0	0	0	0	0	0	0	1 (0.0) [0.0]

Depression and suicidal ideation or behaviour

Estimates of the incidence rate of depression among patients with CD range from 0.38 to 2.48 per 100 PY and the incidence of depression among patients with CD was found to be higher among females (2.48 per 100 PY) compared with males (1.76 per 100 PY). Several studies indicate that CD is associated with a significantly increased risk for depression when compared with either the general population or non-IBD controls.

During Treatment Regimen Period, the incidence rates of narrow scope event in the depression (excluding suicide and self-injury) sub-SMQ (PT: Depression, Depressed mood) were

0 participant (EAIR = 0 per 100 PYE) in the placebo group

2 participants (EAIR = 0.7 per 100 PYE) in the ustekinumab group (PT: Depression [n = 2]), and

5 participants (EAIR = 0.8 per 100 PYE) in the mirikizumab group (PT: Depression [n = 4], Depressed mood [n = 1])

One participant, in mirikizumab induction period reported the events of depression and suicidal ideation on study Day 81. This participant had a prior history of suicide attempt. The participant's baseline and postbaseline max QIDS scores were the same (score = 13). At the time of the event, the participant also reported a concurrent exacerbation of CD, vomiting, nausea, and anxiety. The event was assessed as severe, did not result in treatment discontinuation, and was not considered related to the study treatment by the investigator. For the remaining 4 participants in mirikizumab group, all events were non-serious and of mild-to-moderate severity. Three of these events were not considered related to study treatment by the investigator and did not result in study treatment discontinuation.

Most participants had either preexisting psychiatric disease or co-morbid medical conditions. One event of depression was considered related to study treatment by the investigator and resulted in study treatment discontinuation. This participant did not have a prior history of psychiatric disease but did report pain and fatigue at the time of the depression event. Additional participant risk factors include a history of colectomy.

Frequencies of participants reporting a narrow scope event in the suicide/self-injury sub-SMQ (PT: Suicidal ideation) were

- 0 participant (EAIR = 0 per 100 PYE) in the placebo group
- 0 participant (EAIR = 0 per 100 PYE) in the ustekinumab group, and
- 2 participants (EAIR = 0.3 per 100 PYE) in the mirikizumab group

One of these 2 events was previously reported in the Induction period (PT = Depression and Suicidal ideation). The second event occurred on study Day 224 and lasted 1 day. The event severity was assessed as moderate. The event was not considered related to study treatment by the investigator and did not result in study treatment discontinuation. This participant had a preexisting history of anxiety and chronic pain, both of which are risk factors for suicidal ideation. Indeed, this participant reported exacerbations and AEs of pain around the time of the suicidal ideation onset.

Table Depression or Suicide and Self-Injury TEAEs

CD Induction Placebo- and Active-Controlled, CD Treatment Regimen Placebo-and Active-Controlled, CD Treatment Regimen Placebo-and Active-Controlled, CD Mirikizumab Exposures Integrated, and IBD Integrated Analysis Sets.

Event, n (%) [EAIR]	CD Induction			CD Treatment Regimen			CD Miri Integrated[a]	IBD Induction Integrated		IBD Integrated
	Pbo N = 211 PYE = 49	Miri N = 630 PYE = 150.4	Uste N = 309 PYE = 73.7	Pbo[b] N = 211 PYE = 119.5	Miri N = 630 PYE = 593.6	Uste N = 309 PYE = 293.3	Miri N = 1178 PYE = 2004.2	Pbo N = 532 PYE = 128	Miri N = 1588 PYE = 394.5	Miri N = 2632 PYE = 5475.3
Participants with at least 1 TE depression event (excl. suicide and self-injury)	0	1 (0.2) [0.7]	1 (0.3) [1.4]	0	5 (0.8) [0.8]	2 (0.6) [0.7]	19 (1.6) [1.0]	2 (0.4) [1.6]	5 (0.3) [1.3]	47 (1.8) [0.9]
Depression	0	1 (0.2) [0.7]	1 (0.3) [1.4]	0	4 (0.6) [0.7]	2 (0.6) [0.7]	13 (1.1) [0.7]	1 (0.2) [0.8]	3 (0.2) [0.8]	34 (1.3) [0.6]
Depressed mood	0	0	0	0	1 (0.2) [0.2]	0	5 (0.4) [0.3]	1 (0.2) [0.8]	2 (0.1) [0.5]	11 (0.4) [0.2]
Adjustment disorder with depressed mood	0	0	0	0	0	0	1 (0.1) [0.0]	0	0	1 (0.0) [0.0]
Dysphoria	0	0	0	0	0	0	0	0	0	0
Major depression	0	0	0	0	0	0	0	0	0	0
Mixed anxiety and depressive disorder	0	0	0	0	0	0	0	0	0	1 (0.0) [0.0]
Participants with at least 1 TE suicide or self-injury event	0	1 (0.2) [0.7]	0	0	2 (0.3) [0.3]	0	2 (0.2) [0.1]	0	1 (0.1) [0.3]	3 (0.1) [0.1]
Suicidal ideation	0	1 (0.2) [0.7]	0	0	2 (0.3) [0.3]	0	2 (0.2) [0.1]	0	1 (0.1) [0.3]	2 (0.1) [0.0]
Suicide attempt	0	0	0	0	0	0	0	0	0	1 (0.0) [0.0]
Depression suicidal	0	0	0	0	0	0	0	0	0	1 (0.0) [0.0]

Hypersensitivity reactions

Immediate hypersensitivity reactions

Table Immediate Hypersensitivity TEAEs Occurring in At Least 3 Mirikizumab Treatment Participants in the CD Mirikizumab Exposures Integrated Analysis Set

CD Induction Placebo- and Active-Controlled, CD Treatment Regimen Placebo-and Active-Controlled, CD Treatment Regimen Placebo-and Active-Controlled, CD Mirikizumab Exposures Integrated, and IBD Integrated Analysis Sets.

Event, n (%) [EAIR]	CD Induction			CD Treatment Regimen			CD Miri Integrated[a]	IBD Integrated
	Pbo N = 211 PYE = 49	Miri N = 630 PYE = 150.4	Uste N = 309 PYE = 73.7	Pbo[b] N = 211 PYE = 119.5	Miri N = 630 PYE = 593.6	Uste N = 309 PYE = 293.3	Miri N = 1178 PYE = 2004.2	Miri N = 2632 PYE = 5475.3
Participants with at least 1 TE immediate hypersensitivity event	3 (1.4) [6.2]	12 (1.9) [8.1]	4 (1.3) [5.5]	5 (2.4) [4.2]	24 (3.8) [4.1]	7 (2.3) [2.4]	58 (4.9) [3.0]	96 (3.6) [1.8]
Infusion related hypersensitivity reaction	1 (0.5) [2.0]	3 (0.5) [2.0]	0	1 (0.5) [0.8]	3 (0.5) [0.5]	0	12 (1.0) [0.6]	16 (0.6) [0.3]
Urticaria	0	3 (0.5) [2.0]	0	0	4 (0.6) [0.7]	0	8 (0.7) [0.4]	10 (0.4) [0.2]
Rash	0	2 (0.3) [1.3]	0	0	3 (0.5) [0.5]	0	7 (0.6) [0.4]	10 (0.4) [0.2]
Hypersensitivity	0	1 (0.2) [0.7]	1 (0.3) [1.4]	0	1 (0.2) [0.2]	1 (0.3) [0.3]	5 (0.4) [0.2]	9 (0.3) [0.2]
Infusion related reaction	0	2 (0.3) [1.3]	1 (0.3) [1.4]	0	2 (0.3) [0.3]	1 (0.3) [0.3]	4 (0.3) [0.2]	10 (0.4) [0.2]
Anaphylactic reaction	0	0	0	0	1 (0.2) [0.2]	1 (0.3) [0.3]	3 (0.3) [0.1]	3 (0.1) [0.1]
Injection site hypersensitivity	–	–	–	0	3 (0.5) [0.5]	0	3 (0.3) [0.1]	5 (0.2) [0.1]
Injection site rash	–	–	–	0	2 (0.3) [0.3]	0	3 (0.3) [0.1]	5 (0.2) [0.1]

The frequency of participants who reported TE immediate hypersensitivity events were

- 3 (1.4%) placebo group participants
- 4 (1.3%) ustekinumab treatment participants, and
- 12 (1.9%) mirikizumab treatment participants.

In mirikizumab treatment participants, the most frequently reported TE immediate hypersensitivity events were Infusion related hypersensitivity reaction (n = 3; 0.5%) and Urticaria (n = 3, 0.5%).

No participants reported anaphylaxis.

There was one serious immediate hypersensitivity infusion reaction in one participant receiving placebo.

The frequency of participants who discontinued study treatment due to TE immediate hypersensitivity events were:

- 0 (0%) placebo group participants
- 0 (0%) ustekinumab treatment participants, and
- 5 (0.8%) mirikizumab treatment participants:
    - Infusion related hypersensitivity reaction (n = 3; 0.5%)
    - Hypersensitivity (n = 1; 0.2%), and
    - Urticaria (n = 1; 0.2%)

In the CD Treatment Regimen Placebo- and Active-Controlled Analysis Set the incidence of participants who reported at least 1 TE immediate hypersensitivity events were

- 5 [EAIR = 4.2 per 100 PYE] placebo group participants
- 7 [EAIR = 2.4 per 100 PYE] ustekinumab treatment participants, and
- 24 [EAIR = 4.1 per 100 PYE] mirikizumab treatment participants.

In mirikizumab treatment participants, the highest incidence for reported TE immediate hypersensitivity events were Rash cluster (reported PTs Rash and Rash macular) and Urticaria.

The number and EAIRs of participants who reported Anaphylactic reactions (PT of Anaphylactic reaction for both cases) were

- 0 [EAIR = 0.0 per 100 PYE] placebo group participants
- 1 [EAIR = 0.3 per 100 PYE] ustekinumab treatment participant, and
- 1 [EAIR = 0.2 per 100 PYE] mirikizumab treatment participant

One participant had non-serious Anaphylactic reaction AE (moderate severity) on Study Day 177. The exact term reported by the investigator was Anaphylactoid/syncope event, which was later coded as an Anaphylactic reaction. The participant reported a medical history of seasonal allergy.. On the same day of the last dose, just after the SC injection, the participant fainted. Vital signs prior to the syncope were blood pressure of 102/68 mm Hg and a heart rate of 52 bpm. During the event, vital signs were blood pressure of 98/60 mm Hg and a heart rate of 52 bpm. After 12 minutes and without any specific treatment, the patient completely recovered, with a blood pressure of 103/67 mm Hg and a heart rate of 54 bpm. No other symptoms were reported. Tryptase was not collected. The sponsor assessment of the event was a syncopal event without vital sign changes that did not require epinephrine treatment and resolved within minutes, low likelihood of anaphylaxis, and possible vasovagal reaction or other non-anaphylactic hypersensitivity reaction.

No serious immediate hypersensitivity events were reported in mirikizumab treatment participants.

The EAIRs of participants who discontinued study treatment due to TE immediate hypersensitivity events were:

- 0 [EAIR = 0.0 per 100 PYE] placebo group participants
- 0 [EAIR = 0.0 per 100 PYE] ustekinumab treatment participants, and
- 6 [EAIR = 1.0 per 100 PYE] mirikizumab treatment participants:
    - Infusion related hypersensitivity reaction (n = 3; 0.5%)
    - Anaphylactic reaction (n = 1; 0.2%)
    - Hypersensitivity (n = 1; 0.2%), and
    - Urticaria (n = 1; 0.2%).

The EAIRs of TE immediate hypersensitivity events in the CD Mirikizumab Exposures Integrated and IBD Integrated Analysis Sets were lower than in the CD Treatment Regimen Placebo- and Active-Controlled Analysis Set.

Non immediate hypersensitivity reactions:

Table Immediate Hypersensitivity TEAEs Occurring in At Least 3 Mirikizumab Treatment Participants in the CD Mirikizumab Exposures Integrated Analysis Set

CD Induction Placebo- and Active-Controlled, CD Treatment Regimen Placebo-and Active-Controlled, CD Treatment Regimen Placebo-and Active-Controlled, CD Mirikizumab Exposures Integrated, and IBD Integrated Analysis Sets.

Event, n (%) [EAIR]	CD Induction			CD Treatment Regimen			CD Miri Integrated[a]	IBD Integrated
	Pbo N = 211 PYE = 49	Miri N = 630 PYE = 150.4	Uste N = 309 PYE = 73.7	Pbo[b] N = 211 PYE = 119.5	Miri N = 630 PYE = 593.6	Uste N = 309 PYE = 293.3	Miri N = 1178 PYE = 2004.2	Miri N = 2632 PYE = 5475.3
Participants with at least 1 TE non-immediate hypersensitivity event	3 (1.4) [6.1]	21 (3.3) [14.3]	8 (2.6) [11.0]	11 (5.2) [9.6]	50 (7.9) [8.9]	18 (5.8) [6.4]	104 (8.8) [5.6]	240 (9.1) [4.7]
Rash	0	6 (1.0) [4.0]	1 (0.3) [1.4]	3 (1.4) [2.6]	16 (2.5) [2.7]	1 (0.3) [0.3]	33 (2.8) [1.7]	70 (2.7) [1.3]
Eczema	0	4 (0.6) [2.7]	1 (0.3) [1.4]	1 (0.5) [0.8]	9 (1.4) [1.5]	2 (0.6) [0.7]	15 (1.3) [0.8]	37 (1.4) [0.7]
Urticaria	0	1 (0.2) [0.7]	1 (0.3) [1.4]	0	4 (0.6) [0.7]	2 (0.6) [0.7]	12 (1.0) [0.6]	26 (1.0) [0.5]
Dermatitis contact	0	0	0	0	1 (0.2) [0.2]	0	6 (0.5) [0.3]	12 (0.5) [0.2]
Rhinitis allergic	0	1 (0.2) [0.7]	0	0	1 (0.2) [0.2]	1 (0.3) [0.3]	4 (0.3) [0.2]	16 (0.6) [0.3]
Dermatitis	0	1 (0.2) [0.7]	0	0	2 (0.3) [0.3]	0	5 (0.4) [0.3]	11 (0.4) [0.2]
Hypersensitivity	1 (0.5) [2.0]	2 (0.3) [1.3]	1 (0.3) [1.4]	1 (0.5) [0.8]	2 (0.3) [0.3]	1 (0.3) [0.3]	6 (0.5) [0.3]	11 (0.4) [0.2]
Dermatitis allergic	0	1 (0.2) [0.7]	0	0	3 (0.5) [0.5]	1 (0.3) [0.3]	8 (0.7) [0.4]	11 (0.4) [0.2]
Rash pruritic	0	0	1 (0.3) [1.4]	0	4 (0.6) [0.7]	2 (0.6) [0.7]	5 (0.4) [0.3]	11 (0.4) [0.2]
Erythema nodosum	0	2 (0.3) [1.3]	0	1 (0.5) [0.8]	3 (0.5) [0.5]	1 (0.3) [0.3]	4 (0.3) [0.2]	6 (0.2) [0.1]
Rash pustular	0	0	0	0	0	0	3 (0.3) [0.2]	5 (0.2) [0.1]
Dermatitis atopic	0	1 (0.2) [0.7]	1 (0.3) [1.4]	0	1 (0.2) [0.2]	2 (0.6) [0.7]	3 (0.3) [0.1]	5 (0.2) [0.1]
Allergic sinusitis	0	0	0	0	1 (0.2) [0.2]	0	3 (0.3) [0.2]	4 (0.2) [0.1]

In the CD Induction Placebo- and Active-Controlled Analysis Set, the frequency of participants who reported at least 1 TE non-immediate hypersensitivity event was:

- 3 (1.4%) in placebo group participants
- 8 (2.6%) in ustekinumab treatment participants, and
- 21 (3.3%) in mirikizumab treatment participants.

In the CD Treatment Regimen Placebo- and Active-Controlled Analysis Set, the EAIRs of participants who reported at least 1 TE non-immediate hypersensitivity events were:

- 11 [EAIR = 9.6 per 100 PYE] in placebo group participants
- 18 [EAIR = 6.4 per 100 PYE] in ustekinumab treatment participants, and
- 50 [EAIR = 8.9 per 100 PYE] in mirikizumab treatment participants.

In mirikizumab treatment participants, the most frequently reported TE non-immediate hypersensitivity event was rash.

No participants reported anaphylaxis and none of the reported non-immediate hypersensitivity events were considered serious or led to treatment discontinuation.

In the CD Mirikizumab Exposures Integrated and IBD Integrated Analysis Sets, the EAIRs for most TE non-immediate hypersensitivity events in the CD Mirikizumab Exposures Integrated and IBD Integrated Analysis Sets were lower than those in the CD Treatment Regimen Placebo- and Active-Controlled Analysis Set.

The number of discontinuations due to non-immediate hypersensitivity events in the CD Mirikizumab Exposures Integrated (n = 1) and IBD Integrated Analysis Sets (n = 5) were low.

Infusion site reactions:

CD Induction Placebo- and Active-Controlled and IBD Induction Analysis Sets are used to evaluate IV administration of mirikizumab, as they do not include participants who received SC doses from maintenance period.

Table Infusion Site Reactions TEAEs

CD Induction Placebo- And Active-Controlled and IBD Randomised Induction Integrated Analysis Sets

Event, n (%) [EAIR]	CD Induction			IBD Induction Integrated	
	Pbo N = 211 PYE = 49	Miri N = 630 PYE = 150.4	Uste N = 309 PYE = 49.1	Pbo N = 532 PYE = 128	Miri N = 1588 PYE = 394.5
Participants with at least 1 TE infusion site reaction	0	1 (0.2) [0.7]	4 (1.3) [8.2]	1 (0.2) [0.8]	5 (0.3) [1.3]
Infusion site bruising	0	0	1 (0.3) [2.0]	0	0
Infusion site erythema	0	0	1 (0.3) [2.0]	0	1 (0.1) [0.3]
Infusion site haematoma	0	0	1 (0.3) [2.0]	0	0
Infusion site oedema	0	0	1 (0.3) [2.0]	0	0
Infusion site pruritus	0	1 (0.2) [0.7]	0	0	2 (0.1) [0.5]
Infusion site pain	0	0	0	0	1 (0.1) [0.3]
Infusion site paraesthesia	0	0	0	1 (0.2) [0.8]	1 (0.1) [0.3]

Based on the Infusion site reaction HLT, the number and frequency of participants who reported at least 1 TE Infusion site reaction were:

- 0 (0%) placebo group participants
- 4 (1.3%) ustekinumab treatment participants, and
- 1 (0.2%) mirikizumab treatment participants (PT of Infusion site pruritus).

No Infusion site reactions (HLT) were serious or led to treatment discontinuation.

Injection site reactions:

Participants in the CD Induction Placebo- and Active-Controlled Analysis Set only received IV administration of mirikizumab. Therefore, this dataset was not included in the evaluation of injection site reactions.

Table EAIR of Injection Site Reaction TEAEs

CD Induction Placebo- And Active-Controlled and IBD Randomised Induction Integrated Analysis Sets

Event, n (%) [EAIR]	CD Treatment Regimen[a]			CD Miri Integrated[b]	IBD Integrated
	Pbo[c] N = 108 PYE = 70.5	Miri N = 600 PYE = 443.2	Uste N = 295 PYE = 244.1	Miri N = 1070 PYE = 1637.8	Miri N = 2168 PYE = 4649.9
Participants with at least 1 TE injection site reaction	7 (6.5) [10.4]	65 (10.8) [15.3]	17 (5.8) [7.1]	116 (10.8) [7.9]	224 (10.3) [5.3]
Injection site erythema	0	13 (2.2) [3.0]	1 (0.3) [0.4]	23 (2.1) [1.4]	49 (2.3) [1.1]
Injection site haematoma	0	0	1 (0.3) [0.4]	2 (0.2) [0.1]	5 (0.2) [0.1]
Injection site hypersensitivity	0	3 (0.5) [0.7]	0	3 (0.3) [0.2]	6 (0.3) [0.1]
Injection site induration	0	3 (0.5) [0.7]	0	3 (0.3) [0.2]	6 (0.3) [0.1]
Injection site mass	0	1 (0.2) [0.2]	0	1 (0.1) [0.1]	1 (0.0) [0.0]
Injection site oedema	0	1 (0.2) [0.2]	0	1 (0.1) [0.1]	2 (0.1) [0.0]
Injection site pain	7 (6.5) [10.4]	19 (3.2) [4.4]	11 (3.7) [4.6]	31 (2.9) [2.0]	76 (3.5) [1.7]
Injection site pruritus	0	3 (0.5) [0.7]	1 (0.3) [0.4]	5 (0.5) [0.3]	10 (0.5) [0.2]
Injection site rash	0	2 (0.3) [0.5]	0	3 (0.3) [0.2]	7 (0.3) [0.2]
Injection site reaction	0	24 (4.0) [5.5]	4 (1.4) [1.6]	58 (5.4) [3.8]	92 (4.2) [2.1]
Injection site swelling	0	5 (0.8) [1.1]	0	8 (0.7) [0.5]	9 (0.4) [0.2]

In the CD Treatment Regimen Placebo- and Active-Controlled Analysis Set, based on the Injection site reactions (HLT), the number and EAIRs of participants who reported at least 1 TE Injection site reaction was:

- 7 [EAIR = 10.4 per 100 PYE] placebo group participants
- 17 [EAIR = 7.1 per 100 PYE] ustekinumab treatment participants, and
- 65 [EAIR = 15.3 per 100 PYE] mirikizumab treatment participants.

In mirikizumab treatment participants, the highest EAIR for a reported TE Injection site reactions (HLT) was Injection site reaction [n = 24; EAIR = 5.5 per 100 PYE].

No Injection site reactions (HLT) in mirikizumab treatment participants were serious. One event of Injection site pain led to discontinuation. Study AMAM used a citrate containing formulation that is known to be associated with a higher frequency of injection site pain.

Studies AMBT and AMBY examined use of the citrate-free formulation. There were no injection site reactions reported in these studies.

In the CD Mirikizumab Exposures Integrated and IBD Integrated Analysis Sets, the EAIRs of TE Injection site reactions (HLT) were lower than those in the CD Treatment Regimen Placebo and Active-Controlled Analysis Set.

Infections, including opportunistic infection

Reported rates of infection, and opportunistic infection including herpes zoster, are generally accepted to be higher in Crohn's disease population than in the general or non-IBD population.

All infections

In the CD Induction Placebo- and Active-Controlled Analysis Set, based on the Infections and infestations SOC, the frequency of participants who reported treatment emergent (TE) infections and infestations was:

- 33 (15.6%) in placebo group participants
- 42 (13.6%) in ustekinumab treatment participants, and
- 127 (20.2%) in mirikizumab treatment participants.

In the CD Treatment Regimen Placebo- and Active-Controlled Analysis Set, based on the Infections and infestations SOC, the EAIR of participants who reported TE infections and infestations was:

- 73 [EAIR = 81.3 per 100 PYE] in placebo group participants
- 130 [EAIR = 58.1 per 100 PYE] in ustekinumab treatment participants, and
- 261 [EAIR = 59.7 per 100 PYE] in mirikizumab treatment participants.

Most treatment emergent infections were mild to moderate in severity and did not result in discontinuation of study treatment. The most frequently reported treatment emergent Infections and infestations event was COVID-19.

In the CD Mirikizumab Exposures Integrated Analysis Set, the EAIR of participants who reported TE Infections and infestations was lower than the EAIR in the CD Treatment Regimen Placebo- and Active-Controlled Analysis Set, indicating no increase in EAIRs with an increased exposure.

When treatment emergent infections reported by 12-week intervals in the CD Mirikizumab Exposures Integrated Analysis Set, are analysed they show a higher frequency of TE infections in the Induction period.

Table Treatment Emergent Adverse Events-Infections

By 12 Week Interval

CD Miri Exposures Safety Population-All Treatment Periods Where Miri Is Administered

CD Mirikizumab Exposures Integrated Analysis Set (AMAG/AMAX, AMAM, AMAX)

	CD Miri Exposures Integrated Analysis Set (N=1178)	
Time Intervals *a	Nx	n (%)
Weeks > 0 to <= 12	1178	198 (16.8)
Weeks > 12 to <= 24	1098	132 (12.0)
Weeks > 24 to <= 36	1017	124 (12.2)
Weeks > 36 to <= 48	949	123 (13.0)
Weeks > 48 to <= 60	861	92 (10.7)
Weeks > 60 to <= 72	687	86 (12.5)
Weeks > 72 to <= 84	612	55 (9.0)
Weeks > 84 to <= 96	490	51 (10.4)
Weeks > 96 to <= 108	407	56 (13.8)
Weeks > 108 to <= 120	324	37 (11.4)
Weeks > 120 to <= 132	245	23 (9.4)
Weeks > 132 to <= 144	196	14 (7.1)
Weeks > 144 to <= 156	160	11 (6.9)
Weeks > 156 to <= 168	138	12 (8.7)
Weeks > 168 to <= 180	131	11 (8.4)
Weeks > 180 to <= 192	110	11 (10.0)
Weeks > 192 to <= 204	100	9 (9.0)
Weeks > 204 to <= 216	97	12 (12.4)
Weeks > 216 to <= 228	97	8 (8.2)
Weeks > 228 to <= 240	96	11 (11.5)
Weeks > 240 to <= 252	95	10 (10.5)
Weeks > 252 to <= 264	81	7 (8.6)
Weeks > 264 to <= 276	65	4 (6.2)
Weeks > 276 to <= 288	49	2 (4.1)
Weeks > 288 to <= 300	27	0
Weeks > 300 to <= 312	16	0
Weeks > 312 to <= 324	4	0
Weeks > 324 to <= 336	1	0

Serious infections

In the CD Induction Placebo- and Active-Controlled Analysis Set, serious infection occurred in 7 (1.1%) mirikizumab-treated participants and 1 (0.5%) participant receiving placebo.

In the CD Treatment Regimen Placebo- and Active-Controlled Analysis Sets, serious infection occurred in 14 (EAIR=2.4 per 100 PYE) participants who received mirikizumab and 6 (EAIR= 5.1 per 100 PYE) participants who received placebo. The serious infections reported in mirikizumab-treated participants were primarily COVID-19, anal abscess, and abdominal abscess; the last 2 PTs are known to be CD complications.

In the treatment period, a lower incidence of serious infections was reported in the mirikizumab group than the placebo group. The incidence rate of participants with at least 1 serious infection across treatment groups was

- 6 participants (EAIR = 5.1 per 100 PYE) in placebo group
- 9 participants (EAIR = 3.1 per 100 PYE) in ustekinumab group, and
- 14 participants (EAIR = 2.4 per 100 PYE) in mirikizumab group.

None of the serious infections were considered opportunistic. Overall, 3 mirikizumab-treated participants discontinued from study treatment due to a serious infection. The incidence rate of serious infection in mirikizumab exposures in CD did not increase over longer duration of mirikizumab treatment and no deaths occurred in the mirikizumab arm due to serious infection.

Opportunistic infection

During Induction Period, opportunistic TE infections were reported in 4 participants (0.6%) in the mirikizumab group. No opportunistic TE infections were reported in the placebo or ustekinumab group.

During Induction Period, opportunistic TE infections were reported in 4 participants (0.6%) in the mirikizumab group. No opportunistic TE infections were reported in the placebo or ustekinumab group.

All were mild or moderate in severity and led to one treatment discontinuation in a participant with herpes zoster.

During the treatment period, a higher incidence of opportunistic TE infections (narrow scope) was reported in the mirikizumab group (EAIR = 1.2 per 100 PYE) than in the ustekinumab group (EAIR = 0.3 per 100 PYE). No opportunistic TE infections were reported in the placebo group.

The narrow scope events for TE opportunistic infections included:

- Ustekinumab group
    - Herpes zoster, EAIR = 0.3 per 100 PYE (n=1);
- Mirikizumab group
    - Herpes zoster, EAIR = 0.8 per 100 PYE (n=5)
    - Typhoid fever, EAIR = 0.2 per 100 PYE (n=1), and
    - Oral candidiasis, EAIR = 0.2 per 100 PYE (n=1).

No additional discontinuations were observed in the treatment period.

As discussed above, opportunistic infections were reported in the CD Treatment Regimen Placebo- and Active- Controlled Analysis Sets in mirikizumab-treated participants (n=7, EAIR=1.2 per 100 PYE).

No opportunistic infections were reported in the placebo group participants. The highest EAIR of reported TE opportunistic infections in mirikizumab-treated participants was herpes zoster (n=5, EAIR=0.8 per 100 PYE). The EAIR of opportunistic infections in the CD Mirikizumab Exposures Integrated Analysis Set was low (EAIR=1.4 per 100 PYE), and the EAIR for herpes zoster was within the incidence rates reported in the literature (0.76 to 1.83 per 100 PY).

Cerebrocardiovascular events

The incidence rates for cerebrovascular disorders among patients with CD in published observational studies range from 0.16 to 0.58 per 100 PY for MI and 0.06 to 0.43 per 100 PY for stroke and the reported rate for MACE among patients with CD was 0.82 per 100 PY.

Table Adjudicated and Confirmed CCV and MACE TEAEs by Subcategory

CD Induction Placebo- and Active-Controlled, CD Treatment Regimen Placebo-and Active-Controlled, CD Mirikizumab Exposures Integrated, and IBD Integrated Analysis Sets.

Event, n (%) [EAIR]	CD Induction			CD Treatment Regimen			CD Miri Integrated[a]	IBD Integrated
	Pbo N = 211 PYE = 49	Miri N = 630 PYE = 150.4	Uste N = 309 PYE = 73.7	Pbo[b] N = 211 PYE = 119.5	Miri N = 630 PYE = 593.6	Uste N = 309 PYE = 293.3	Miri N = 1098 PYE = 1921.7	Miri N = 2459 PYE = 5342.4
Participants with at least 1 CCV event	1 (0.5) [2.0]	0	0	2 (0.9) [1.7]	3 (0.5) [0.5]	2 (0.6) [0.7]	7 (0.6) [0.4]	25 (1.0) [0.5]
Death	1 (0.5) [2.0]	0	0	1 (0.5) [0.8]	0	0	0	0
Myocardial infarction	0	0	0	1 (0.5) [0.8]	0	1 (0.3) [0.3]	0	3 (0.1) [0.1]
Hospitalization for unstable angina	0	0	0	0	0	0	0	0
Hospitalization for heart failure	0	0	0	0	1 (0.2) [0.2]	0	1 (0.1) [0.1]	2 (0.1) [0.0]
Hospitalization for hypertension	0	0	0	0	0	0	0	2 (0.1) [0.0]
Serious arrhythmia	0	0	0	1 (0.5) [0.8]	2 (0.3) [0.3]	0	4 (0.4) [0.2]	14 (0.6) [0.3]
Resuscitated sudden death	0	0	0	1 (0.5) [0.8]	0	0	0	1 (0.0) [0.0]
Cardiogenic shock	0	0	0	0	0	0	0	0
Coronary revascularization procedure	0	0	0	0	0	0	0	2 (0.1) [0.0]
Transient ischemic attack	0	0	0	0	0	0	0	1 (0.0) [0.0]
Stroke	0	0	0	0	0	1 (0.3) [0.3]	2 (0.2) [0.1]	5 (0.2) [0.1]
Peripheral arterial event	0	0	0	0	0	0	0	0
Peripheral revascularization procedure	0	0	0	0	0	0	0	0
Participants with at least 1 MACE	1 (0.5) [2.0]	0	0	2 (0.9) [1.7]	0	2 (0.6) [0.7]	2 (0.2) [0.1]	8 (0.3) [0.2]
Cardiovascular death	1 (0.5) [2.0]	0	0	1 (0.5) [0.8]	0	0	0	0
Nonfatal myocardial infarction	0	0	0	1 (0.5) [0.8]	0	1 (0.3) [0.3]	0	3 (0.1) [0.1]
Nonfatal stroke	0	0	0	0	0	1 (0.3) [0.3]	2 (0.2) [0.1]	5 (0.2) [0.1]

In the CD Induction Placebo- and Active-Controlled Analysis Set, the only CCV event was reported by a placebo group participant (n = 1; 0.5%). The reported CCV event was a cardiac arrest because of a pulmonary embolism, which was subsequently adjudicated as death (cardiovascular). This event was considered a MACE.

No treatment emergent cerebrocardiovascular events were seen in the mirikizumab treatment group.

In the CD Treatment Regimen Placebo- and Active-Controlled Analysis, the EAIR of participants who reported TE CCV events was similar in mirikizumab treatment participants compared with the EAIR for placebo group participants.

Overall, 7 participants reported at least 1 treatment emergent cerebrocardiovascular event:

- 2 [EAIR = 1.7 per 100 PYE] placebo group participants
- 2 [EAIR = 0.7 per 100 PYE] ustekinumab treatment participants, and
- 3 [EAIR = 0.5 per 100 PYE] mirikizumab treatment participants.

The events were

reported by the investigator as…	**which was subsequently adjudicated as…**	**in a…**
Cardiac arrest in consequence of a Pulmonary embolism	Death (cardiovascular)	placebo group participant (Table 2.7.4.12)
Cerebrovascular accident	Stroke	ustekinumab treatment participant (Table 2.7.4.53)
Cardio-respiratory arrest	Myocardial infarction (type 2), Serious Arrhythmia, and Resuscitated sudden death	placebo group participant (Table 2.7.4.53)
Angina pectoris	Myocardial infarction	ustekinumab treatment participant (Table 2.7.4.53)
Cardiac failure acute	Hospitalization for heart failure	mirikizumab treatment participant (AMAM-679-22289)
Atrial fibrillation	Serious arrhythmia	mirikizumab treatment participant (AMAM-262-20506)
Atrial fibrillation	Serious arrhythmia	mirikizumab treatment participant (AMAM-407-22676)

Of these 7 events, 4 were considered as MACE and were adjudicated as

- Death (cardiovascular)
- Stroke
- Myocardial infarction (type 2), Serious arrhythmia, and resuscitated sudden death, and
- Myocardial infarction

Narratives have been provided for all events.

In the CD Mirikizumab Exposures Integrated Analysis Set, 7 [EAIR = 0.4 per 100 PYE] mirikizumab treatment participants reported at least 1 cerebrocardiovascular event.

The events were

reported by the investigator as...	which was subsequently adjudicated as...
Cardiac failure acute	Hospitalization for heart failure
Atrial fibrillation	Serious arrhythmia
Atrial fibrillation	Serious arrhythmia
Bradycardia	Serious arrhythmia
Sinus tachycardia	Serious arrhythmia
Ischemic stroke (cardioembolic)	Stroke
Central paresis of the VII nerve on the basis of vascular genesis altered by COVID-19	Stroke

Of these 7 mirikizumab treatment participants, the 2 (0.2%) strokes were considered MACE. In the CD Mirikizumab Exposures Integrated Analysis Set, the EAIRs for treatment emergent cerebrocardiovascular events and MACE in mirikizumab treatment participants were numerically lower than EAIR for placebo group participants (from the CD Treatment Regimen Placebo- and Active-

Controlled Analysis Set) and within the background rates of cerebrocardiovascular disease and MACE in the CD population.

In the IBD Integrated Analysis Set, the EAIRs for treatment emergent cerebrocardiovascular events and MACE were within the background rates of cerebrocardiovascular disease and MACE in the IBD population.

In the CD Induction Placebo- and Active-Controlled Analysis Set, 1 (0.5%) placebo group participant reported at least 1 serious cerebrocardiovascular event (MACE).

In the CD Treatment Regimen Placebo- and Active-Controlled Analysis Set, the EAIRs of participants who reported at least 1 serious CCV event were:

- 2 [EAIR = 1.7 per 100 PYE] placebo group participants
- 1 [EAIR = 0.3 per 100 PYE] ustekinumab treatment participant, and
- 2 [EAIR = 0.3 per 100 PYE] mirikizumab treatment participants.

In mirikizumab treatment participants, the reported serious cerebrocardiovascular events were Cardiac failure acute (n = 1) and Atrial fibrillation (n = 1) (Table AMAM.8.133).

In mirikizumab treatment participants, no discontinuations occurred due to treatment emergent cerebrocardiovascular events or MACE in any CD analysis set.

In the CD Induction Placebo- and Active-Controlled Analysis Set, 1 placebo group participant discontinued due to a CCV event (MACE) of Cardiovascular death.

In the CD Treatment Regimen Placebo- and Active-Controlled Analysis Set, 1 (0.3%) ustekinumab treatment participant discontinued treatment due to a CCV event (MACE) of Angina pectoris.

Deaths

In total, 5 deaths were reported in the mirikizumab CD clinical program, of which

- 3 deaths occurred in Study AMAM, including
    - 1 reported in the Induction Period in a placebo group participant, and
    - 2 reported in the Maintenance Period, with
        - 1 in an ustekinumab treatment participant, and
        - 1 in a placebo group non responder participant who switched to mirikizumab after Week 12, and
- 2 deaths occurred in the LTE Study AMAX (after the Study AMAX data cutoff date, 15 June 2023).

In the SCS for the UC indication, 5 deaths had been reported in all studies of UC and 11 in all studies of psoriasis.

Three additional deaths were reported in the UC clinical development program after DBL for the UC submission. All were reported in the LTE Study AMAP.

Table Adverse Events Leading to Treatment Discontinuation

MedDRA Preferred Term by Decreasing Frequency

Safety Population

16T-MC-AMAM- Study Treatment Period

Preferred Term	placebo# (N=211) n (%)	miri (N=630) n (%)	uste (N=309) n (%)	Total (N=1150) n (%)	p-values*a miri vs. uste	Odds ratio*b miri/ uste
Subjects with >= 1 AE leading to treatment discontinuation	20 (9.5)	32 (5.1)	8 (2.6)	60 (5.2)	0.086	2.01
Crohn's disease	12 (5.7)	5 (0.8)	3 (1.0)	20 (1.7)	0.723	0.82
Infusion related hypersensitivity reaction	0	3 (0.5)	0	3 (0.3)	0.555	NA
Abdominal abscess	0	2 (0.3)	0	2 (0.2)	>0.999	NA
Small intestinal obstruction	1 (0.5)	2 (0.3)	0	3 (0.3)	>0.999	NA
Abdominal pain	0	1 (0.2)	0	1 (0.1)	>0.999	NA
Anaphylactic reaction	0	1 (0.2)	0	1 (0.1)	>0.999	NA
Arthralgia	0	1 (0.2)	0	1 (0.1)	>0.999	NA
Breast cancer	0	1 (0.2)	0	1 (0.1)	>0.999	NA
Colectomy	0	1 (0.2)	0	1 (0.1)	>0.999	NA
Depression	0	1 (0.2)	0	1 (0.1)	>0.999	NA
Dyspnoea	0	1 (0.2)	0	1 (0.1)	>0.999	NA
Fatigue	0	1 (0.2)	0	1 (0.1)	>0.999	NA
Haematuria	0	1 (0.2)	0	1 (0.1)	>0.999	NA
Headache	0	1 (0.2)	0	1 (0.1)	>0.999	NA
Hepatitis B DNA assay positive	0	1 (0.2)	0	1 (0.1)	>0.999	NA
Herpes zoster	0	1 (0.2)	0	1 (0.1)	>0.999	NA
Hypersensitivity	0	1 (0.2)	0	1 (0.1)	>0.999	NA
Ileectomy	0	1 (0.2)	0	1 (0.1)	>0.999	NA
Injection site pain	0	1 (0.2)	0	1 (0.1)	>0.999	NA
Large intestine perforation	0	1 (0.2)	0	1 (0.1)	>0.999	NA
Large intestine polyp	0	1 (0.2)	0	1 (0.1)	>0.999	NA
Non-alcoholic fatty liver	0	1 (0.2)	0	1 (0.1)	>0.999	NA
Urosepsis	0	1 (0.2)	0	1 (0.1)	>0.999	NA
Urticaria	0	1 (0.2)	0	1 (0.1)	>0.999	NA
Abscess intestinal	1 (0.5)	0	0	1 (0.1)	NA	NA
Alanine aminotransferase increased	0	0	1 (0.3)	1 (0.1)	0.329	0.00
Angina pectoris	0	0	1 (0.3)	1 (0.1)	0.329	0.00
Anorectal disorder	0	0	1 (0.3)	1 (0.1)	0.329	0.00
Bile duct stone	1 (0.5)	0	0	1 (0.1)	NA	NA
Enterocolonic fistula	1 (0.5)	0	0	1 (0.1)	NA	NA
Hepatitis cholestatic	1 (0.5)	0	0	1 (0.1)	NA	NA
Interstitial lung disease	0	0	1 (0.3)	1 (0.1)	0.329	0.00
Pulmonary embolism	1 (0.5)	0	0	1 (0.1)	NA	NA
Sepsis	0	0	1 (0.3)	1 (0.1)	0.329	0.00
Septic shock	1 (0.5)	0	0	1 (0.1)	NA	NA
Weight decreased	1 (0.5)	0	0	1 (0.1)	NA	NA

In the CD Treatment Regimen Placebo- and Active-Controlled Analysis Set, overall EAIRs for TEAEs, SAEs, and discontinuations due to AEs were higher in placebo group participants compared with mirikizumab treatment participants.

2.6.8.4. Laboratory findings

Haematology

Blood leukocytes- Low

Table TE Shifts, Mean Changes from Baseline, and Associated TEAEs in Blood Leukocytes

CD Induction Placebo-And Active-Controlled and CD Treatment Regimen Placebo-and Active Controlled Analysis Sets

	CD Induction			CD Treatment Regimen		
	Pbo N = 211	Miri N = 630	Uste N = 309	Pbo[a] N = 211	Miri N = 630	Uste N = 309
TE shifts, n/NAR (%)						
TE-low values	12/192 (6.3)	54/591 (9.1)	28/293 (9.6)	24/192 (12.5)	123/592 (20.8)	48/297 (16.2)
Mean changes from baseline (10^9/L)						
Minimum baseline to minimum postbaseline	-0.477	-1.257	-1.113	-0.936	-2.214	-1.989
LSM difference	-0.728	–	-0.113	–	–	-0.184
Baseline to last observation	-0.084	-1.079	-1.062	-0.027	-1.446	-1.205
LSM difference	-0.888	–	0.005	–	–	-0.213
Shift in CTCAE category, n/NAR (%)[b]						
Any shift to a higher Grade	20/204 (9.8)	79/626 (12.6)	34/302 (11.3)	35/204 (17.2)	159/627 (25.4)	60/306 (19.6)
Shift to Grade 1	13/189 (6.9)	65/581 (11.2)	28/287 (9.8)	20/189 (10.6)	118/582 (20.3)	43/291 (14.8)
Shift to Grade 2	7/203 (3.4)	14/616 (2.3)	6/301 (2.0)	13/203 (6.4)	38/617 (6.2)	16/305 (5.2)
Shift to Grade 3	0/204	0/626	0/302	2/204 (1.0)	3/627 (0.5)	1/306 (0.3)
Shift to Grade 4	0/204	0/626	0/302	0/204	0/627	0/306
Participants with at least 1 TEAE of Leukopenia or White blood cell count decreased, n (%) [EAIR]						
	PYE = 49	**PYE = 150.4**	**PYE = 73.7**	**PYE = 119.5**	**PYE = 593.6**	**PYE = 293.3**
Leukopenia	0	6 (1.0) [4.0]	1 (0.3) [1.4]	0	9 (1.4) [1.5]	3 (1.0) [1.0]
White blood cell count decreased	1 (0.5) [2.0]	8 (1.3) [5.4]	1 (0.3) [1.4]	1 (0.5) [0.8]	15 (2.4) [2.6]	5 (1.6) [1.7]

Participants with TE-low values and at least 1 TEAE within the Infections and infestations (SOC), n (%) [EAIR]						
	Nx = 12 PYE = 2.8	**Nx = 54 PYE = 12.8**	**Nx = 28 PYE = 6.7**	**Nx = 24 PYE = 20.5**	**Nx = 123 PYE = 122.3**	**Nx = 48 PYE = 47.8**
Infections and infestations (SOC)	0	3 (5.6) [24.0]	1 (3.6) [15.4]	2 (8.3) [10.3]	10 (8.1) [8.6]	6 (12.5) [13.2]

In the CD Induction Placebo- and Active-Controlled and CD Treatment Regimen Placebo- and Active-Controlled Analysis Sets, the frequency of participants with shifts to TE-low values for blood leukocytes was higher for mirikizumab treatment participants compared with placebo group participants.

Mean changes in blood leukocytes were small and not considered clinically meaningful. Greater decreases in leukocytes were reported in mirikizumab treatment participants compared with placebo group participants.

Three mirikizumab treatment participants reported shifts to CTCAE Grade 3:

- One participant had a single isolated CTCAE Grade 3 leukocyte concentration of 1.99 x 109/L recorded at Day 366, which resolved while continuing on mirikizumab. No associated AE (including infections) was reported. Relevant concomitant medication included azathioprine.
- A second participant had a single isolated CTCAE Grade 3 leukocyte concentration of 1.97 x 109/L at Day 197, which resolved while continuing on mirikizumab. A mild, non-serious AE of COVID-19 had been reported approximately 1 month earlier, with normal leukocyte concentrations before and after the infection. No relevant concomitant medications were reported.
- A third participant had 2 CTCAE Grade 3 leukocyte concentrations at Days 146 and 160, which resolved while continuing on mirikizumab. A mild non-serious AE of URTI at Days 104 to 108 and concurrent AEs of White blood cell count decreased, Neutrophil count decreased, Monocyte count decreased, and Lymphocyte count increased were reported. No relevant concomitant medications were reported.

The proportion of participants who reported a TEAE of Leukopenia or White blood cell count decreased was higher in mirikizumab treatment participants compared with placebo group.

In the CD Treatment Regimen Placebo- and Active-Controlled Analysis Set, the Leukopenia cluster, which includes the Leukopenia and White blood cell count decreased PTs, was reported at a higher incidence in mirikizumab treatment participants [EAIR = 4.2 per 100 PYE] compared with placebo group participants [EAIR = 0.8 per 100 PYE.

Blood lymphocytes-low

Table TE Shifts, Mean Changes from Baseline, and Associated TEAEs in Blood Lymphocytes

CD Induction Placebo-And Active-Controlled and CD Treatment Regimen Placebo-and Active Controlled Analysis Sets

	CD Induction			CD Treatment Regimen		
	Pbo N = 211	Miri N = 630	Uste N = 309	Pbo[a] N = 211	Miri N = 630	Uste N = 309
TE shifts, n/NAR (%)						
TE-low values	19/161 (11.8)	58/509 (11.4)	24/239 (10.0)	28/161 (17.4)	115/510 (22.5)	49/243 (20.2)
Mean changes from baseline (10^9/L)						
Minimum baseline to minimum postbaseline	-0.151	-0.096	-0.080	-0.241	-0.266	-0.274
LSM difference	0.046	–	-0.010	–	–	0.011
Baseline to last observation	-0.124	-0.029	-0.060	-0.098	-0.007	-0.047
LSM difference	0.090	–	0.036	–	–	0.041
Shift in CTCAE category, n/NAR (%)[b]						
Any shift to a higher Grade	40/204 (19.6)	120/626 (19.2)	53/302 (17.5)	60/204 (29.4)	199/627 (31.7)	101/306 (33.0)
Shift to Grade 1	17/133 (12.8)	69/431 (16.0)	23/197 (11.7)	22/133 (16.5)	98/432 (22.7)	47/201 (23.4)
Shift to Grade 2	17/174 (9.8)	40/544 (7.4)	24/258 (9.3)	21/174 (12.1)	77/545 (14.1)	40/262 (15.3)
Shift to Grade 3	5/201 (2.5)	11/613 (1.8)	5/299 (1.7)	14/201 (7.0)	21/614 (3.4)	13/303 (4.3)
Shift to Grade 4	1/204 (0.5)	0/626	1/302 (0.3)	3/204 (1.5)	3/627 (0.5)	1/306 (0.3)
Participants with at least 1 TEAE of Lymphopenia or Lymphocyte count decreased, n (%) [EAIR]						
	PYE = 49	**PYE = 150.4**	**PYE = 73.7**	**PYE = 119.5**	**PYE = 593.6**	**PYE = 293.3**
Lymphopenia	3 (1.4) [6.2]	5 (0.8) [3.3]	3 (1.0) [4.1]	6 (2.8) [5.2]	9 (1.4) [1.5]	6 (1.9) [2.1]
Lymphocyte count decreased	1 (0.5) [2.0]	12 (1.9) [8.1]	3 (1.0) [4.1]	4 (1.9) [3.4]	15 (2.4) [2.6]	5 (1.6) [1.7]

	CD Induction			CD Treatment Regimen		
	Pbo N = 211	Miri N = 630	Uste N = 309	Pbo[a] N = 211	Miri N = 630	Uste N = 309
Participants with TE-low values and at least 1 TEAE within Infections and infestations (SOC), n (%) [EAIR]						
	Nx = 19 PYE = 4.5	**Nx = 58 PYE = 14.2**	**Nx = 24 PYE = 5.7**	**Nx = 28 PYE = 16.6**	**Nx = 115 PYE = 112.7**	**Nx = 49 PYE = 47.1**
Infections and infestations (SOC)	1 (5.3) [22.4]	7 (12.1) [52.1]	1 (4.2) [17.8]	2 (7.1) [12.6]	17 (14.8) [16.5]	8 (16.3) [18.4]

In the CD Induction Placebo- and Active-Controlled Analysis Set, the frequency of participants with TE-low values for blood lymphocytes was similar between mirikizumab treatment participants and placebo group participants.

The mean decrease in blood lymphocytes was similar between mirikizumab treatment participants and placebo group participants for minimum baseline to minimum postbaseline.

The frequency of participants with shifts to higher CTCAE grades was similar between mirikizumab treatment participants and placebo group participants. A lower frequency of mirikizumab treatment participants reported shifts to CTCAE Grades 3 and 4 compared with placebo group participants.

In the CD Treatment Regimen Placebo- and Active-Controlled Analysis Set, the frequency of participants with TE-low values for blood lymphocytes was higher for mirikizumab treatment participants compared with placebo group participants.

The mean decrease in blood lymphocytes was similar between mirikizumab treatment participants and placebo group participants for minimum baseline to minimum postbaseline. Most shifts were mild, to Grade 1 or 2. A higher frequency of mirikizumab treatment participants reported shifts to CTCAE Grades 1 and 2 compared with placebo group participants. A lower frequency of mirikizumab treatment participants reported shifts to CTCAE Grades 3 and 4 compared with placebo group participants.

The EAIR of TEAEs within the Infections and infestations SOC in participants who reported TE-low values was lower than the EAIR of the Infections and infestations SOC in mirikizumab treatment participants in the CD Treatment Regimen Placebo- and Active-Controlled Analysis Set [EAIR = 16.5 versus 59.7 per 100 PYE], indicating no association of lymphopenia and infections in this study.

In the CD Induction Placebo- and Active-Controlled Analysis Set, the TEAE of Lymphocyte count decreased was reported more frequently in mirikizumab treatment participants (1.9%) compared with placebo group participants (0.5%). In mirikizumab treatment participants, all 12 Lymphocyte count decreased events were reported as mild or moderate in severity. None were reported as serious or led to study treatment discontinuation. Of the 12 events, 8 were considered related to study drug by the investigator.

No pattern in the time-to-onset, duration of the events, or common underlying etiology was observed besides the standard-of-care therapy, which is known to cause lymphopenia. Most participants who reported Lymphocyte count decreased were taking concomitant corticosteroids, azathioprine, or mesalazine (or a combination of these).

Blood Neutrophils-Low

Table TE Shifts, Mean Changes from Baseline, and Associated TEAEs in Blood Neutrophils

CD Induction Placebo-And Active-Controlled and CD Treatment Regimen Placebo-and Active Controlled Analysis Sets

	CD Induction			CD Treatment Regimen		
	Pbo N = 211	Miri N = 630	Uste N = 309	Pbo[a] N = 211	Miri N = 630	Uste N = 309
TE shifts, n/NAR (%)						
TE-low values	10/198 (5.1)	35/602 (5.8)	18/300 (6.0)	16/198 (8.1)	95/603 (15.8)	48/304 (15.8)
Mean changes from baseline (10^9/L)						
Minimum baseline to minimum postbaseline	-0.342	-1.118	-1.021	-0.741	-1.962	-1.761
LSM difference	-0.720	–	-0.094	–	–	-0.190
Baseline to last observation	0.068	-0.974	-0.941	0.084	-1.338	-1.104
LSM difference	-0.915	–	-0.027	–	–	-0.216
Shift in CTCAE category, n/NAR (%)[b]						
Any shift to a higher Grade	12/204 (5.9)	43/625 (6.9)	20/302 (6.6)	21/204 (10.3)	108/626 (17.3)	50/306 (16.3)
Shift to Grade 1	10/197 (5.1)	29/601 (4.8)	17/300 (5.7)	15/197 (7.6)	65/602 (10.8)	35/304 (11.5)
Shift to Grade 2	2/204 (1.0)	10/619 (1.6)	3/302 (1.0)	4/204 (2.0)	36/620 (5.8)	14/306 (4.6)
Shift to Grade 3	0/204	4/624 (0.6)	0/302 (0.0)	2/204 (1.0)	7/625 (1.1)	1/306 (0.3)
Shift to Grade 4	0/204	0/625	0/302	0/204	0/626	0/306
Participants with at least 1 TEAE of Neutropenia or Neutrophil count decreased, n (%) [EAIR]						
	PYE = 49	**PYE = 150.4**	**PYE = 73.7**	**PYE = 119.5**	**PYE = 593.6**	**PYE = 293.3**
Neutropenia	1 (0.5) [2.0]	1 (0.2) [0.7]	1 (0.3) [1.4]	1 (0.5) [0.8]	1 (0.2) [0.2]	2 (0.6) [0.7]
Neutrophil count decreased	0	3 (0.5) [2.0]	1 (0.3) [1.4]	0	10 (1.6) [1.7]	5 (1.6) [1.7]

	CD Induction			CD Treatment Regimen		
	Pbo N = 211	Miri N = 630	Uste N = 309	Pbo[a] N = 211	Miri N = 630	Uste N = 309
Participants with TE-low values and at least 1 TEAE within Infections and infestations (SOC), n (%) [EAIR]						
	Nx = 10 PYE = 2.3	**Nx = 35 PYE = 8.4**	**Nx = 18 PYE = 4.2**	**Nx = 16 PYE = 13.8**	**Nx = 95 PYE = 95**	**Nx = 48 PYE = 47.1**
Infections and Infestations (SOC)	0	1 (2.9) [11.9]	0	0	8 (8.4) [8.8]	2 (4.2) [4.3]

In the CD Induction Placebo- and Active-Controlled and CD Treatment Regimen Placebo- and Active-Controlled Analysis Sets, the frequency of participants with TE-low values for segmented blood neutrophils was higher for mirikizumab treatment participants compared with placebo group participants. A greater mean decrease in segmented blood neutrophils was reported in mirikizumab treatment participants compared with placebo group participants for minimum baseline to minimum postbaseline.

A higher frequency of mirikizumab treatment participants reported shifts to CTCAE Grades 1 and 2 compared with placebo group participants. No shifts to CTCAE Grades 4 were reported.

The EAIR of TEAEs within the Infections and infestations SOC in participants with a concomitant TE-low value was lower than the EAIR of the Infections and infestations SOC in mirikizumab treatment participants in the CD Treatment Regimen Placebo- and Active-Controlled Analysis Set [EAIR = 8.8 versus 59.7 per 100 PYE].

In the CD Treatment Regimen Placebo- and Active-Controlled Analysis Set, the TEAE of Neutrophil count decreased was reported at a higher incidence in mirikizumab treatment participants compared with placebo group participants (Table 2.7.4.15). 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 etiology was observed. Half of the cases were considered related to study drug by the investigator.

Table Mirikizumab Treatment Participants Reporting Treatment-Emergent Shifts to CTCAE Grade 3

CTCAE Grade At Least 3 at Baseline? (Y or N)	Shifts to CTCAE Grade 3 Cells x 10^9/L (Study Day)	Transient? (Y or N)[a]	Associated AEs? Labs or Infections
N	0.88 (Day 365)	Y	Anaemia
N	0.98 (Day 30)	Y	Anemia of chronic disease.
N	0.86 (Day 141)	Y	Gastroenteritis viral.
N	0.92 (Day 68)	Y	None
N	0.85 (Day 314)	Y	None
Y	0.58 (Day 29)	Y	White blood cell count decreased and Neutrophil count decreased
N	0.97 (Day 29) 0.78 (Day 85) 0.81 (Day 309)	Y	Leukopenia, Neutropenia, and Anemia.

Blood eosinophils-high

Table TE Shifts, Mean Changes from Baseline, and Associated TEAEs in Blood Eosinophils

CD Induction Placebo-And Active-Controlled and CD Treatment Regimen Placebo-and Active Controlled Analysis Sets

	CD Induction			CD Treatment Regimen		
	Pbo N = 211 PYE =49	Miri N = 630 PYE = 150.4	Uste N = 309 PYE = 73.7	Pbo[a] N = 211 PYE = 119.5	Miri N = 630 PYE = 593.6	Uste N = 309 PYE = 293.3
TE shifts, n/NAR (%)						
TE-high values	2/197 (1.0)	9/608 (1.5)	2/292 (0.7)	4/197 (2.0)	26/609 (4.3)	13/296 (4.4)
Mean changes from baseline (10^9/L)						
Maximum baseline to maximum postbaseline	0.019	0.009	0.020	0.054	0.079	0.092
LSM difference	-0.010	–	-0.005	–	–	-0.008
Baseline to last observation	-0.020	-0.020	-0.010	-0.022	-0.018	0.002
LSM difference	-0.005	–	-0.005	–	–	-0.013
Participants with at least 1 TEAE of Eosinophilia or Eosinophils count increased, n (%) [EAIR]						
Eosinophilia	0	0	0	0	0	2 (0.6) [0.7]
Eosinophils count increased	0	0	0	0	0	0

In the CD Induction Placebo- and Active-Controlled and CD Treatment Regimen Placebo- and Active-Controlled Analysis Sets, the frequency of participants with TE-high values for blood eosinophils was higher for mirikizumab treatment participants compared with placebo group participants; however, overall, the frequency was low. No clinically relevant TEAEs were reported by mirikizumab treatment participants. Mean increases were small and not clinically meaningful.

Blood platelets- Low

Table TE Shifts, Mean Changes from Baseline, and Associated TEAEs in Blood Platelets

CD Induction Placebo-And Active-Controlled and CD Treatment Regimen Placebo-and Active Controlled Analysis Sets

	CD Induction			CD Treatment Regimen		
	Pbo N = 211 PYE = 49	Miri N = 630 PYE = 150.4	Uste N = 309 PYE = 73.7	Pbo[a] N = 211 PYE = 119.5	Miri N = 630 PYE = 593.6	Uste N = 309 PYE = 293.3
TE shifts, n/NAR (%)						
TE-low values	3/203 (1.5)	12/621 (1.9)	4/301 (1.3)	3/203 (1.5)	29/623 (4.7)	13/305 (4.3)
Mean changes from baseline (10^9/L)						
Minimum baseline to minimum postbaseline	-4.1	-39.7	-38.1	-15.8	-76.6	-69.9
LSM difference	-32.0	–	-5.2	–	–	-12.0
Baseline to last observation	8.3	-37.5	-37.9	16.1	-52.3	-36.7
LSM difference	-42.1	–	-4.4	–	–	-21.8
Shift in CTCAE category, n/NAR (%)[b]						
Any shift to a higher Grade	4/204 (2.0)	14/624 (2.2)	5/301 (1.7)	5/204 (2.5)	36/626 (5.8)	15/305 (4.9)
Shift to Grade 1	4/201 (2.0)	14/617 (2.3)	5/300 (1.7)	5/201 (2.5)	34/619 (5.5)	15/304 (4.9)
Shift to Grade 2	0/204	0/624	0/301	0/204	2/626 (0.3)	0/305
Shift to Grade 3	0/204	0/624	0/301	0/204	0/626	0/305
Shift to Grade 4	0/204	0/624	0/301	0/204	0/626	0/305
Participants with at least 1 TEAE of Thrombocytopenia or Platelet count decreased, n (%) [EAIR]						
Thrombocytopenia	0	1 (0.2) [0.7]	1 (0.3) [1.4]	0	3 (0.5) [0.5]	2 (0.6) [0.7]
Platelet count decreased	0	3 (0.5) [2.0]	0	0	5 (0.8) [0.8]	2 (0.6) [0.7]

In the CD Induction Placebo- and Active-Controlled and CD Treatment Regimen Placebo- and Active-Controlled Analysis Sets, the frequency of participants with TE-low values for blood platelets was higher in mirikizumab treatment participants compared with placebo group participants.

A higher decrease in mean blood platelets was reported in mirikizumab treatment participants compared with placebo group participants for minimum baseline to minimum postbaseline.

Overall, the frequency of shifts to higher CTCAE Grades was greater in mirikizumab treatment participants compared with placebo group participants. Nearly all of the shifts were to CTCAE

Grade 1, except for 2 mirikizumab treatment participants, who reported a shift to CTCAE Grade 2. No shifts to CTCAE Grade 3 or 4 were reported.

Chemistry

Serum albumin-high

Table TE Shifts, Mean Changes from Baseline in Serum Albumin

CD Induction Placebo-And Active-Controlled and CD Treatment Regimen Placebo-and Active Controlled Analysis Sets

	CD Induction			CD Treatment Regimen		
	Pbo N = 211	Miri N = 630	Uste N = 309	Pbo[a] N = 211	Miri N = 630	Uste N = 309
TE shifts, n/NAR (%)						
TE-high values	20/192 (10.4)	62/582 (10.7)	20/277 (7.2)	23/192 (12.0)	165/582 (28.4)	61/278 (21.9)
Mean changes from baseline (g/L)						
Maximum baseline to maximum postbaseline	0.2	1.6	1.9	0.9	3.8	3.7
LSM difference	1.3	–	-0.1	–	–	0.3
Baseline to last observation	-0.1	2.0	1.9	-0.3	3.2	2.3
LSM difference	1.8	–	0.1	–	–	1.0

In the CD Induction Placebo- and Active-Controlled Analysis Set, a similar frequency of mirikizumab treatment participants reported a TE-high serum albumin compared with placebo group participants. In the and CD Treatment Regimen Placebo- and Active-Controlled Analysis Set, the frequency was higher in mirikizumab treatment participants.

Creatinine kinase-high

Table TE Shifts, Mean Changes from Baseline, and Associated TEAEs in Serum Creatinine Kinase

CD Induction Placebo-And Active-Controlled and CD Treatment Regimen Placebo-and Active Controlled Analysis Sets

	CD Induction			CD Treatment Regimen		
	Pbo N = 211	Miri N = 630	Uste N = 309	Pbo[a] N = 211	Miri N = 630	Uste N = 309
TE shifts, n/NAR (%)						
TE-high values	8/196 (4.1)	47/595 (7.9)	18/292 (6.2)	19/196 (9.7)	132/595 (22.2)	77/293 (26.3)
Mean changes from baseline (U/L)						
Maximum baseline to maximum postbaseline	-20.5	35.1	153.6	70.6	277.0	513.2
LSM difference	26.9	–	-104.5	–	–	-224.5
Baseline to last observation	-4.9	21.6	20.1	-2.8	29.0	30.5
LSM difference	27.1	–	7.5	–	–	4.4
Shift in CTCAE category, n/NAR (%)[b]						
Any shift to a higher Grade	9/206 (4.4)	47/627 (7.5)	20/303 (6.6)	22/206 (10.7)	136/627 (21.7)	79/304 (26.0)
Shift to Grade 1	6/196 (3.1)	40/595 (6.7)	15/292 (5.1)	12/196 (6.1)	93/595 (15.6)	54/293 (18.4)
Shift to Grade 2	2/204 (1.0)	3/621 (0.5)	3/302 (1.0)	7/204 (3.4)	22/621 (3.5)	16/303 (5.3)
Shift to Grade 3	1/206 (0.5)	3/623 (0.5)	1/303 (0.3)	1/206 (0.5)	7/623 (1.1)	3/304 (1.0)
Shift to Grade 4	0/206	1/627 (0.2)	1/303 (0.3)	2/206 (1.0)	14/627 (2.2)	6/304 (2.0)
Participants with at least 1 TEAE of Blood creatine phosphokinase increased, n (%) [EAIR]						
	PYE = 49	**PYE = 150.4**	**PYE = 73.7**	**PYE = 119.5**	**PYE = 593.6**	**PYE = 293.3**
Blood creatine phosphokinase increased	0	4 (0.6) [2.7]	3 (1.0) [4.1]	2 (0.9) [1.7]	15 (2.4) [2.6]	7 (2.3) [2.4]

	CD Induction			CD Treatment Regimen		
	Pbo N = 211	Miri N = 630	Uste N = 309	Pbo[a] N = 211	Miri N = 630	Uste N = 309
Participants with shifts to higher CTCAE grades and at least 1 TEAE of Rhabdomyolysis, Myalgia, Myopathy or Musculoskeletal pain, n (%) [EAIR]						
	Nx = 8 PYE = 1.9	**Nx = 47 PYE = 10.9**	**Nx = 18 PYE = 4.3**	**Nx = 19 PYE = 17.4**	**Nx = 132 PYE = 131.6**	**Nx = 77 PYE = 77.1**
Rhabdomyolysis	0	0	0	0	0	1 (1.3) [1.3]
Myalgia	0	0	0	0	1 (0.8) [0.8]	1 (1.3) [1.3]
Myopathy	0	0	0	0	0	0
Musculoskeletal pain	0	0	0	0	1 (0.8) [0.8]	0

In the CD Induction Placebo- and Active-Controlled and CD Treatment Regimen Placebo- and Active-Controlled Analysis Sets, an increase in shifts to high serum CK was reported in mirikizumab treatment participants compared with placebo group participants for maximum baseline to maximum postbaseline.

Most shifts to TE-high serum CK were to CTCAE Grade 1. The frequency of participants with shift to TE-high and all CTCAE grades was higher in mirikizumab treatment participants compared with placebo group participants. Additionally, most elevations in serum CK were transient and did not result in treatment discontinuation.

Blood creatine phosphokinase increased was the most frequently reported clinically relevant TEAE in mirikizumab treatment participants compared with placebo group participants. No cases of Myopathy or Rhabdomyolysis were reported by mirikizumab treatment participants with TE-serum CK shifts. Three mirikizumab treatment participants reported concurrent Myalgia (0.5%).

In mirikizumab treatment participants, a total of 21 mirikizumab treatment participants reported shifts to CTCAE Grade 3 or 4.

Table Mirikizumab Treatment Participants Reporting Shifts to CTCAE Grade 3 or 4

Sex (M or F)	CTCAE Grade at Baseline	Lab Value (Shifts to CTCAE Grade 3 or 4) [Study Day]	Transient? (Y or N)	Associated AEs or Any Known Recent Increase in Physical Activity
M	Grade	2387 (Grade 3) [273]	Y	None
F	Grade 0	992 (Grade 3) [206]	Y	None
M	Grade 0	1763 (Grade 3) [196]	Y	Blood creatine phosphokinase increased
M	Grade 0	1961 (Grade 3) [337]	Y	None
M	Grade 0	2146 (Grade 3) [60]	Y	Blood creatine phosphokinase increased; AST, ALT, and GGT increased
M	Grade 0	1769 (Grade 3) [87]	Y	None
M	Grade 0	2545 (Grade 3) [125]	Y	AST and ALT increased
M	Grade 0	4626 (Grade 4) [148]	Y	Blood creatine phosphokinase increased

Sex (M or F)	CTCAE Grade at Baseline	Lab Value (Shifts to CTCAE Grade 3 or 4) [Study Day]	Transient? (Y or N)	Associated AEs or Any Known Recent Increase in Physical Activity
F	Grade 0	2208 (Grade 4) [225]	Y	Blood creatine phosphokinase increased
M	Grade 0	11324 (Grade 4) [227]	Y	None. Reported starting physical activity.
M	Grade 0	3947 (Grade 4) [281]	Y	Blood creatine phosphokinase increased and Myalgia
M	Grade 0	12028 (Grade 4) [260]	Y	None. Reported overlapping of intense exercise and taking herbal medicines.
M	Grade 0	28947 (Grade 4) [141]	Y	AST increased. Reported starting intense physical activity.
M	Grade 0	3582 (Grade 4) [176]	Y	None
M	Grade 0	6035 (Grade 4) [120]	Y	None. Reported excessive fitness training.
M	Grade 0	4001 (Grade 4) [138]	Y	None
F	Grade 0	2579 (Grade 4) [339]	Y	Blood creatine phosphokinase increased; AST increased. Routinely performs sports and muscle training 3 times a week.
M	Grade 3	3928 (Grade 4) [377]	Y	None
M	Grade 0	6177 (Grade 4) [85]	Y	None. Reported starting physical activity.
M	Grade 3	3164 (Grade 4) [382]	N[a]	None. Attributed to strenuous exercise.
M	Grade 0	9843 (Grade 4) [288]	Y	Blood creatine phosphokinase increased

In the CD Induction Placebo- and Active-Controlled and CD Treatment Regimen Placebo- and Active-Controlled Analysis Sets, TE increases in serum CK were more frequently reported in mirikizumab treatment participants compared with placebo group participants. Most of the increases were mild per CTCAE grading.

Vital Signs

Blood pressure and pulse

Table Mean Changes and Shifts in Systolic and Diastolic Blood Pressure, and Associated TEAEs

CD induction Placebo-and Active-Controlled and CD Treatment Regimen Placebo-and Active-Controlled Analysis Sets

	CD Induction			CD Treatment Regimen		
	Pbo N = 211 PYE = 49	Miri N = 630 PYE = 150.4	Uste N = 309 PYE = 73.7	Pbo[a] N = 211 PYE = 119.5	Miri N = 630 PYE = 593.6	Uste N = 309 PYE = 293.3
Systolic BP						
Mean changes from baseline (mm Hg)						
Maximum baseline to maximum postbaseline	1.0	2.0	1.7	3.9	8.9	8.3
LSM difference	0.9	–	0.5	–	–	0.8
Baseline to last observation	-0.7	-0.2	-0.5	-1.3	0.8	0.4
LSM difference	0.5	–	0.6	–	–	0.7
TE shifts, n/NAR (%)						
TE-high	3/178 (1.7)	8/553 (1.4)	4/268 (1.5)	6/178 (3.4)	46/553 (8.3)	18/268 (6.7)
TE-low	1/203 (0.5)	3/608 (0.5)	0	3/203 (1.5)	9/608 (1.5)	3/297 (1.0)
Diastolic BP						
Mean changes from baseline (mm Hg)						
Maximum baseline to maximum postbaseline	1.2	1.5	1.0	3.5	6.2	6.3
LSM difference	0.3	–	0.5	–	–	-0.1
Baseline to last observation	0.2	-0.6	-0.7	-0.5	0.9	-0.0
LSM difference	-0.4	–	0.1	–	–	0.9
TE shifts, n/NAR (%)						
TE-high	8/186 (4.3)	26/554 (4.7)	9/268 (3.4)	13/186 (7.0)	70/554 (12.6)	35/268 (13.1)
TE-low	1/207 (0.5)	3/621 (0.5)	0	3/207 (1.4)	11/621 (1.8)	9/302 (3.0)
Participants with at least 1 TEAE of Hypertension or Blood Pressure increased, PTs, n (%) [EAIR]						
Hypertension	0	7 (1.1) [4.7]	2 (0.6) [2.7]	3 (1.4) [2.5]	19 (3.0) [3.3]	3 (1.0) [1.0]
Blood pressure increased	1 (0.5) [2.0]	0	1 (0.3) [1.4]	1 (0.5) [0.8]	2 (0.3) [0.3]	1 (0.3) [0.3]

A small mean increase in systolic and diastolic BP from baseline was observed in mirikizumab treatment participants compared with placebo group participants. Threse were transient, fluctuant and did not require management with antihypertensives.

In the CD Treatment Regimen Placebo- and Active-Controlled Analysis Set, the incidence of the TEAEs Hypertension and Blood pressure increased were higher for mirikizumab treatment participants compared with placebo group participants.

There was no impact on pulse with mirikizumab use.

Weight

In the CD Induction Placebo- and Active-Controlled Analysis Set, TE-increase in weight was reported in:

- 6 (2.9%) placebo group participants
- 30 (9.8%) ustekinumab treatment participants, and
- 73 (11.7%) mirikizumab treatment participants.

Treatment emergent decrease in weight was reported in

- 18 (8.7%) placebo group participants
- 4 (1.3%) ustekinumab treatment participants, and
- 11 (1.8%) mirikizumab treatment participants.

Mean increases from baseline in weight were small (up to 1.3 kg) across treatment groups

In CD Treatment Regimen Placebo- and Active-Controlled Analysis Set treatment emergent-increase in weight was reported in:

- 22 (10.6%) placebo group participants
- 93 (30.5%) ustekinumab treatment participants, and
- 274 (43.8%) mirikizumab treatment participants.

Treatment emergent decrease in weight was reported in:

- 33 (15.9%) placebo group participants
- 20 (6.6%) ustekinumab treatment participants, and
- 36 (5.8%) mirikizumab treatment participants.

Mean increases from baseline in weight were small (less than 3.2 kg) across treatment groups

In the CD Induction Placebo- and Active-Controlled and CD Treatment Regimen Placebo- and Active-Controlled Analysis Sets, the TEAE of Weight increased was reported at a higher frequency and incidence in mirikizumab treatment participants compared with placebo group participants. In mirikizumab treatment participants, most events (15 of 17) were reported as mild or moderate in severity. None were reported as serious or led to study treatment discontinuation. Of the 17 participants who reported Weight increased, 12 were considered related to study drug by the investigator.

2.6.8.5. Safety in special populations

Intrinsic factors

Table Intrinsic Factors – CD Induction and Placebo- and Active Controlled Analysis Sets

Baseline Characteristic	Subgroups
Age	• <65 years of age • ≥65 years of age
Sex	• Male • Female
Race	• American Indian or Alaska Native • Asian • Black or African American • Native Hawaiian or other Pacific Islanders • White • Multiracial
Region	Subgroup Set 1 • Asia • North America • Europe and ROW • Central America/South America
	Subgroup Set 2 • North America • Europe • Other
Participants enrolled in the US by ethnicity	• Hispanic/Latino, or • Non-Hispanic/Non-Latino.
BMI	• Underweight (<18.5 kg/m^2) • Normal (≥18.5 and <25 kg/m^2) • Overweight (≥25 and <30 kg/m^2) • Obese (≥30 kg/m^2)
Weight	• <80 kg • ≥80 kg

Extrinsic factors

Table Extrinsic Factors

CD Induction and Placebo- and Active Controlled Analysis Sets

Baseline Characteristic	Subgroups
SES-CD	Subgroup Set 1 • <12 • ≥12
Corticosteroid and immunomodulator use	• Corticosteroid use only • Immunomodulator use only • Both, or • Neither.
Prior biologic failure	• Yes • No

The frequencies of TEAEs were generally comparable across age, sex, race, region, and disease severity subgroups within the treatment groups.

Rates of TEAEs were similar in participants with prior biologic failure. Overall, the type and frequency of TEAEs and SAEs observed in mirikizumab treatment participants with SES-CD scores less than 7 (or less than 3 for isolated ileal disease) were similar to those observed in mirikizumab treatment participants within the CD Induction Placebo- and Active-Controlled Analysis Set

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

WOCBP are advised to use contraception during and up to 10 weeks after treatment. This along with limitations of data regarding use in pregnancy or breastfeeding are captured in section 4.6 of the SmPC.

There were limited numbers of particpants ages >65 years, with only 22 of 630 participants who received mirikizumab in that age range.

2.6.8.6. Immunological events

Hypersensitivity reactions

When assessing narrow search terms in the CD Treatment Regimen Immunogenicity Analysis Set, the frequency of treatment-emergent adverse event hypersensitivity reactions in the mirikizumab treatment participants was similar between TE ADA-positive and TE ADA negative participants (n=11, N=79 [13.9%] and n=61, N=543 [11.2%], respectively). With the small number of participants with these individual preferred terms, these differences are not considered clinically meaningful, and a causative link between hypersensitivity reactions and ADA status could not be made.

Infusion site reaction

The frequency of participants reporting at least 1 TE infusion site reaction was higher in TE ADA-positive participants compared with TE ADA-negative participants (n=2, N = 79 [2.5%] and n=3, N = 543 [0.6%], respectively). However, given the small number of participants with these events, this difference is not considered clinically meaningful, and a causative link between infusion site reactions and ADA status could not be made.

Table Treatment-Emergent Adverse Events-Infusion Site Reactions-Anti Drug Antibody Status-Safety Population- Mirikizumab Only

Category/ Preferred Term	Patient TE ADA Status	N	n (%)	TE ADA+ vs. TE ADA-	
				OR *a	p-value *b
Patients with >=1 TEAE in Infusion Site Reactions	TE ADA+	79	2 (2.5%)	4.68	0.123
	TE ADA INC	0	0		
	TE ADA-	543	3 (0.6%)		
	Not Evaluable	8	0		
Infusion site haematoma	TE ADA+	79	1 (1.3%)	6.95	0.238
	TE ADA-	543	1 (0.2%)		
Infusion site pruritus	TE ADA+	79	0	0	>0.999
	TE ADA-	543	1 (0.2%)		
Infusion site rash	TE ADA+	79	1 (1.3%)	NA	0.127
	TE ADA-	543	0		
Infusion site reaction	TE ADA+	79	0	0	>0.999
	TE ADA-	543	1 (0.2%)		

Injection site reaction

The frequency of participants reporting at least 1 TE injection site reaction was higher in TE ADA-positive participants compared with TE ADA-negative participants (n=12, N = 79 [15.2%] and n=51, N = 543 [9.4%], respectively). However, given the small number of participants with these events, this difference is not considered clinically meaningful, and a causative link between injection site reactions and TE ADA status could not be made.

Table Treatment-Emergent Adverse Events-Injection Site Reactions-Anti Drug Antibody Status-Safety Population- Mirikizumab Only

Category/ Preferred Term	Patient TB ADA Status	N	n (%)	TB ADA+ vs. TB ADA-	
				OR *a	p-value *b
Patients with >=1 TEAE in Injection Site Reactions	TB ADA+	79	12 (15.2%)	1.73	0.113
	TB ADA INC	0	0		
	TB ADA-	543	51 (9.4%)		
	Not Evaluable	8	3 (37.5%)		
Injection site reaction	TB ADA+	79	6 (7.6%)	2.54	0.059
	TB ADA-	543	17 (3.1%)		
Injection site pain	TB ADA+	79	2 (2.5%)	0.76	>0.999
	TB ADA-	543	18 (3.3%)		
Injection site erythema	TB ADA+	79	2 (2.5%)	1.26	0.675
	TB ADA-	543	11 (2.0%)		
Injection site swelling	TB ADA+	79	0	0	>0.999
	TB ADA-	543	4 (0.7%)		
Injection site hypersensitivity	TB ADA+	79	1 (1.3%)	3.47	0.335
	TB ADA-	543	2 (0.4%)		
Injection site induration	TB ADA+	79	2 (2.5%)	14.08	0.044
	TB ADA-	543	1 (0.2%)		
Injection site pruritus	TB ADA+	79	0	0	>0.999
	TB ADA-	543	3 (0.6%)		
Injection site rash	TB ADA+	79	1 (1.3%)	NA	0.127
Injection site rash	TB ADA-	543	0		
Injection site mass	TB ADA+	79	0	0	>0.999
	TB ADA-	543	1 (0.2%)		
Injection site oedema	TB ADA+	79	0	0	>0.999
	TB ADA-	543	1 (0.2%)		

2.6.8.7. Safety related to drug-drug interactions and other interactions

One drug–drug interaction study of mirikizumab was completed in participants with moderate-to-severe psoriasis (Study AMBP). This was submitted during the MAA for the UC indication.

Study AMBP 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 substrates

- CYP3A
- CYP2C9
- CYP2D6
- CYP2C19, or
- CYP1A2.

Additionally, in Study AMBP, the following events were not reported:

- Deaths
- SAEs, or
- AEs resulting in discontinuation of treatment.

The following concomitant medications were permitted during the study period:

Table Permitted Prior/Concomitant Medications with Dose Stabilisation

Drug Class	Stabilization
Oral 5-ASAs	○ Prescribed dose must have been stable for at least 2 weeks before screening endoscopy; doses should remain stable throughout the study unless medication is discontinued due to a toxicity related to the medication.
Oral corticosteroids (prednisone ≤30 mg/day or equivalent, or budesonide ≤9 mg/day)	○ Prescribed dose must have been stable for at least 2 weeks before screening endoscopy and should remain stable until Week 12.
Immunomodulators (for example, AZA, 6-MP, or MTX)	○ Prescribed at stable dose for at least 8 weeks before screening endoscopy; doses should remain stable throughout study unless medication is discontinued due to a toxicity related to the medication.
Antibiotics (for treatment of CD)	○ May continue if the prescribed dose has been stable 4 weeks prior to baseline or stopped treatment at least 3 weeks prior to screening endoscopy.

2.6.8.8. Discontinuation due to adverse events

Table Adverse Events Leading to Treatment Discontinuation

MedDRA Preferred Term by Decreasing Frequency

Safety Population

16T-MC-AMAM- Study Treatment Period

Preferred Term	placebo# (N=211) n (%)	miri (N=630) n (%)	uste (N=309) n (%)	Total (N=1150) n (%)	p-values*a miri vs. uste	Odds ratio*b miri/ uste
Subjects with >= 1 AE leading to treatment discontinuation	20 (9.5)	32 (5.1)	8 (2.6)	60 (5.2)	0.086	2.01
Crohn's disease	12 (5.7)	5 (0.8)	3 (1.0)	20 (1.7)	0.723	0.82
Infusion related hypersensitivity reaction	0	3 (0.5)	0	3 (0.3)	0.555	NA
Abdominal abscess	0	2 (0.3)	0	2 (0.2)	>0.999	NA
Small intestinal obstruction	1 (0.5)	2 (0.3)	0	3 (0.3)	>0.999	NA
Abdominal pain	0	1 (0.2)	0	1 (0.1)	>0.999	NA
Anaphylactic reaction	0	1 (0.2)	0	1 (0.1)	>0.999	NA
Arthralgia	0	1 (0.2)	0	1 (0.1)	>0.999	NA
Breast cancer	0	1 (0.2)	0	1 (0.1)	>0.999	NA
Colectomy	0	1 (0.2)	0	1 (0.1)	>0.999	NA
Depression	0	1 (0.2)	0	1 (0.1)	>0.999	NA
Dyspnoea	0	1 (0.2)	0	1 (0.1)	>0.999	NA
Fatigue	0	1 (0.2)	0	1 (0.1)	>0.999	NA
Haematuria	0	1 (0.2)	0	1 (0.1)	>0.999	NA
Headache	0	1 (0.2)	0	1 (0.1)	>0.999	NA
Hepatitis B DNA assay positive	0	1 (0.2)	0	1 (0.1)	>0.999	NA
Herpes zoster	0	1 (0.2)	0	1 (0.1)	>0.999	NA
Hypersensitivity	0	1 (0.2)	0	1 (0.1)	>0.999	NA
Ileectomy	0	1 (0.2)	0	1 (0.1)	>0.999	NA
Injection site pain	0	1 (0.2)	0	1 (0.1)	>0.999	NA
Large intestine perforation	0	1 (0.2)	0	1 (0.1)	>0.999	NA
Large intestine polyp	0	1 (0.2)	0	1 (0.1)	>0.999	NA
Non-alcoholic fatty liver	0	1 (0.2)	0	1 (0.1)	>0.999	NA
Urosepsis	0	1 (0.2)	0	1 (0.1)	>0.999	NA
Urticaria	0	1 (0.2)	0	1 (0.1)	>0.999	NA
Abscess intestinal	1 (0.5)	0	0	1 (0.1)	NA	NA
Alanine aminotransferase increased	0	0	1 (0.3)	1 (0.1)	0.329	0.00
Angina pectoris	0	0	1 (0.3)	1 (0.1)	0.329	0.00
Anorectal disorder	0	0	1 (0.3)	1 (0.1)	0.329	0.00
Bile duct stone	1 (0.5)	0	0	1 (0.1)	NA	NA
Enterocolonic fistula	1 (0.5)	0	0	1 (0.1)	NA	NA
Hepatitis cholestatic	1 (0.5)	0	0	1 (0.1)	NA	NA
Interstitial lung disease	0	0	1 (0.3)	1 (0.1)	0.329	0.00
Pulmonary embolism	1 (0.5)	0	0	1 (0.1)	NA	NA
Sepsis	0	0	1 (0.3)	1 (0.1)	0.329	0.00
Septic shock	1 (0.5)	0	0	1 (0.1)	NA	NA
Weight decreased	1 (0.5)	0	0	1 (0.1)	NA	NA

In the CD Treatment Regimen Placebo- and Active-Controlled Analysis Set, overall EAIRs for TEAEs, SAEs, and discontinuations due to AEs were higher in placebo group participants compared with mirikizumab treatment participants.

There was no clear pattern seen regarding treatment discontinuations.

The most common adverse event leading to discontinuation of treatment was disease related and was seen amongst those receiving placebo at higher rate than participants receiving mirikizumab.

Infusion related reactions were the AE which most commonly led to discontinuation in the mirikizumab group, along with abdominal abscess and small intestine obstruction which were disease related.

One participant (PT: Injection site pain) in the mirikizumab group discontinued study treatment due to injection site reactions (HLT) during the Treatment Regimen Period.

One participant each from the placebo (PT: Hepatitis cholestatic), mirikizumab (PT: Non-alcoholic fatty liver), and ustekinumab (PT: Alanine aminotransferase increased) groups discontinued treatment due to hepatic-related TEAEs during the Treatment Regimen Period.

2.6.8.9. Post marketing experience

The first marketing approval for mirikizumab occurred on 27 March 2023 when the Pharmaceuticals and Medical Devices Agency approved mirikizumab for the treatment of adults with moderately to severely active UC in Japan. Mirikizumab was recommend for approval by CHMP May 2023.

The first PSUR-PBRER, completed in accordance with the ICH E2C (R2) format, summarized safety and other pertinent data arising from worldwide sources received since the International Birth Date 27 March 2023.

Overall, no new significant safety information has been identified from post marketing sources.

The PSUR-PBRER supported the previously established favourable benefit–risk profile for mirikizumab in the currently approved UC indication.

2.6.9. Discussion on clinical safety

The primary source of safety data supporting this extension of indication comes from the Phase 3 pivotal study in adults with moderate to severely active CD:

- Phase 3 Study I6T-MC-AMAM (AMAM).

Supportive safety data is provided from two other studies in adults with moderate to severely active CD:

- Phase 2 Study I6T-MC-AMAG (AMAG), and
- Phase 3 LTE Study I6T-MC-AMAX (AMAX)

In addition to the safety data from the above 3 trials for moderately to severely active CD, additional supportive safety data is provided from adult participants with UC and psoriasis from:

- 4 studies in participants with moderately to severely active UC and 5 studies in Psoriasis.

Six analysis sets are used to assess safety (3 controlled, 3 uncontrolled). There are 3 CD analysis sets, 2 IBD analysis sets (CD and UC) and 1 all-disease- state analysis set (CD, UC and psoriasis).

There is a new dose form proposed 200mg in 2mL in PFS and a new citrate-free formula proposed.

The mirikizumab CD safety database includes 1178 patients with CD who received at least 1 dose of mirikizumab (CD Mirikizumab Exposures Integrated Analysis Set) with a total 2004.2 patient-years of exposure. This includes 715 patients who received the to-be-marketed dose, with a total 1122.3 patient years of exposure. 581 patients with CD had at least 6 months of exposure to the to-be marketed mirikizumab dose, and 557 patients with CD had at least 52 weeks of mirikizumab exposure to the to-be marketed mirikizumab dose. The exposure is adequate.

The All-Miri Integrated Set includes 4802 mirikizumab-treated patients with 11003.1 patient years of exposure across all 3 studied diseases (UC, CD, and psoriasis).

Common treatment emergent adverse events

The most frequently reported SOCs were Infections and infestations and Gastrointestinal disorders. TEAEs under the Gastrointestinal disorders SOC were more frequently reported by placebo group participants compared with mirikizumab treatment participants. On the other hand, mirikizumab treatment participants had a higher frequency of TEAEs under the Infections and infestations SOC compared with placebo group participants. The most frequently reported TEAEs were from the URTI including COVID-19 (cluster).

In the CD Treatment Regimen Placebo- and Active-Controlled Analysis Set, most SOCs presented higher EAIRs in placebo group participants compared with mirikizumab treatment participants, including the Infections and infestations SOC.

The most common TEAEs reported in the mirikizumab treatment participants were COVID-19, Nasopharyngitis, and URTI. These TEAEs are listed in the SmPC as an agreed adverse drug reaction (ADR).

Rates of headache were slightly higher in patients treated with mirikizumab during the CD induction and maintenance period as compared to patients receiving ustekinumab. Headache is labelled as a common ADR in the SmPC.

The frequency of UTIs was higher in participants treated with mirikizumab as compared to those on ustekinumab or on placebo. However, the difference between the groups was small. Therefore, the CHMP agreed that a small numerical imbalance for mirikizumab compared with ustekinumab in urinary tract infections events is likely random, and based on the placebo-controlled data, there is no reason to include urinary tract infection as an ADR in the SmPC.

An imbalance in the EAIR of vomiting TEAEs was observed between ustekinumab and mirikizumab treatment participants. However, as most vomiting events lasted no more than 2 days, recovered while on treatment, and did not recur in the subsequent dosing, the CHMP agreed these imbalances were probably random and updates to the SmPC are not required in this respect.

TEAEs by severity

Most TEAEs were mild or moderate in severity. The frequency of severe TEAEs was higher in placebo group participants compared with mirikizumab treatment participants, and mainly related to CD complications.

Deaths

In total, 5 deaths were reported in the mirikizumab CD clinical programme. Information on cause of death was unavailable for 1 participant. For the remaining 4, the deaths were not considered related to the study drug, 2 occurred in the placebo group, 1 in the Ustekinumab group and 2 in the long-term extension study.

<u>Adverse drug reactions (ADR):</u>

There were 2 events of severe, and 1 mild, hypersensitivity reactions which were considered infusion related. All events led to discontinuation. Infusion-related hypersensitivity reactions is a listed ADR (frequency uncommon) based on the UC population.

The injection site reaction was reported in 65 participants (EAIR = 15.3 per 100 PYE) in the mirikizumab group, 7 participants (EAIR = 10.4 per 100 PYE) in the placebo group, and 17 participants (EAIR = 7.1 per 100 PYE) in the ustekinumab group. The frequency has been updated for injection site reactions from common to very common.

8 mirikizumab treatment participants reported Rash and all remained on mirikizumab. Rash is a listed ADR (frequency common) based on the UC population. No change is recommended.

Most participants were enrolled to the pivotal phase 3 study after 2021. A profile of mild or moderate COVID-19 cases were mainly seen in this study. One mirikizumab treated patient developed what was considered a COVID-19 related pneumonia. Given the pattern of presentation of covid 19 in trial participants, with the majority experiencing mild or moderate URTI symptoms, and the evolution of covid 19 since first emerging, the CHMP agreed that covid 19 is included within the URTI cluster.

Adverse events of special interests

Hepatic toxicity

The potential for hepatic toxicity was highlighted during the UC application resulting in inclusion of text on hepatic enzyme elevations in section 4.4 of the SmPC.

Imbalances, in particular in respect to frequencies of alanine aminotransferase increased and aspartate aminotransferase increased, were also seen in the CD development program.

The highest imbalances were seen in the CD Treatment Regimen Placebo- and Active-Controlled Analysis Set, where ALT increased was reported in 1 [EAIR = 0.8 per 100 PYE] placebo group participant, 2 [EAIR = 0.7 per 100 PYE] ustekinumab treatment participants, and 17 [EAIR = 2.9 per 100 PYE] mirikizumab treatment participants.

However, the review of these cases indicated that most of them were mild, not considered related to the study drug and resolved while the treatment with mirikizumab was continued.

Further, the imbalance observed between mirikizumab and ustekinumab treatment participants in Alanine aminotransferase increased TEAEs was not consistent with the results found in the TE ALT laboratory assessment. This could be explained by a lack of uniform reporting of laboratory shifts as AEs among different investigators.

In the CD development programme, one non-serious case of DILI was reported during the induction period in the mirikizumab group. The case was not considered related to study treatment and attributed to a concomitant medication (rivaroxaban). Study drug was not discontinued, and the participant recovered after the removal of rivaroxaban. Of note, DILI was seen at higher rates in the UC indication.

2 mirikizumab treatment participant reported SAE of transaminases increased. In the first case, the investigator attributed the abnormal hepatic laboratory values to possible inhalant hepatotoxicity (work exposure). In the second case, liver abnormalities were linked to the hospitalization due to insufficient blood flow of basilar cerebral artery leading to seizure, and hepatopathy shortly after episodes of atrial fibrillation.

Discontinuations from study treatment due to a narrow scope hepatic AE were reported by 3 (0.3%) mirikizumab treatment participants in the CD development programme.

Alanine aminotransferase increased and aspartate aminotransferase increased are included in section 4.8 as an uncommon ADRs. A relevant warning is also included in SmPC section 4.4. Severe liver injury is listed in the RMP as an important potential risk.

Based on the data recorded in the CD development programme, is the CHMP agreed that no further update to the SmPC is necessary in respect to liver abnormalities. However, these cases are required to be monitored and discussed in each PSUR.

Malignancies

Malignancies were not reported in the CD Induction Placebo- and Active-Controlled Analysis Set.

In the CD Treatment Regimen Placebo- and Active-Controlled Analysis Set, the frequencies of reported malignancies and NMSC were low. Similarly, in the uncontrolled, integrated CD and IBD analysis sets, the frequencies of malignancies and non-melanoma skin cancer (NMSC) were low.

The EAIRs for malignancies in the CD analysis sets were consistent with the reported background IRs in the CD population and within the reported background IRs in the IBD population.

Malignancy is included in the RMP as an important identified risk. It is not included in the SmPC which is accepted based on the currently available data.

Depressive symptoms and suicidal ideation

A higher frequency of placebo group participants reported a worsening of depressive symptoms by QIDS assessment compared with mirikizumab treatment participants in the CD Induction Placebo- and Active-Controlled and CD Treatment Regimen Placebo- and Active-Controlled Analysis Sets, which is possibly related to a poor CD activity control in placebo group participants.

The EAIRs of depression and suicidal ideation or behaviour TEAEs in the CD analysis sets were within background rates (0.38 to 2.48 per 100 PY depression and 0.03 per 100 PY, suicidal ideation), for the CD population.

Depression or suicidal ideation is not captured in the SmPC which is acceptable to the CHMP based on the currently available data.

Hypersensitivity

Immediate and non-immediate hypersensitivity events were more frequently reported in mirikizumab treatment participants in comparison to those on placebo in the CD Induction Placebo- and Active-Controlled Analysis Set whereas in the CD Treatment Regimen Placebo- and Active-Controlled set these frequencies were similar.

In comparison to Ustekinumab, frequencies were higher, but this could be explained by the fact that mirikizumab treatment participants received almost twice as many doses of active treatment compared with ustekinumab treatment participants, increasing the chance of a hypersensitivity reaction being reported.

Infusion related hypersensitivity reaction, rash cluster (reported PTs Rash and Rash macular) and urticaria were the most common immediate hypersensitivity events. The most common non-immediate hypersensitivity event was rash.

There was no serious immediate or non-immediate hypersensitivity reactions reported.

A non-serious anaphylactic reaction recorded in a patient receiving the last dose of mirikizumab could be in fact a syncopal event.

Infusion-related hypersensitivity reactions and rash (cluster) are listed in SmPC section 4.8 and the CHMP agreed that no further updates to the SmPC are necessary.

Injection and infusion site reactions

A small number of Infusion site reactions were reported in the mirikizumab treatment participants 1 (0.2%) and the ustekinumab treatment participants (4 (1.3%). No Infusion site reactions (HLT) were serious or led to treatment discontinuation.

In relation to injection site reactions, these were reported most frequently in patients treated with mirikizumab 65 [EAIR = 15.3 per 100 PYE] followed by patients treated with ustekinumab 17 [EAIR = 7.1 per 100 PYE]. The lowest number of injection site reactions was reported in patients on placebo. A higher number of injection site reactions in patients treated with mirikizumab as compared to those receiving ustekinumab could be explained by a higher injection frequency in the mirikizumab group than in the ustekinuma group (i.e. mirikizumab during the maintenance period was given every 4 weeks whereas ustekinumab was given every 8 weeks). Further, in the pivotal study mirikizumab formulations containing Citrate have been used (citrate has been associated with injection site reactions).

Infusion site reactions and injection site reactions are listed in section 4.8 of the SmPC.

Of note, the mirikizumab Citrate-Free Formulation, which is the new mirikizumab formulation submitted in this variation application, was shown to reduce injection site reactions (see below).

New citrate-free formula

A new citrate-free formulation is proposed in this application. The applicant provided the clinical study reports from two bioequivalence studies comparing two formulations of Mirikizumab (Original Formulation versus Citrate-Free Formulation). In the AMBY study, prefilled syringes were used for the administration of mirikizumab whereas an autoinjector was used in the AMBT study. Both studies used the pain visual analogue scale to assess improvements in injection site pain. An improvement was seen in mild, moderate and severe pain across all injection sites. In addition, the frequency of other Injection site reactions, including Erythema, Induration, Pruritus, and Edema, was also reduced in participants receiving a new citrate free formula as compared to those who received the mirikizumab original formulation. No other notable impacts in the overall safety were observed.

Infections

The most frequently reported treatment emergent infection PTs in mirikizumab treatment participants were Nasopharyngitis, COVID-19, and URTI, which are consistent with the data from the integrated UC clinical development program. The risk of developing infections is captured in the RMP and in SmPC Sections 4.4 and 4.8. In Smpc section 4.3, use in those with clinically important active infections is contraindicated. The EAIR of opportunistic infections in the CD Mirikizumab Exposures Integrated Analysis Set was low [EAIR = 1.4 per 100 PYE]. The most frequently reported opportunistic infections was Herpes zoster. Most Herpes zoster events were mild to moderate in severity. Whilst this number is low, the EAIR for opportunistic infections was 0.3 per 100 PYE in the Ustekinumab group and 0 per 100 PYE in the placebo group. Herpes zoster is included in the mirikizumab SmPC as an uncommon ADR and is the CHMP agreed with the MAH that no further updates to the SmPC is required in this respect.

Regarding serious infections, it is noted that 2 participants receiving mirikizumab reported abdominal abscess. One participant reported a complication of anal abscess, which was also seen in a participant receiving ustekinumab. It is agreed that given the low number and frequency of abdominal abscess and anal abscess events, small differences observed between mirikizumab treatment participants and ustekinumab treatment participants were likely due to the underlying CD and concomitant immunosuppressant medicines and are not considered clinically meaningful. No updates to the SmPC are required in this respect.

MACE

In the CD Induction Placebo- and Active-Controlled and CD Treatment Regimen Placebo- and Active-Controlled Analysis Sets, the frequencies of CCV and MACE were low. No imbalance was noted in CCV

between mirikizumab treatment participants and placebo group participants in the controlled periods of the trials. No cases of MACE were reported in mirikizumab treatment participants in the placebo-controlled analysis sets.

In the CD Mirikizumab Exposures Integrated Analysis Set, the EAIR for MACE was 0.1 per 100 PYE, which is numerically lower than the EAIR of placebo group participants in the CD treatment Regimen Placebo- and Active-Controlled Analysis Set and within the background rates of MACE in the CD population.

A causal relationship of MACE with mirikizumab treatment was not determined based on the data available.

Nevertheless, taking into consideration small imbalances of MACEs in psoriasis studies, these cases will be monitored post-marketing. Further, in line with other IL-23 inhibitors major adverse cardiovascular events (MACE) was included as an important potential risk to the RMP.

It is noted that in the CD Mirikizumab Exposures Integrated Analysis Set, 4 of the 7 reported arrythmias events were in the mirikizumab group. However, based on a description of these cases, the CHMP agreed that they are unlikely to be related to mirikizumab and that an update to the SmPC is unnecessary in this regard.

Treatment discontinuations

There was no clear pattern regarding treatment discontinuations.

The most common adverse event leading to discontinuation of treatment was disease related and was seen amongst those receiving placebo at higher rate than participants receiving mirikizumab.

Infusion related reactions were the AE which most led to discontinuation in the mirikizumab group, along with abdominal abscess and small intestine obstruction which were considered disease related by the applicant.

The frequencies of TEAEs were generally comparable across age, sex, race, region, and disease severity subgroups within the treatment groups.

Rates of TEAEs were similar in participants with prior biologic failure. Overall, the type and frequency of TEAEs and SAEs observed in mirikizumab treatment participants with SES-CD scores less than 7 (or less than 3 for isolated ileal disease) were similar to those observed in mirikizumab treatment participants within the CD Induction Placebo- and Active-Controlled Analysis Set.

Special populations

Use in pregnancy

There were no adverse effects on the embryos, foetuses, and offspring demonstrated in non-clinical studies using pregnant monkeys. Pregnant or lactating women were excluded from the development program.

As of 04 October 2023, a total of 11 women exposed to mirikizumab became pregnant during a CD clinical study. Of the 11 pregnant participants receiving mirikizumab, 8 had a maternal exposure to mirikizumab during pregnancy and 3 had a maternal exposure before pregnancy.

In the entire development mirikizumab program 39 women exposed to mirikizumab became pregnant. Therefore, the available data are insufficient to conclude on the safety of mirikizumab use in pregnancy or lactation and the SmPC wording is reflects this. Further, it is recommended that women of childbearing potential should use an effective method of contraception during treatment and for at least 10 weeks after treatment. In addition, safety of mirikizumab in pregnant women and lactating women is included as missing information in the RMP which is supported.

Hepatically Impaired Participants

An analysis of AEs in hepatically impaired participants cannot be provided as these patients were excluded from studies.

Renally Impaired Participants

There were 83 mirikizumab treatment participants with abnormal creatinine clearance of less than 90 ml/min.

No clinically meaningful differences were observed between renally impaired and non-renally impaired mirikizumab treatment participants in overall.

The SmPC include the following information:

Renal or hepatic impairment

Omvoh has not been studied in these patient populations. These conditions are generally not expected to have any significant impact on the pharmacokinetics of monoclonal antibodies and no dose adjustments are considered necessary.

No amendments are required in this respect.

Elderly

As indicated by the MAH, no patients 75 to 84 years, and 85 years or older were recruited in studies.

Twenty-two of the 630 mirikizumab treatment participants were within the age range from 65 years to 74 years. Although numbers are too small to derive definitive conclusions, the safety profile observed in these participants is in general consistent with the safety profile observed for the participants aged less than 65 years. Frequencies observed in the prespecified analysis requested for the participants 65 years of age or older are within the background rates expected for this age group population.

Laboratory findings

The Leukopenia cluster, including both the Leukopenia and White blood cell count decreased PTs, was reported more frequently in mirikizumab treated participants. However, none of the events were reported as serious or led to study treatment discontinuation. No pattern in the time-to-onset or common underlying etiology was observed. Most mirikizumab treatment participants who reported a TEAE of Leukopenia or White blood cell decrease already presented low white blood cell count at baseline (or first lab sample collection) or had just 1 lab sample collection during the study. Further, review of the laboratory results indicated that In the CD Treatment Regimen Placebo- and Active-Controlled Analysis Set, the EAIR of shifts to TE low values for blood leukocytes in mirikizumab treatment participants [EAIR = 22.0 per 100 PYE] was comparable to placebo group participants [EAIR = 22.1 per 100 PYE]. Therefore, no update to the SmPC is required.

Lower lymphocytes, neutrophils and platelets were also seen in those treated with mirikizumab. However these events were transient or had confounding concomitant medications. Of note, based on the request made during the initial authorisation procedure, the MAH 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.

At week 52, improved serum albumin was seen in mirikizumab participants which is suggestive of treatment effect.

Most elevations in serum CK were transient and did not result in treatment discontinuation. An individual analysis of the CTCAE Grade 4 serum CK increases indicated that at least half of those increases were related to increases in physical activity.

Increases in serum CK are expected in patients who start to improve from serious, debilitating conditions. The applicant suggests that those shifts may be related to an increase in physical activity that was previously not possible due to the disease state. This could be considered plausible given no alternative pharmacologic or biologic mechanism.

The magnitude of change in mean blood pressure readings was small. They did not have any clinical sequelae. There was no clear clinical impact on pulse, although cases of arrythmia have been reported.

Increases from baseline in weight were observed in the mirikizumab treated patients as compared to those on placebo which was likely reflecting an improvement in CD disease severity status in these patients. A similar pattern was seen in the UC population.

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

ADA rates seen in the CD population were lower than in the already approved UC population.

2.6.10. Conclusions on the clinical safety

Overall, the safety profile seen in the Crohn's disease population is similar to that seen in the ulcerative colitis population. The application is considered approvable from a safety perspective.

2.7. Risk Management Plan

2.7.1. 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

2.7.2. Pharmacovigilance plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
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				

I6T-MC-B003: Observational Study of Pregnancy and Infant Outcomes among Women Exposed to Mirikizumab during Pregnancy in US-Based Administrative Claims Data
 	
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 UC or CD 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 UC or CD who are exposed to mirikizumab during pregnancy to women with UC or CD who are not exposed to mirikizumab and/or who are exposed to other medications indicated for the treatment of UC or CD during pregnancy.
		Missing information: Safety of mirikizumab in pregnant women	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
		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)

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
I6T-MC-B004: Observational Secondary Database Study to Assess the Long-Term Safety of Mirikizumab in Routine Clinical Practice Using US Administrative Claims Data Planned	• The objective of this study is to examine the incidence of severe acute liver injury, serious infections including opportunistic infections, malignancies excluding non-melanoma skin cancer and MACE among patients with a diagnosis of UC or CD who are exposed to mirikizumab compared to patients with a diagnosis of UC or CD who are not exposed to mirikizumab and/or who are exposed to other medications indicated for the treatment of UC or CD, respectively, in real world clinical practice in the US. The incidence of the study outcomes will also be examined among subgroups of interest including elderly patients 65 years of age and older.			Approximately 7 years after the start of data collection
			Final report	31 Dec 2037

2.7.3. Risk minimisation measures

Safety concern	Routine risk minimisation activities
Serious infections	Routine risk communication: SmPC Section 4.3 SmPC Section 4.4 PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk:

Safety concern	Routine risk minimisation activities
	SmPC Section 4.3 contains a contraindication for the use of mirikizumab in patients with:clinically important active infections (active TB). SmPC Section 4.4 advises: Mirikizumab may increase the risk of severe infection (see Section 4.8). Treatment with mirikizumab should not be initiated in patients with a clinically important active infection until the infection resolves or is adequately treated. The risks and benefits of treatment should be considered prior to initiating use of mirikizumab in patients with a chronic infection or a history of recurrent infection. Patients should be instructed to seek medical advice if signs or symptoms of clinically important acute or chronic infection occur. If a serious infection develops, discontinuation of mirikizumab should be considered until the infection resolves. Pre-treatment evaluation for tuberculosis Prior to initiating treatment, patients should be evaluated for TB infection. Patients receiving mirikizumab should be monitored for signs and symptoms of active TB during and after treatment. Anti-TB therapy should be considered prior to initiating treatment in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. PL Section 2 advises: Do not use mirikizumab if you have important active infections (active TB). Mirikizumab can potentially cause serious infections. Treatment with mirikizumab should not be started if you have an active infection until the infection is gone. After starting the treatment, tell your doctor right away if you have any symptoms of an infection such as fever chills muscle aches cough shortness of breath runny nose sore throat pain during urination Also tell your doctor if you have recently been near anyone who might have TB. Your doctor will examine you and may do a test for TB, before you have mirikizumab. If your doctor thinks you are at risk of an active TB, you may be given medicines to treat it.

Safety concern	Routine risk minimisation activities
	Pack size: Not applicable Legal status: Not applicable
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: Cases of drug-induced liver injury (including one case meeting Hy's Law criteria) occurred in patients receiving mirikizumab in clinical trials. Liver enzymes and bilirubin should be evaluated at baseline and monthly during induction (including extended induction period, if applicable). Thereafter, liver enzymes and bilirubin should be monitored (every 1-4 months) according to standard practice for patient management and as clinically indicated. If increases in ALT or AST are observed and drug-induced liver injury is suspected, mirikizumab must be discontinued until this diagnosis is excluded. SmPC Section 4.8 indicates: Overall mirikizumab treatment periods in the ulcerative colitis and Crohn's disease clinical development programme (including the placebo-controlled and open-label induction and maintenance periods), there have been elevations of ALT to ≥3× upper limit of normal (ULN) (2.3%), ≥5×ULN (0.7%) and ≥10×ULN (0.1%) and AST to ≥3×ULN (2.2%), ≥5×ULN (0.8%), and ≥10×ULN (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 will conduct blood tests before starting and during treatment with mirikizumab to check 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
Malignancies	Routine risk communication: None
MACE	Routine risk communication: None
Safety of mirikizumab in pregnant women and lactating women	Routine risk communication: SmPC Section 4.6 PL Section 2

Safety concern	Routine risk minimisation activities
	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. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Omvoh therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. 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.

Abbreviation: ALT = alanine aminotransferase; AST = aspartate aminotransferase; MACE = major adverse cardiac event; PL = package leaflet; SmPC = summary of product characteristics; TB = tuberculosis; ULN = upper limit of normal.

2.7.4. Conclusion

The CHMP considered that the risk management plan version 1.2 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH 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 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.

2.9. Product information

2.9.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

As the concept of the package insert covering the indication CD strictly follows the concept applied and tested for the package leaflet used to treat UC, the user test is not considered necessary.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Crohn's disease (CD) is a chronic, immune-mediated disease of multifactorial aetiology that is characterized by transmural inflammation of the gastrointestinal tract that can involve any segment from the oral cavity to the perianal area. CD is a serious disease with associated morbidity and mortality when inadequately treated and has no cure.

3.1.2. Available therapies and unmet medical need

As CD is a lifelong disease, the overall goal in the treatment and management of CD is to induce remission and achieve mucosal healing with response maintained in the long term. It is recognized that early intervention and continued monitoring may prevent complications (Torres et al. 2020). There is emerging evidence that achieving both clinical and endoscopic remission in patients with moderate-to-severe CD results in a decreased risk of disease progression (Ungaro et al. 2020).

Existing treatment options for CD include:

- conventional therapies such as corticosteroids (e.g. prednisone, budesonide) and immunomodulators (e.g. AZA, 6-MP, and MTX)
- biologic therapies (e.g. TNFα blockers, IL-12/23 and IL-23 inhibitors, integrin receptor antagonists)
- targeted oral therapies (e.g. JAK inhibitors), and
- surgery, for patients who fail available therapies or develop complications beyond the scope of medical management.

The goals of treatment for active Crohn's disease (CD) are to achieve clinical remission and improve quality of life. Many patients however do not respond or lose their response to conventional therapy as well as to anti-TNF therapy. It is estimated that up to one-third of patients will not respond to anti-TNF therapy and 30–40% with initial response, lose response over time or become intolerant to these medications. (M Scheurlen et al, 2023). Therefore, there is a medical need for development of products which could be used after treatment failure. Although, anti-integrin, anti-IL-12/23 monoclonal antibodies and Janus kinase (JAK) inhibitor are approved for patients which failed biological therapy, an additional treatment option for this difficult population of patients could be beneficial.

3.1.3. Main clinical studies

The clinical development of mirikizumab for the treatment of Crohn's disease includes:

- 1 pivotal Phase 3 study (Study I6T-MC-AMAM [AMAM])
- 1 supportive Phase 2 study (Study I6T-MC-AMAG [AMAG]), and
- 1 long-term extension Phase 3 study (Study I6T-MC-AMAX [AMAX]- ongoing

All studies enrolled patients with moderate to severe CD as defined by an unweighted daily average SF ≥4 (loose and watery stools defined as Bristol Stool Scale Category 6 or 7), and/or an unweighted daily average AP ≥2 at baseline. In relation to signs of mucosal inflammation, patients had to have a SES-CD score ≥7 in participants with ileal-colonic or ≥4 in participants with isolated ileal disease within 21 days before randomization.

All studies enrolled patients with a history of an inadequate response to, loss of response to, or intolerance to other CD treatments in order to support the requested second line indication.

3.2. Favourable effects

Primary endpoint results

The primary objective of the study was met. The data showed that 38% of patients on mirikizumab achieved clinical response by patient-reported outcomes (PRO) at week 12 and endoscopic response at week 52, compared to 9% patients on placebo (RD 28.7 (99.5% CI:20.6, 36.8;p value <.000001). In addition, 45.4% of patients on mirikizumab achieved clinical response by patient-reported outcomes (PRO) at week 12 and clinical remission by CDAI at week 52, compared to 19.6% patients on placebo (RD 25.8 (99.5% CI:15.9, 35.6;p value <.000001). Supplementary analyses and sensitivity analyses showed consistent findings with the primary analyses.

Secondary endpoints results

All main secondary endpoints (under multiplicity adjustment) investigated in the study in comparison to placebo were met including the most challenging such as Clinical Remission by CDAI at Week 12 (RD 12.4 (99.5% CI: (2.2, 22.7); p-value =.001431) and Endoscopic Remission by SES-CD at Week 12 (RD 6.8 (99.5% CI: (1.6, 12.1);p-value =.003414).

The percentage of patients with clinical remission by CDAI as compared to placebo increased at week 52 with RD 34.6 (99.5% CI 24.7, 44.4), p-value <.000001.

At week 12, there was an improvement in Fatigue as measured by FACIT-Fatigue score. LSM Difference versus placebo was 3.22 (99.5% CI 1.24, 5.19, p=.000005).

Mirikizumab was also superior as compared to placebo in composite endpoints captured at the end of the induction period and at the end of the maintenance period. For endoscopic response and clinical

remission by CDAI at week 12, or versus placebo was 3.22 (95%CI 1.63;6.36). For clinical response by PRO at Week 12, and endoscopic response and clinical remission by CDAI at week 52 RD was 23.6% (95% CI 18.7, 28.6). The observed difference is also considered as clinically relevant.

Early onset of efficacy was observed in clinical remission by CDAI, with differentiation between mirikizumab and placebo groups at Week 4. Mirikizumab treatment group also showed nominally significantly greater mean reductions compared to placebo in AP at Week 4, and in SF at Week 6.

Mirikizumab showed significant improvements (non-multiplicity controlled) across most efficacy measures in biologic-failed and not-biologic failed subgroups compared with placebo. For the co-primary endpoints by Prior Biologic Failure the risk difference versus placebo ranged from 20.8% to 27.5% for the not-biologic failed group and ranged from 30.5% to 31.0 % for the biologic failed group.

Mirikizumab demonstrated noninferiority to ustekinumab in Week 52 clinical remission by CDAI. Superiority over ustekinumab in Week 52 endoscopic response by SES-CD was not achieved.

Participants treated with mirikizumab reported greater mean change (improvement) from baseline in Urgency NRS score compared to placebo at Week 12, with a mean improvement of 2.4 points (SE = 0.1) for those in the mirikizumab group and 1.6 points (SE = 0.2) for the placebo group (p-value = .000011).

Subgroup analysis

The results reported across the subgroups analyzed were in general consistent with the results for the overall population. The point estimates for all subgroups were in favour of mirikizumab. 95% confidence interval contains the value of zero only for few smaller subgroups, i.e. patients with baseline Faecal Calprotectin <=250 ug/g, with Ileal disease location, obese and in patients with a short history of the disease.

The MAH also performed the subgroup analysis depending on baseline CDAI score, baseline SF score (average: <7, >=7), and baseline AP score (average <2, >=2). In general, the results for these subgroups were consistent with the results for the overall population.

In the subgroup of patients with baseline CDAI score >=220 and <450 (used to define moderate to severe disease) mirikizumab was superior in comparison to placebo for clinical remission and endoscopic remission at week 12 and 52.

3.3. Uncertainties and limitations about favourable effects

There are no uncertainties in relation to the efficacy affecting the benefit / risk of the product.

Although, the MAH submitted one pivotal study in support of this application, the majority of the criteria as per (CPMP/EWP/2330/99) guideline are fulfilled. Mirikizumab is a drug with known mechanism of action, and it is already approved in a related indication (i.e. ulcerative colitis). Other anti-IL-23 inhibitors are approved for the same indication.

3.4. Unfavourable effects

In the CD Induction and 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 56.4% in the placebo group and 51.7% in the miri group in the CD induction period and in 73% in the placebo and 78.6% in the miri group in the CD placebo-controlled maintenance period. Rates of TEAEs were similar between ustekinumab and mirikizumab treated participants.

SOCs for which TEAEs were reported by more than 10% of the participants in any treatment group were Infections and infestations, Gastrointestinal disorders and general disorders and administration site conditions, Musculoskeletal and connective tissue disorders, and Skin and subcutaneous tissue disorders. In mirikizumab treatment participants, the most frequently reported TEAEs within the Infections and infestations SOC were COVID-19, URTI, and Nasopharyngitis. In the treatment period, a lower incidence of serious infections was reported in the mirikizumab group than the placebo group. The incidence rate of participants with at least 1 serious infection across treatment groups was 6 participants (EAIR = 5.1 per 100 PYE) in placebo group, 9 participants (EAIR = 3.1 per 100 PYE) in ustekinumab group, and 14 participants (EAIR = 2.4 per 100 PYE) in mirikizumab group.

The EAIR of OIs in the CD Mirikizumab Exposures Integrated Analysis Set was low [EAIR = 1.4 per 100 PYE]. The most frequently reported OI was Herpes zoster, and most Herpes zoster events were mild to moderate in severity. Whilst this number is low, the EAIR for opportunistic infections was 0.3 per 100 PYE in the Ustekinumab group and 0 per 100 PYE in the placebo group. Herpes zoster is listed as an ADR in section 4.8 of the SmPC.

In the CD Induction Placebo- and Active-Controlled and CD Treatment Regimen Placebo- and Active-Controlled Analysis Sets, the frequencies of CCV and MACE were low. No imbalance was noted in CCV between mirikizumab treatment participants and placebo group participants in the controlled periods of the trials. No cases of MACE were reported in mirikizumab treatment participants in the placebo-controlled analysis sets.

In the CD Mirikizumab Exposures Integrated Analysis Set, the EAIR for MACE was 0.1 per 100 PYE, which is numerically lower than the EAIR of placebo group participants in the CD treatment Regimen Placebo- and Active-Controlled Analysis Set and within the background rates of MACE in the CD population. Across the CD and UC development programmes, the data do not suggest an association between mirikizumab treatment and an increased risk of CCV or MACE.

There are recognised potential liver disease sequelae in patients with Crohn’s disease, in the CD Treatment Regimen Placebo- and Active-Controlled Analysis Set, the TE hepatic disorder of ALT increased was seen in 1 [EAIR = 0.8 per 100 PYE] placebo group participant, 2 [EAIR = 0.7 per 100 PYE] ustekinumab treatment participants, and 17 [EAIR = 2.9 per 100 PYE] mirikizumab treatment participants. The incidence rate of ALT increase is significantly higher in the mirikizumab treated group.

Hepatoxicity is a known important risk associated with mirikizumab use and a related warning is included in section 4.4 of the SmPC. Alanine aminotransferase increased and Aspartate aminotransferase increases are listed as ADRs in section 4.8 of the SmPC.

Immediate and non-immediate hypersensitivity events were more frequently reported in mirikizumab treatment participants in comparison to those on placebo in the CD Induction Placebo- and Active-Controlled Analysis Set whereas in the CD Treatment Regimen Placebo- and Active-Controlled set these frequencies were similar.

In comparison to Ustekinumab, frequencies were higher, but this could be explained by the fact that mirikizumab treatment participants received almost twice as many doses of active treatment compared with ustekinumab treatment participants, increasing the chance of a hypersensitivity reaction being reported.

Infusion related hypersensitivity reaction, rash cluster (reported PTs Rash and Rash macular) and urticaria were the most common immediate hypersensitivity events. The most common non-immediate hypersensitivity event was rash. There was no serious immediate or non-immediate hypersensitivity reactions reported. A non-serious anaphylactic reaction recorded in a patient receiving the last dose of mirikizumab could be in fact a syncopal event.

Infusion-related hypersensitivity reactions and rash (cluster) are listed in SmPC section 4.8.

3.5. Uncertainties and limitations about unfavourable effects

There were no adverse effects on the embryos, foetuses, and offspring demonstrated in non-clinical studies using pregnant monkeys. Pregnant or lactating women were excluded from the development program.

In the entire development mirikizumab program 39 women exposed to mirikizumab became pregnant. Therefore, the available data are insufficient to conclude on the safety of mirikizumab use in pregnancy or lactation and the SmPC wording is reflects this. Further, it is recommended that women of childbearing potential should use an effective method of contraception during treatment and for at least 10 weeks after treatment. In addition, safety of mirikizumab in pregnant women and lactating women is included as missing information in the RMP which is supported.

3.6. Effects Table

Table. Effects Table for Omvoh for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with lost response to, or were intolerant to either conventional therapy or a biologic treatment. Database Lock Date 04 October 2023

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Clinical Response by PROb at Week 12 and Endoscopic Response by SES-CD at Week 52 (Co-Primary Endpoint)		Response, n (%)	220 (38.0)	18 (9.0)	Common Risk Difference versus Pbo (99.5% CI), 28.7 (20.6, 36.8),	AMAM study Co-primary endpoint
Clinical Response by PROb at Week 12 and Clinical Remission by CDAI at Week 52 (Co-Primary Endpoint)		Response, n (%)	263 (45.4)	39 (19.6)	Common Risk Difference versus Pbo (99.5% CI), 25.8 (15.9, 35.6)	AMAM study Co-primary endpoint
Endoscopic Remission by SES-CD at Week 12		Response, n (%)	63 (10.9)	8 (4.0)	Common Risk Difference versus Pbo (99.5% CI), 6.8 (1.6, 12.1),	AMAM study Major Secondary Endpoints
Clinical Response by PROb at Week 12 and Endoscopic Remission by SES-CD at Week 52		Response, n (%)	92 (15.9)	4 (2.0)	Common Risk Difference versus Pbo (99.5% CI), 13.8 (8.7, 18.9),	AMAM study Major Secondary Endpoints
Unfavourable Effects						

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Potential serious infection, through Week 12	Patients reporting at least 1 serious infection through Week 12	% Difference of percent, miri vs pbo (95% CI)	1.1	0.5	**Strengths:** Safety database included data for 4802 mirikizumab treated participants with 10872.9 patient-years of exposure across the 3 indications of UC, CD, and psoriasis. Programme enrolled a population representative of the proposed indication, including those who have failed other treatments. Mirikizumab was studied against both placebo and an active comparator in a treat through design to allow participants to achieve clinical benefit but also to evaluate safety. **Uncertainties:** Female patients who are pregnant or breastfeeding were excluded from mirikizumab trials, and the efficacy and safety of mirikizumab in this population are uncertain and not well defined. The long-term safety of mirikizumab for events with a low frequency, and/or long latency will continue to be evaluated in the long-term extension Study I6T-MC-AMAX for up to 3 years, and with post-marketing follow-up of reported events and planned pharmacovigilance.	
			0.0064 (-0.006, 0.0187)			
Potential serious infection, through Week 52	Patients reporting at least 1 serious infection through Week 52	% Difference of percent, miri vs pbo (95% CI)	2.2	2.8		Study I6T-MC-AMAM
			-0.0062 (-0.0314, 0.019)			
Potential severe liver injury, through Week 12	ALT or AST elevation ⩾5X through Week 12	% Difference of percent, miri vs pbo (95% CI)	0.2	0.0		
			0.0016 (-0.0015, 0.0047)			
Potential severe liver injury, through Week 52	ALT or AST elevation ⩾5X through Week 52	% Difference of percent, miri vs pbo (95% CI)	0.6	0.0		
			0.00638 (0.000148, 0.012611)			

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The pivotal study for this application enrolled patients moderately to severely active Crohn's disease with a history of failure or intolerance to other CD treatments. The target population is "patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic treatment".

In this population of patients, statistically significant and clinically relevant improvement was observed for outcome measures considered as highly relevant for CD population such as clinical response and remission (by PRO and CDAI) and endoscopic response and remission (by SES-CD $\leq$4).

In comparison to placebo, these improvements were shown for the primary endpoints and all main secondary endpoints. In respect to the primary endpoint, the data showed that 38% of patients on mirikizumab achieved clinical response by patient-reported outcomes (PRO) at week 12 and endoscopic response at week 52, compared to 9% patients in the placebo cohort (RD 28.7 (99.5% CI:20.6, 36.8; p value <.000001). In addition, 45.4% of patients on mirikizumab achieved clinical response by patient-reported outcomes (PRO) at week 12 and clinical remission by CDAI at week 52, compared to 19.6% patients on placebo (RD 25.8 (99.5% CI:15.9, 35.6; p value <.000001).

The safety profile seen in the Crohn's disease population is similar to that seen in the ulcerative colitis population.

3.7.2. Balance of benefits and risks

In the claimed indication of "patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic treatment", clinically relevant improvement was observed for outcome measures considered as highly relevant for CD population. This is weighed against a safety profile similar to the one for the authorised indication in the treatment of ulcerative colitis with main safety concerns being potential serious infection and severe liver injury which are both considered manageable with implemented routine risk minimisation measures as described in the RMP.

The benefit risk balance is positive.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable

3.7.4. 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 and safety and efficacy, the CHMP considers by

consensus that the benefit-risk balance of, Omvoh 200 mg/2ml

is favourable in the following indication:

Crohn’s disease

Omvoh is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic treatment.”

The CHMP therefore recommends the extension(s) of the marketing authorisation for Omvoh 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).

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.

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.

In addition, CHMP recommends the variation(s) to the terms of the marketing authorisation, concerning the following change(s):

Variations requested		**Type**	**Annexes affected**
B.II.a.3.b.5	B.II.a.3.b.5 - Changes in the composition (excipients) of the finished product - Other excipients - Change that is supported by a bioequivalence study	Type II	I, IIIA and IIIB
B.I.a.2.z	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	Type IB	None
B.II.b.4.a	B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to	Type IB	None

	the originally approved batch size		
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB
A.5.b	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	Type IA	None
X.02.III	Annex I_2.(c) Change or addition of a new strength/potency	Line Extension	I, IIIA, IIIB and A
B.I.a.2.c	B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol	Type II	None

Extension application to add a new strength of 200 mg grouped with an extension of indication (C.I.6) to include treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic treatment, for Omvoh, based mainly on final results from study I6T-MC-AMAM; this is a phase 3, multicenter, randomized, double-blind, placebo- and active-controlled, treat-through study to evaluate the efficacy and safety of mirikizumab in patients with moderately to severely active Crohn's disease. As a consequence, sections 1, 2, 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2, 5.3, 6.1, 6.5, 6.6 and 8 of the SmPC are updated. The Labelling and Package Leaflet are updated in accordance. Version 1.2 of the RMP is agreed. In addition, the MAH took the opportunity to introduce minor editorial changes and to update the list of local representatives in the Package Leaflet.

The following Quality variations are also included as part of this application, applicable to the 1 mL PFP and PFS presentation, unless otherwise specified:

Type IA - A.5.b: To change the name of the site responsible for secondary packaging of the finished product from "Silvano Chiapparoli Logistica S.p.A" in Via Delle Industrie Snc, Livraga, LO, 26814, Italy to "Chiapparoli Logistica S.p.A". The address remains unchanged.

Type II - B.II.a.3.b.5: To change the finished product composition (for Omvoh 100 mg strength presentations), by replacing the citrate buffer with a histidine-based buffer. This resulted in tightening the pH specification and widening the osmolality specification in 3.2.P.5.1, Specification as a direct consequence of this change.

Type IB - B.II.b.4.a: To increase the finished product batch size (for Omvoh 100 mg strength presentations).

Type II - B.I.a.2.c: Changes in the active substance buffer manufacturing process to support the finished product formulation change:
- Optimization of several unit operations to increase the active substance manufacturing efficiency.
- Active substance changes to maximize process productivity/manufacturing efficiency and introduce a more caustic-resistant chromatography resin.
- Change in polishing column resin.

- As a consequence of the change in finished product composition, the active substance buffer and final matrix in Unit Operations 10 and 11 were changed to align with the new drug product formulation.
- Minor changes to the active substance specifications as a result of the reformulated active substance. The pH specification was tightened.
- Introduction of an automated dispensing train, which is applicable to both original and reformulated mirikizumab active substance. This change also applies to the active substance used in the 300 mg vial presentation.

Type IB - B.I.a.2.z: To update the unit operation 10 hold time for original mirikizumab active substance This change also applies to the active substance used in the 300 mg vial presentation.