25 July 2024
EMA/CHMP/221068/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Omvoh

Mirikizumab

Procedure no: EMEA/H/C/005122/P46/004

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Current step[1]	Description	Planned date	Actual Date	Need for discussion [2]
☐	Start of procedure	01 April 2024	01 April 2024	☐
☐	CHMP Rapporteur Assessment Report	03 May 2024	03 May 2024	☐
☐	CHMP members comments	21 May 2024	21 May 2024	☐
☐	Updated CHMP Rapporteur Assessment Report	23 May 2024	23 May 2024	☐
☐	CHMP adoption of conclusions:	30 May 2024	30 May 2024	☐
☐	Submission	25 June 2024	25 June 2024	☐
☐	CHMP Rapporteur Assessment Report	10 July 2024	10 July 2024	☐
☐	CHMP members comments	15 July 2024	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	18 July 2024	n/a	☐
☒	CHMP adoption of conclusions:	25 July 2024	25 July 2024	☐

Table of contents

1. Introduction

On 16/02/2024, the MAH submitted a final clinical study report (CSR) for a completed paediatric study for mirikizumab, I6T-MC-AMBU, which is part of a PIP, in accordance with Article 46 of Regulation (EC) No 1901/2006, as amended.

A short critical expert overview statement was provided as part of this application.

2. Scientific discussion

2.1. Information on the development program

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

On the 30/3/2023, the CHMP granted a positive opinion for mirakizumab for the indication:

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

The EC decision was received on 26 May 2023 and mirikizumab (Omvoh) was authorised two pharmaceutical forms:

- 300mg sterile concentrate mirikizumab for IV use after dilution
- Omvoh 100mg injection mirikizumab SC

At time of submission, the Applicant had included the EMA Decision P/0088/2022 on the agreement of a paediatric investigation plan.

Two indications were initially targeted within the PIP; Ulcerative Colitis and Crohns disease. For the Ulcerative Colitis indication, one of the agreed studies, was Study 7: A Multicentre, open-label pharmacokinetic (PK) study of mirikizumab in children and adolescents from 2 years to less than 18 years of age with ulcerative colitis (AMBU).

As a post-authorisation measure, the MAH has now submitted a final study report and OUS addendum for this clinical study which is part of the PIP, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended:

I6T-MC-AMBU: A Multicenter, Open-Label PK Study of Mirikizumab in Pediatric Patients with Moderately to Severely Active Ulcerative Colitis (AMBU).

Of note, no regulatory consequences have been identified with this submission.

The pivotal study to potentially support a future extension of indication in a paediatric population, Study I6T-MC-AMBA is currently ongoing and will be part of a future submission.

2.2. Information on the pharmaceutical formulation used in the study

Concentrate for solution for infusion in vial and solution for injection in prefilled syringes.

The MAH confirmed the pharmaceutical formulations used in Study AMBU are the same as the OMVOH adult formulations currently authorised in the EU for treatment of UC in adults.

- Omvoh 300 mg concentrate for solution for infusion, each vial containing 300mg mirakizumab in 15ml solution
- Omvoh 100 mg solution for injection in pre-filled syringe, each PFS containing 100mg mirakizumab in 1 mL of solution

It is understood that Study 1 of the PIP to develop a PFS for subcutaneous use is currently deferred and that a specific paediatric formulation has thus not yet been developed.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report and OUS addendum for:

- Study I6T-MC-AMBU: A Multicenter, Open-Label PK Study of Mirikizumab in Pediatric Patients with Moderately to Severely Active Ulcerative Colitis

2.3.2. Clinical study

I6T-MC-AMBU: A Multicenter, Open-Label PK Study of Mirikizumab in Pediatric Patients with Moderately to Severely Active Ulcerative Colitis (SHINE-1/ Study AMBU)

Description

Study AMBU, also known as SHINE-1, was a Phase 2 open label multicenter study to evaluate the safety, pharmacokinetics, pharmacodynamics and clinical response to mirikizumab and to establish the induction and maintenance doses to evaluate in Phase 3 in children and adolescents with ulcerative colitis aged 2 to less than 18 years.

Study AMBU was also conducted to comply with a requirement from the European Union pediatric investigational plan (Study 7 in EMEA-002208-PIP01-17-M02 from 11 March 2022).

This study was conducted at 19 centers that screened participants in Canada, Israel, Japan, South Korea, and United States.

The study was initiated in May 2020 and completed in March 2023. The analyses in the final study report are based on a database lock of 25 April 2023.

Study AMBU included 12 weeks of open-label IV treatment with mirikizumab (induction period), followed by:

• 40-week open-label SC treatment with mirikizumab (maintenance period) to evaluate long-term safety and durability of clinical response and remission in participants who achieved clinical response at Week 12, or

• extended induction period (12 additional weeks of IV treatment for participants who did not achieve response at Week 12) to explore the effect of additional IV dosing on clinical response at Week 24.

Participants were also eligible for rescue treatment with mirikizumab for LOR once in the maintenance period between Weeks 16 and 40.

Approximately 60 participants with moderately to severely active UC were planned to be screened to enroll approximately 30 participants in the study.

Upon completion of the maintenance period (Week 52), participants who achieved clinical benefit were offered continued treatment in a separate 3-year long-term extension Study I6T-MC-AMAZ (AMAZ). Participants who did not meet enrollment criteria for Study AMAZ or chose not to continue into Study AMAZ entered the post-treatment follow-up period (12 weeks following SC administration or 16 weeks following IV administration).

The study population included pediatric participants with moderately to severely active UC, who had an inadequate response to, loss of response to, or were intolerant to nonbiologic therapy for UC (biologic-naive), and/or those who had been exposed to at least 1 biologic and/or JAK inhibitor therapy for UC (biologic/ JAK inhibitor-experienced).

At Weeks 0, 4 and 8 participants received a mirikizumab IV infusion induction dose.

Participants weighing:

- >40 kg received 300 mg, and
- ≤40 kg received 5 or 10 mg/kg.

Participants who met the clinical response criteria at Week 12 received SC maintenance doses via PFS (100 mg/mL) from Weeks 12 to 48:

- >40 kg received 200 mg Q4W as two 1-mL PFS injections
- >20 kg to ≤40 kg received 100 mg Q4W
    - o at the start of the study, as two 0.5 mL injections using two 1-mL PFSs, carefully expelling the entire contents of each PFS into a sterile, pre-sealed empty glass vial, attaching a 21G needle, and withdrawing 0.5 mL of solution from the vial and injecting using a 27G needle, or
    - o beginning with amendment (c), as one 1-mL PFS injection.
- ≤20 kg received 50 mg Q4W
    - o as one 1-mL PFS, carefully expelling the entire contents of the syringe into a sterile, pre-sealed empty glass vial, attaching a 21G needle, and withdrawing 0.5 mL of solution from the vial and injecting using a 27G needle.

Participants who did not achieve clinical response at Week 12 either received extended induction treatment or were discontinued.

In cases where there was no higher dose, participants could receive extended induction dosing at the current dose.

The 12-week IV dosing induction period was chosen in order to allow sufficient time for participants to achieve clinical remission and endoscopic healing. The 40-week maintenance period enabled the evaluation of continued maintenance of clinical benefit. The timing of the induction and maintenance endpoints was chosen based on characterization of the safety and efficacy of mirikizumab through 52 weeks of continuous treatment in Study I6T-MC-AMAC (AMAC) (Phase 2, placebo controlled, double-blind adult clinical trial of mirikizumab in moderately to severely active UC), as well as consistency with the timing of the induction and maintenance endpoints of the ongoing Phase 3 adult program Studies I6T-MC-AMAN (AMAN) and I6T-MC-AMBG (AMBG).

Methods

Study AMBU, also known as SHINE-1, was a multicenter, open-label study designed to

- evaluate the safety, pharmacokinetics (PK), pharmacodynamics, and clinical response of mirikizumab in paediatric participants (aged 2 to <18 years old),

• provide data for dose confirmation for Phase 3, and

• was conducted to comply with a requirement from the European Union pediatric investigational plan (Study 7 in EMEA-002208-PIP01-17-M02 from 11 March 2022).

Study participants

Inclusion/Exclusion Criteria

Investigators enrolled participants with moderately to severely active UC who met the following criteria.

Key inclusion criteria

• Male or female participants weighing >10 kg and ≥2 and <18 years of age at the time of informed consent

• Both the parent or legal representative and child (if capable) must agree to comply with the requirements of the protocol.

• Venous access sufficient to allow blood sampling and IV administration (if applicable), as per the protocol.

• Have an established diagnosis of UC of ≥3 months in duration before baseline

Have moderately to severely active UC as defined by a MMS of 4 to 9 with an ES ≥2 within 14 days before first dose of study treatment (baseline).

• Have evidence of UC extending proximal to the rectum involving the distal sigmoid colon.

• Participants must have an inadequate response to, loss of response to, or intolerance to at least 1 of the following medications:

    o Corticosteroids

    o Immunomodulators

    o Biologics/JAK inhibitors

Key exclusion criteria

• Have a current diagnosis of Crohn's disease, inflammatory bowel disease-unclassified (formerly known as indeterminate colitis), ulcerative proctitis (distal disease limited to the rectum), or primary sclerosing cholangitis.

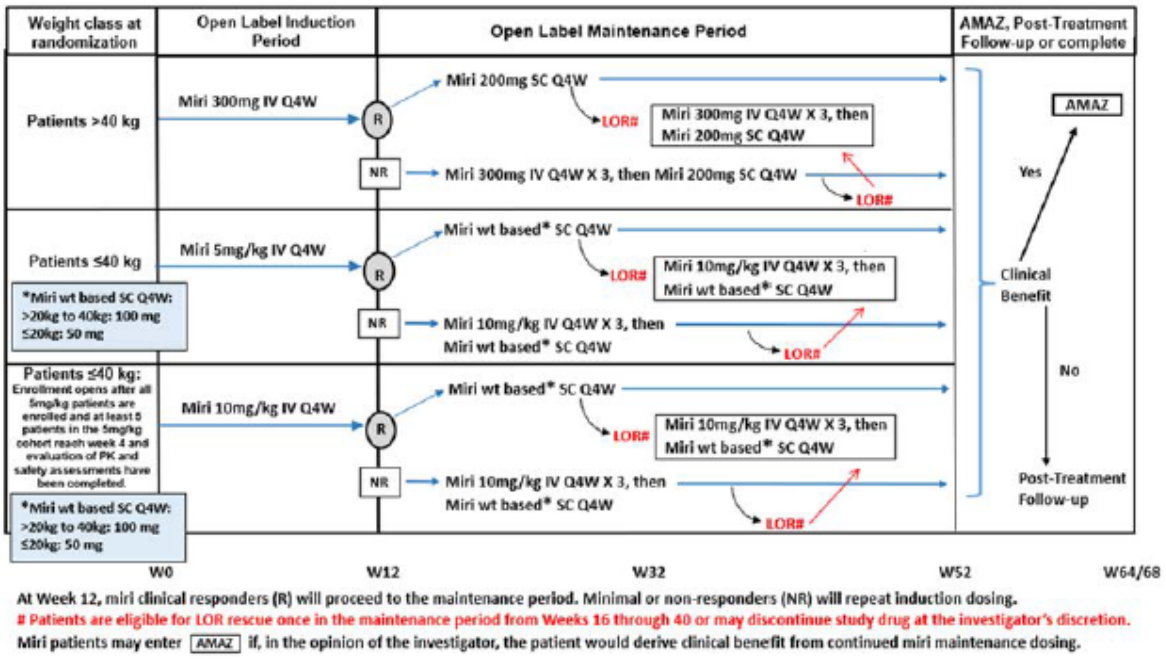
• Have a documented history of an immune deficiency syndrome or a monogenic cause of UC

• Previous bowel resection or intestinal or intra-abdominal surgery

• Have evidence of toxic megacolon, intra-abdominal abscess, or stricture/stenosis within the small bowel or colon.

• Have any history or current evidence of cancer of the gastrointestinal tract.

Study Design



Abbreviations: IV = intravenous; Miri = mirikizumab; LOR = loss of response; Q4W = every 4 weeks; SC = subcutaneous; wt = weight; W = week.

Figure AMBU.3.1. Study design for Study AMBU.

Treatments

Table AMBU.3.2. Study Intervention(s) Administered: Week 12 Clinical Responders

Weight Cohort	Dose Weeks 0, 4, and 8	Dose Weeks 12 through 48	Enrollment Initiation
>40 kg	300 mg miri IV	200 mg[a] miri Q4W SC	Initial cohort
≤40 kg	5 mg/kg miri IV	≤20 kg: 50 mg[b] miri Q4W SC >20 to ≤40 kg: 100 mg[c] miri SC Q4W	Enrolled at the same time as >40 kg 300 mg cohort
≤40 kg	10 mg/kg miri IV	≤20 kg: 50 mg[b] miri Q4W SC >20 to ≤40 kg: 100 mg[c] miri Q4W SC	After all participants in 5 mg/kg cohort were enrolled AND at least 5 participants received 2 doses, and the Week 4 evaluation of PK samples and safety assessment were completed

Abbreviations: G = gauge; IV = intravenous; miri = mirikizumab; PFS = prefilled syringe; PK = pharmacokinetics; Q4W = every 4 weeks; SC = subcutaneous.

[a] Two 1-mL PFSs (100 mg/mL each)

[b] One 1-mL PFS (100 mg/mL), carefully expelling the entire contents of the PFS into a sterile, pre-sealed empty glass vial, attaching a 21G needle, and withdrawing 0.5 mL of solution from the vial and injecting using a 27G needle.

[c] At the start of the study, as two 0.5 mL injections using two 1-mL PFSs, carefully expelling the entire contents of each PFS into a sterile, pre-sealed empty glass vial, attaching a 21G needle, and withdrawing 0.5 mL of solution from the vial and injecting using a 27G needle, then beginning with amendment (c), as one 1-mL PFS (100 mg/mL).

Table AMBU.3.3. Study Intervention(s) Administered: Week 12 Clinical Nonresponders

Weight Cohort	Dose Weeks 0, 4, and 8	Dose Weeks 12 through 48
>40 kg	300 mg miri IV	Repeated 300 mg[a] miri IV Q4W for 12 weeks or discontinued After repeat induction, then 200 mg[b] miri SC Q4W
≤40 kg	5 mg/kg miri IV	Escalated to 10 mg/kg[c] miri IV Q4W for 12 weeks or discontinued After escalation, then ≤20 kg: 50 mg[d] miri SC Q4W >20 to ≤40 kg: 100 mg[e] miri SC Q4W
≤40 kg	10 mg/kg miri IV	Repeated 10 mg/kg[c] miri IV Q4W for 12 weeks or discontinued After repeat induction, then ≤20 kg: 50 mg[d] miri SC Q4W >20 to ≤40 kg: 100 mg[e] miri SC Q4W

Abbreviations: G = gauge; IV = intravenous; miri = mirikizumab; PFS = prefilled syringe; Q4W = every 4 weeks; SC = subcutaneous.

a 15-mL vials (20 mg/mL miri)

b Two 1-mL PFSs (100 mg/mL each)

c Per Week 12 participant weight, utilizing 15-mL vials (20 mg/mL miri)

d One 1-mL PFS, carefully expelling the entire contents of each PFS into a sterile, pre-sealed empty glass vial, attaching a 21G needle, and withdrawing 0.5 mL of solution from the vial and injecting using a 27G needle.

e At the start of the study as two 0.5 mL injections using two 1-mL PFSs, carefully expelling the entire contents of each PFS into a sterile, pre-sealed empty glass vial, attaching a 21G needle, and withdrawing 0.5 mL of solution from the vial and injecting using a 27G needle, then beginning with amendment (c), as one 1-mL PFS (100 mg/mL) .

Assessor comments

For subjects weighing >20kg and </= 40kg eligible to receive 100mg SC, initially they received two 0.5 mL injections using two 1-mL PFS, withdrawing 0.5 mL from each vial, but that beginning with amendment c in October 2021, they instead received one injection of a 1 mL PFS. The amendment was prompted by study site feedback indicating that injecting 1 mL SC in participants weighing 20 kg to ≤40 kg was acceptable and, importantly, avoided 2 injections in a child. Therefore, the maximum volume limitation was removed. Three participants receiving 100 mg SC during the maintenance period were dosed with two 0.5 mL injections (prior to amendment c), and 9 participants were dosed with one 1 mL prefilled syringe after the amendment.

Study Objective(s) and Outcomes/endpoints

Objectives	Endpoints
Primary	
To evaluate the PK of mirikizumab treatment in pediatric patients	Clearance and volume of distribution of mirikizumab.
Secondary	
To evaluate the effect of treatment with mirikizumab on achieving **clinical remission** at Week 12 and/or Week 52	• The proportion of patients in MMS clinical remission at Week 12. • The proportion of patients in MMS clinical remission at Week 52. • The proportion of patients in MMS clinical remission at Week 52 among the MMS clinical remitters at Week 12 (durable clinical remission). • The proportion of patients in MMS clinical remission at Week 52 among the MMS clinical responders from Week 12. **MMS clinical remission** is defined as: SF subscore = 0, or SF = 1, and RB subscore = 0, and ES subscore = 0 or 1 (excluding friability) **MMS clinical response** is defined below.
To evaluate the effect of treatment with mirikizumab on achieving **clinical response** at Week 12 and/or Week 52	The proportion of patients in clinical response at Week 12. The proportion of patients in clinical response at Week 52. The proportion of patients in clinical response at Week 12 who achieve clinical response at Week 52. **Clinical response** is based on the MMS and is defined as: • A decrease in the MMS of ≥2 points and ≥30% decrease from baseline, and • A decrease of ≥1 point in the RB subscore from baseline or a RB score of 0 or 1.
To evaluate the effect of treatment with mirikizumab on achieving **corticosteroid-free remission** without surgery among patients in clinical remission at Week 52 and receiving corticosteroids at baseline[a]	The proportion of patients who entered the study on corticosteroids and who are in MMS clinical remission at Week 52 without the use of corticosteroids. **Corticosteroid-free remission** without surgery at Week 52 defined as: • Clinical remission at Week 52, and • No corticosteroid use or UC-related surgery for ≥12 weeks prior to Week 52.

To evaluate the effect of treatment with mirikizumab on **PUCAI clinical remission** at Week 12 and/or Week 52	The proportion of patients in PUCAI clinical remission at Week 12. The proportion of patients in PUCAI clinical remission at Week 52. The proportion of patients in PUCAI clinical remission at Week 12 who achieve clinical remission at Week 52. The proportion of patients in PUCAI clinical response at Week 12 who achieve clinical remission at Week 52. **PUCAI clinical remission** is defined as a PUCAI score of <10 points. **PUCAI clinical response** is defined below.
To evaluate the effect of treatment with mirikizumab on **PUCAI clinical response** at Week 12 and/or Week 52	The proportion of patients in PUCAI clinical response at Week 12. The proportion of patients in PUCAI clinical response at Week 52. The proportion of patients in PUCAI clinical response at Week 12 who achieve PUCAI clinical response at Week 52. **PUCAI clinical response** is defined as a reduction in baseline PUCAI score of ≥20 points.
To evaluate the effect of treatment with mirikizumab on achieving **endoscopic remission** at Week 12 and/or Week 52	The proportion of patients in endoscopic remission at Week 12. The proportion of patients in endoscopic remission at Week 52. The proportion of patients in endoscopic remission at Week 12 who maintain endoscopic remission at Week 52 (durable endoscopic remission). **Endoscopic remission** is defined as: ES = 0 or 1 (excluding friability)
To evaluate the effect of treatment with mirikizumab on achieving **ES = 0** at Week 12 or Week 52	The proportion of patients with ES = 0 at Week 12. The proportion of patients with ES = 0 at Week 52.
To evaluate the effect of treatment with mirikizumab on **symptomatic remission** over time	Proportion of patients in symptomatic remission at applicable study visits. **Symptomatic remission** is defined as: • SF = 0, or SF =1 with a ≥1-point decrease from baseline, and • RB = 0
To evaluate the effect of treatment with mirikizumab on height velocity at Weeks 12, 24, and 52	Observed height velocity by gender and age group will be calculated at baseline, Week 12, Week 24, and Week 52.
To evaluate the effect of treatment with mirikizumab on weight throughout the trial	Change from baseline in weight (kg) at all study visits by gender and age group.
To evaluate the effect of treatment with mirikizumab on pubertal development throughout the trial in appropriate patient groups	Hormone levels and/or other related clinical measures will be evaluated.
To evaluate the effect of treatment with mirikizumab on **improving patient-reported**	Change from baseline in 7-day average of Abdominal Pain (in past 24 hours) NRS score at Week 12 and Week 52. The proportion of patients with an Abdominal Pain NRS pain score ≥3 at baseline who achieve an improvement of ≥30% from baseline

outcome endpoints at Week 12 and Week 52	in 7-day average Abdominal Pain NRS score at Week 12 and Week 52. Change from baseline in Urgency NRS score at Week 12 and Week 52.
To evaluate **histologic-endoscopic mucosal remission** following mirikizumab treatment at Week 12 or Week 52	Proportion of patients with histologic-endoscopic mucosal remission at Week 12. Proportion of patients with histologic-endoscopic mucosal remission at Week 52. **Histologic-endoscopic mucosal remission** is defined as achieving both histologic remission and endoscopic remission. **Histologic remission** is defined as Geboes histological subscores of 0 for parameters: 2B (neutrophils in lamina propria), 3 (neutrophils in epithelium), 4 (crypt destruction), and 5 (erosion or ulceration).
To evaluate the development of anti-mirikizumab antibodies and their effect on efficacy, safety, and mirikizumab exposure	Proportion of patients who have TEADA. Relationship between TEADA and efficacy. Relationship between TEADA and safety. Relationship between TEADA and mirikizumab PK.
To evaluate tolerability and acceptability of two 1-mL subcutaneous injections	Tolerability and acceptability will be assessed by comparing reports of injection site pain to total number of injections per patient.
Exploratory	
To summarize the change in baseline in biomarkers	Change from baseline in fecal calprotectin. Change from baseline in C-reactive protein.
To evaluate the time to **symptomatic response**	Time to **symptomatic response** (defined as at least a 30% decrease from baseline in the composite clinical endpoint of the sum of SF and RB subscores).
To evaluate the time to **symptomatic remission**	Time to **symptomatic remission** (defined as SF = 0, or SF = 1 with a ≥1-point decrease from baseline, and RB = 0).
To summarize the change from baseline of individual MMS subscores and the composite symptomatic subscore over time in patients receiving mirikizumab	The numerical value and change from baseline in each of the following items: • SF (at each visit) • RB (at each visit) • ES (Weeks 12 and 52) • The composite clinical endpoint of the sum of the SF and RB subscores (at each visit)
To summarize the proportion of emergency room visits for UC, hospitalizations for UC, and to undergo surgery for UC over the course of the study	Proportion of patients who had UC related emergency room visits. Proportion of patients who had UC related hospitalizations. Proportion of patients who had UC related surgeries.
To summarize patient-reported outcome endpoints at Week 52	• PGIC score at Week 52. Change from baseline at Week 52 in the following: • PGRS score • Bristol Stool Scale score • Nocturnal stool • Fatigue NRS score

Assessor comments

The primary objective of the study was to evaluate the PK of mirikizumab treatment in pediatric participants. The PK of mirikizumab following induction and maintenance treatment was characterized using a population PK approach. Potential impact of participant factors on the PK of mirikizumab was evaluated. The relationship between key efficacy responses and mirikizumab exposure was also explored.

The study included a large number of efficacy-related secondary objectives and endpoints, focused on clinical remission and responses (MMS, PUCAI), symptomatic and endoscopic remission and response amongst others.

The study objectives and endpoints are considered standard and acceptable for a Phase 2 study with intent to assess mirikizumab and establish dosing for Phase 3 in children and adolescents with ulcerative colitis.

Sample size

According to the PIP at least 25 subjects were required to be evaluable for the primary analysis.

Approximately 60 participants with moderately to severely active UC were planned to be screened to enroll approximately 30 participants in the study.

Randomisation and blinding (masking)

This was an open-label study.

Changes to the conduct of the study

Key changes in the conduct of the study are summarized in Table AMBU.3.1.

Table AMBU.3.1. Protocol Amendment Summary

Milestone	Approval Date	Key Changes
I6T-MC-AMBU (Original protocol)	24 Apr 2019	N/A
Protocol Amendments		
I6T-MC-AMBU (a)	26 Aug 2019	The primary purpose of this amendment was to update the definition of mucosal healing and exploratory objective and endpoints added. All other changes are visible in the Amendment Summary protocol content.
I6T-MC-AMBU (b)	30 Apr 2021	The primary purpose of this amendment was to revise secondary objective wording for MMS clinical remission definition and updated secondary objective mucosal healing endpoint. All other changes are visible in the Amendment Summary protocol content.
I6T-MC-AMBU (c)	23 Oct 2021	The primary purpose of this amendment was to modify dosing instructions for the ≥20-40 kg participants during the maintenance period. Each participant received one injection of a 1 mL prefilled syringe instead of two 0.5 mL injections for SC maintenance dosing. All other changes are visible in the Overall Rationale for the Amendment protocol content.
Japan Protocol Addendum		
I6T-MC-AMBU (1.1)	11 Oct 2019	• Adjustment to the duration of corticosteroid therapy required to meet the definition of corticosteroid-refractory colitis in Inclusion Criterion [8a], to make this consistent with clinical practice in Japan. • Added additional exclusion criteria for hepatitis B based on age groups. • Modified hepatitis B virus deoxyribonucleic acid monitoring based on age groups.
		• Exclusion criterion [28] was clarified that serious, opportunistic, or chronic/recurring extraintestinal infections include pneumocystis pneumonia.

Abbreviations: COVID-19 = Coronavirus Disease 2019; MMS = modified Mayo score; N/A = not applicable; SC = subcutaneous.

Statistical Methods

No multiplicity adjustments were made due to the nature of the open-label study with no comparison arm or formal statistical hypothesis tests.

Additional analyses were conducted using the mITT population for secondary endpoints in the subgroup of previous biologic therapy failure status. The 2 categories are "biologic failed," and "biologic not failed." The "biologic not failed" category includes

• biologic naive participants, and

• participants who may have started and discontinued a biologic but did not fail or lose response to the biologic.

Results

Participant flow

This study was conducted at 19 centers that screened 49 participants in Canada, Israel, Japan, South Korea, and United States and enrolled 26 participants in Israel, Japan, South Korea and the United States.

Of 23 participants that had screen failure, 5 were later rescreened and met all eligibility criteria to be able to enrol in the study. At the time of their initial screening, 3 of these participants did not have moderately to severely active UC as defined by an MMS of 4 to 9 with ES ≥2. The other 2 of the 5 participants had Clostridium difficile or tested positive for Clostridium difficile or other intestinal pathogens within 30 days of the screening endoscopy in the initial screening period. The remaining 18 of the 23 screen failures did not meet the eligibility criteria or consent was withdrawn prior to enrolment. The reasons for their screen failure are provided:

Reason for Discontinuation	Details	Number of Participants
Inclusion/Exclusion #3	Both the parent or legal representative and child (if capable) must agree to comply with the requirements of the protocol.	1
Inclusion/Exclusion #6	Have moderately to severely active UC as defined by a MMS of 4 to 9 with an ES ≥2 within 14 days before first dose of study treatment (baseline).	8
Inclusion/Exclusion #11	Have clinically acceptable central laboratory results or local laboratory results reviewed and approved by the sponsor medical monitor or designee during screening, as assessed by the investigator see protocol for details of specific laboratory levels).	1
Inclusion/Exclusion #13	Have a current diagnosis of CD, IBD-Unclassified, ulcerative proctitis (distal disease limited to the rectum), or primary sclerosing cholangitis.	1
Inclusion/Exclusion #20	Have failed anti-IL12p40 antibodies (for example, ustekinumab) or have ever received anti-IL-23p19 antibodies for any indication, including investigational use.	1
Inclusion/Exclusion #21	Have evidence of active TB or have past history of active TB, regardless of treatment, or have past history of latent tuberculosis infection (LTBI) and have not completed an appropriate TB treatment regimen, or are diagnosed with LTBI at screening.	1
Inclusion/Exclusion #26	Have *Clostridium difficile* or other intestinal infection within 30 days of screening endoscopy, or test positive at screening for *C. difficile* or for other intestinal pathogens.	4
Withdrawal by Parent or Guardian	Withdrawal by Parent or Guardian.	1

Abbreviations: CD = Crohn's disease; ES = endoscopy subscore; IBD = inflammatory bowel disease; LTBI = latent tuberculosis infection; MMS = modified Mayo score; TB = tuberculosis; UC = ulcerative colitis.

Screening Period

The screening period occurred less than or equal to 28 days prior to the start of study drug. A total of 49 participants entered the study; among which 23 failed screening.

Induction Period

The remaining 26 participants were assigned to 1 of 3 treatment groups based on current body weight. All participants completed the Week 12 Induction Period.

Maintenance Period

All participants who achieved a MMS clinical response at Week 12 or Week 24 (non-responders at Week 12 who received extended IV induction dosing for 12 more weeks) were eligible for the Maintenance Period.

All 26 participants entered the maintenance period and were assigned to 1 of 3 mirikizumab SC treatment groups based on current body weight.

Nineteen of the 26 (73.1%) participants completed the Week 52 maintenance period and 7 (26.9%) participants discontinued the study treatment.

Protocol deviations

Table AMBU.8.3. Summary of Study and Treatment Disposition
Modified Intent-to-Treat Population
16T-MC-AMBU - All Periods

Protocol Deviation Category Protocol Deviation Subcategory Study Specific Deviation Term	<=40 kg 5mg/kg miri IV (N=10) n (%)	<=40 kg 10mg/kg miri IV (N=5) n (%)	>40 kg 300mg miri IV (N=11) n (%)	Total (N=26) n (%)
Subjects with >=1 Important Protocol Deviation	7 (70)	2 (40)	4 (36.4)	13 (50.0)
STUDY PROCEDURES	2 (20)	0	4 (36.4)	6 (23.1)
OTHER	2 (20)	0	4 (36.4)	6 (23.1)
Failure to verify lab and endoscopy results prior to V2	2 (20)	0	2 (18.2)	4 (15.4)
Missing more than 3 days of 7-day diary	0	0	1 (9.1)	1 (3.8)
Missing PUCAI: baseline, V6, or V16	0	0	1 (9.1)	1 (3.8)
EXCLUDED CONMEDS	0	0	1 (9.1)	1 (3.8)
Use of prohibited medications	0	0	1 (9.1)	1 (3.8)
INVESTIGATIONAL PRODUCT	4 (40)	1 (20)	0	5 (19.2)
DOSING ERROR	4 (40)	1 (20)	0	5 (19.2)
Incorrect IP administration	4 (40)	1 (20)	0	5 (19.2)
ELIGIBILITY	3 (30)	0	0	3 (11.5)
INCLUSION	2 (20)	0	0	2 (7.7)
Are not on stable doses of permitted drugs	1 (10)	0	0	1 (3.8)
UC diagnosis not 3 months or more prior to baseline	1 (10)	0	0	1 (3.8)
EXCLUSION	1 (10)	0	0	1 (3.8)
Acute EI infection in violation of protocol	1 (10)	0	0	1 (3.8)
INFORMED CONSENT	0	1 (20)	1 (9.1)	2 (7.7)
INFORMED CONSENT NOT OBTAINED	0	1 (20)	1 (9.1)	2 (7.7)
No reconsent for safety update	0	0	1 (9.1)	1 (3.8)
Procedure done prior to or without consent	0	1 (20)	0	1 (3.8)
SAFETY	0	1 (20)	1 (9.1)	2 (7.7)
SAEs	0	1 (20)	1 (9.1)	2 (7.7)
SAEs not reported in 24 hours	0	1 (20)	1 (9.1)	2 (7.7)

Abbreviations: N = number of subjects in the analysis population; n = number of subjects in the specified category; IV = intravenous; kg = kilogram; miri = mirikizumab; mg = milligram; SC = subcutaneous.
Percentages are based on the treatment column denominator, N.
Program Location: /lillyce/prd/ly3074828/i6t_mc_ambu/final/programs/tfl/t_c_pd_sum_mitt_all.R
Output Location: /lillyce/prd/ly3074828/i6t_mc_ambu/final/output/shared/tfl/t_c_pd_sum_mitt_all.docx
Data Set Location: /lillyce/prd/ly3074828/i6t_mc_ambu/final/data/analysis/shared

A total of 13 (50.0%) participants reported important protocol deviations during the study. The most frequent protocol deviations were related to:

• Study procedures (n=6 [23.1%])

• Investigational product (n=5 [19.2%])

• Eligibility (n=3 [11.5%])

• Informed consent (n=2 [7.7%])

• Safety (n=2 [7.7%])

Study procedures violations were unique site errors including missing minimum diary entries required for MMS evaluation, use of prohibited medications and failure to verify central lab results before randomization. Investigational product violations were inclusive of pharmacy preparation dosing errors using the participants current weight at that visit versus the study design noting induction period dose weight is per baseline/Week 0 weight and maintenance period dose weight is per participants Week Visit 6/Week 12 weight.

The sponsor concluded that these deviations did not impact the efficacy or safety results of the study in a clinically meaningful manner as the procedures were without specific trends and the dosing preparation errors were under 1.5× or matching the highest dose per treatment arm.

Recruitment

The study was conducted from 18 May 2020 until 15 March 2023. Participants were enrolled in 4 countries:

• United States (n=17, 65.4%)

• Korea, Republic of (n=4, 15.4%)

• Japan (n=4, 15.4%), and

• Israel (n=1, 3.8%).

Assessor comments

All subjects were enrolled at sites outside of the EU. 49 subjects were screened of which there were 23 screen failures. The majority of these were due to not meeting specific inclusion/exclusion criteria. A total of 26 subjects were enrolled in the study.

19 subjects (73.1%) completed the Week 52 maintenance period and 7 (26.9%) subjects discontinued the study treatment. 5 subjects discontinued due to lack of efficacy, 1 subject for an adverse event and for 1 subject it was reported as withdrawal by parent or guardian.

All the subjects (N = 26) were compliant to the study treatment, meaning they had at least 80% treatment compliant visits (i.e., received planned infusion/SC doses) before treatment discontinuation.

13 subjects (50%) had >/=1 important protocol deviation. It is noted 5 subjects (19.2%) had a dosing error. The sponsor concluded this did not impact study results in a clinically meaningful manner.

For some of the other deviations, e.g. not obtaining informed consent, not reporting SAEs within 24 hours, the MAH confirmed that site education and training were provided to address these issues and their occurrence in future studies

Baseline data

Table AMBU.4.2. Summary of Demographics and Other Baseline Characteristics (mITT population)

Parameter		Induction Treatment			
		5 mg/kg Miri IV (N = 10)	10 mg/kg Miri IV (N = 5)	300 mg Miri IV (N = 11)	Total (N = 26)
Demographics characteristics					
Age (years), mean (SD)		9.6 (4.2)	11.6 (1.1)	14.0 (1.3)	11.8 (3.4)
Age category (years), n (%)	*2 to <8*	3 (30.0)	0	0	3 (11.5)
	8 to <12	2 (20.0)	2 (40.0)	0	4 (15.4)
	≥12	5 (50.0)	3 (60.0)	11 (110.0)	19 (73.1)
Sex, n (%)	*Female*	6 (60.0)	3 (60.0)	6 (54.5)	15 (57.7)
	Male	4 (40.0)	2 (40.0)	5 (45.5)	11 (42.3)
Race, n (%)	*Asian*	4 (40.0)	2 (40.0)	1 (10.0)	7 (28.0)
	White	5 (50.0)	3 (60.0)	9 (90.0)	17 (68.0)
	Multiple	1 (10.0)	0	0	1 (4.0)
Weight (kg), mean (SD)		28.6 (9.0)	33.0 (2.4)	54.7 (13.3)	40.5 (16.0)
Weight category (kg), n (%)	*≤20*	2 (20.0)	0	0	2 (7.7)
	>20 and ≤40	8 (80.0)	5 (100.0)	0	13 (50.0)
	>40	0	0	11 (100.0)	11 (42.3)
BMI (kg/m²), mean (SD)		15.8 (2.3)	17.0 (0.6)	21.1 (5.0)	18.3 (4.3)
Baseline disease characteristics					
Baseline MMS, mean (SD)		6.4 (1.3)	6.6 (0.6)	6.2 (1.3)	6.3 (1.2)
Baseline MMS category, n (%)	*Moderate (4-6)*[a]	7 (70.0)	2 (40.0)	6 (54.5)	15 (57.7)
	Severe (7-9)	3 (30.0)	3 (60.0)	5 (45.5)	11 (42.3)
Duration of UC (years), mean (SD)		1.3 (1.1)	3.1 (3.5)	2.4 (2.1)	2.1 (2.2)
Baseline PUCAI, n (%)	*Mild (10-30)*	1 (10.0)	0	0	1 (3.8)
	Moderate (35-60)	4 (40.0)	4 (80.0)	8 (72.7)	16 (61.5)
	Severe (65-85)	5 (50.0)	1 (20.0)	3 (27.3)	9 (34.6)
Baseline Rectal Bleeding Mayo Subscore, n (%)	*0*	0	1 (20.0)	1 (9.1)	2 (7.7)
	1	3 (30.0)	0	3 (27.3)	6 (23.1)
	2	5 (50.0)	3 (60.0)	6 (54.5)	14 (53.8)
	3	2 (20.0)	1 (20.0)	1 (9.1)	4 (15.4)
Baseline Stool Frequency Mayo Subscore, n (%)	*0*	0	1 (20.0)	0	1 (3.8)
	1	3 (30.0)	0	2 (18.2)	5 (19.2)
	2	4 (40.0)	1 (20.0)	6 (54.5)	11 (42.3)
	3	3 (30.0)	3 (30.0)	3 (27.3)	9 (34.6)
Baseline C-reactive protein (µg/g), mean (SD)		2.6 (4.8)	6.1 (8.1)	3.6 (3.8)	3.7 (5.1)
Baseline Fecal Calprotectin (µg/g), mean (SD)		4952.0 (5128.4)	2829.0 (1466.3)	3962.9 (5698.4)	4097.6 (4782.4)

Abbreviations: BMI = body mass index; IV = intravenous; miri = mirikizumab; mITT = modified intent-to-treat; MMS = modified Mayo score; N = number of participants in the analysis population; n = number of participants in the specified category; PUCAI = Pediatric Ulcerative Colitis Activity Index; SD = standard deviation; UC = ulcerative colitis.

[a] 1 of the 26 participants had a baseline MMS of 4, all others had a baseline MMS of 5 or greater.

Source: Table AMBU.8.6

Assessor comments

Of the 26 subjects enrolled, there were 15 females (57.7%) and 11 males. The mean age of participants was 11.8 years. Most subjects were >/=12 years, 19 subjects (73.1%). Three subjects were aged between 2 and 8 years and four subjects between 8 and 12 years. Most subjects were white (68%), followed by Asian (28%). The mean weight was 40.5kg. Only 2 subjects weighed </= 20kg. Thirteen subjects weighed >20 and </=40kg and the remaining 11 subjects were > 40kg.

The mean duration of ulcerative colitis at enrolment was 2.1 years. All subjects had a baseline MMS of moderate (57.7%) or severe (42.3%), with mean MMS at baseline of 6.3. At baseline 1 subject had a mild PUCAI score, 16 subjects (61.5%) had a moderate PUCAI score and 9 subjects (34.6%) a severe PUCAI score.

Prior UC therapy

All patients received at least one prior treatment for UC. The most commonly used treatments were systemic corticosteroid therapy (69.2%) and biologics (65.4%).

Table AMBU.4.3. Summary of Prior Ulcerative Colitis Therapies (mITT population)

Prior UC therapy	≤40 kg 5 mg/kg Miri Q4W (N = 10) n (%)	≤40 kg 10 mg/kg Miri Q4W (N = 5) n (%)	>40 kg 300 mg Miri Q4W (N = 11) n (%)	Total (N = 26) n (%)
Participants with ≥1 prior ulcerative colitis therapies	10 (100)	5 (100)	11 (100)	26 (100)
Biologics	5 (50.0)	4 (80.0)	8 (72.7)	17 (65.4)
Anti-TNF	5 (50.0)	4 (80.0)	7 (63.6)	16 (61.5)
Vedolizumab	1 (10.0)	2 (40.0)	6 (54.5)	9 (34.6)
Tofacitinib	0	0	0	0
Systemic corticosteroid therapy	9 (90.0)	3 (60.0)	6 (54.5)	18 (69.2)
Prednisone	7 (70.0)	3 (60.0)	6 (54.5)	16 (61.5)
Budesonide MMX	0	0	0	0
Other oral corticosteroid	2 (20.0)	0	2 (18.2)	4 (15.4)
Immunomodulators	3 (30.0)	1 (20.0)	2 (18.2)	6 (23.1)
Azathioprine	3 (30.0)	0	1 (9.1)	4 (15.4)
6-mercaptopurine	0	1 (20.0)	1 (9.1)	2 (7.7)
Methotrexate	0	0	0	0

Abbreviations: miri = mirikizumab; mITT = modified intent-to-treat; MMX = multi matrix colonic delivery technology; N = number of participants in the analysis population; n = number of participants in the specified category; Q4W = every 4 weeks; TNF = tumor necrosis factor; UC = ulcerative colitis.
Source: Table AMBU.8.8

Table AMBU.4.4. Summary of Prior Ulcerative Colitis Therapies Failed (mITT Population)

	Induction Treatment			
Prior UC therapy, n (%)	5 mg/kg Miri IV (N = 10)	10 mg/kg Miri IV (N = 5)	300 mg Miri IV (N = 11)	Total (N = 26)
Biologic failed excluding JAK inhibitors	5 (50.0)	4 (80.0)	8 (72.7)	17 (65.4)
Anti-TNF failed	5 (50.0)	4 (80.0)	7 (63.6)	16 (61.5)
Anti-integrin failed	1 (10.0)	2 (40.0)	6 (54.5)	9 (34.6)
JAK inhibitor failed	0	0	0	0
Systemic corticosteroid failed	8 (80.0)	2 (40.0)	4 (36.4)	14 (53.8)
Systemic immunomodulator failed	3 (30.0)	1 (20.0)	2 (18.2)	6 (23.1)

Abbreviations: IV = intravenous; JAK = Janus kinase; miri = mirikizumab; mITT = modified intent-to-treat; N = number of participants in the analysis population; n = number of participants in the specified category; TNF = tumor necrosis factor; UC = ulcerative colitis.

Source: Table AMBU.8.6

Concomitant therapy

Stable doses of permitted UC concomitant medications (other than oral corticosteroids) were encouraged. Participants taking oral corticosteroids were to follow the corticosteroid taper instructions described in the protocol.

During the induction and maintenance periods of Study AMBU, 17 (65.4%) participants received at least 1 concomitant medication for UC.

Table AMBU 8.10. Concomitant Therapy within Class of Interest Preferred Name by Decreasing Frequency Modified Intent-to-Treat Population Study 16T-MC-AMBU – Induction and Maintenance Periods

Class of Interest Preferred Name	<=40kg 5mg/kg miri Q4W (N=10) n (%)	<=40kg 10mg/kg miri Q4W (N=5) n (%)	>40kg 300mg miri Q4W (N=11) n (%)	Total (N=26) n (%)
Patients with >= 1 medication within class of interest	6 (60.0)	1 (20.0)	10 (90.9)	17 (65.4)
Corticosteroid	6 (60.0)	0	7 (63.6)	13 (50.0)
PREDNISONE	5 (50.0)	0	6 (54.5)	11 (42.3)
DEXAMETHASONE	1 (10.0)	0	0	1 (3.8)
HYDROCORTISONE	0	0	1 (9.1)	1 (3.8)
METHYLPREDNISOLONE	0	0	1 (9.1)	1 (3.8)
Immunomodulators	2 (20.0)	1 (20.0)	5 (45.5)	8 (30.8)
AZATHIOPRINE	2 (20.0)	0	2 (18.2)	4 (15.4)
MERCAPTOPURINE	0	1 (20.0)	1 (9.1)	2 (7.7)
METHOTREXATE	0	0	2 (18.2)	2 (7.7)

Assessor comments

All subjects had received at least 1 prior UC therapy.

17 subjects (65.4%) had prior biologic exposure and failure and 9 subjects had no prior biologic exposure. Of the 17 subjects with prior biologic exposure, 9 subjects had 1 prior biologic treatment and 8 subjects had 2 prior biologics. All 17 subjects had a loss of response to a biologic and 13 of these subjects also had inadequate response to a biologic. No subjects were reported as having had prior intolerance to a biologic.

18 subjects (69.2%) had prior systemic corticosteroid therapy, with 14 (53.8%) having failed systemic corticosteroids. 6 subjects had prior immunomodulators, 4 had prior azathioprine and 2 had prior 6-mercaptopurine, and all 6 subjects had failed prior immunomodulators. No subjects had received prior JAK inhibitors.

Number analysed

Table AMBU.4.1. Analysis Populations in Phase 2 AMBU Study

Population	Description	N
mITT Population	All enrolled participants that received at least 1 dose of treatment, even if the participant does not receive the correct dose, or otherwise does not follow the protocol. Participants will be analyzed according to the treatment to which they were assigned. Unless otherwise noted, efficacy and health outcomes analyses will be conducted on this population.	26
Safety population[a]	All participants who received at least 1 dose of the study drug. Participants will be analyzed according to the weight/treatment dose group to which they were assigned.	26
PK evaluable	All participants who received at least 1 dose of investigational product and have sufficient blood sampling to allow for PK evaluation.	26

Abbreviation: PK = pharmacokinetics; mITT = modified intent-to- treat; N = number of participants in each analysis population.

[a] Safety population to include induction period and overall (combined induction and maintenance period). Any additional population or subpopulations that are of interest may also be considered for safety assessment.

Pharmacokinetic results

The primary objective of the study was to evaluate the PK of mirikizumab treatment in pediatric participants***.***

As provided in Protocol AMBU Section 5.5. Justification of Dose, dose regimens, and weight categories are based on analyses of

☐ PK

☐ exposure-response, and

☐ safety data from the Phase 2 adult Study I6T-MC-AMAC (AMAC) in participants with UC.

Based on adult data from Study AMAC, paediatric participants with a body weight greater than 40 kg were expected to have comparable PK to adults, and therefore, evaluation of an IV dose of 300 mg was planned for the Induction Period dose in participants with body weight greater than 40 kg.

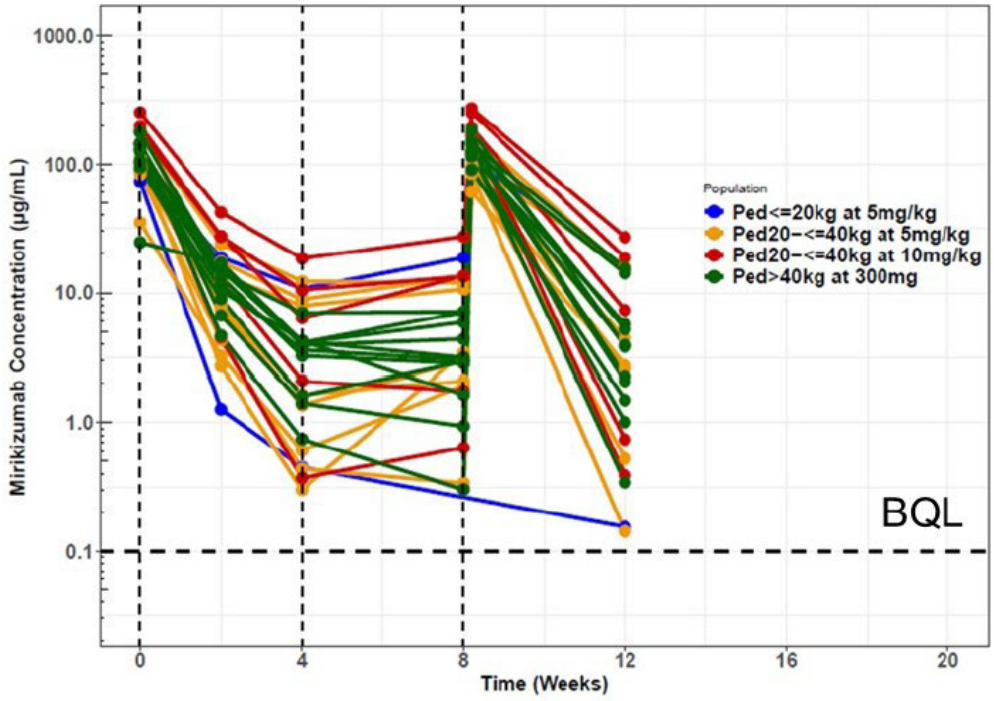
For paediatric participants less than or equal to 40 kg, participants were expected to provide comparable systemic exposures to Study AMAC and Phase 3 Studies I6T-MC-AMAN (AMAN) and I6T-MC-AMBG (AMBG), where

☐ 5 mg/kg IV was planned for the Induction Period dose, and

☐ 10 mg/kg IV was evaluated as dosing comparable to a 600 mg IV dose.

These doses were not expected to produce exposures higher than those evaluated in adults in Study AMAC. The dose regimens selected for the Maintenance Period were expected to provide comparable maintenance exposures to the 200 mg SC Q4W regimen in Study AMAC, which was subsequently evaluated in the Phase 3 adult Study AMBG.

Summary of Observed Mirikizumab Concentration During Induction



Abbreviations: BQL = lower limit of quantification of the LY3074828 (mirikizumab) bioanalytical assay; Ped = Pediatric population; PK = pharmacokinetic(s).
Notes: The samples collected at Week 4 in Study AMBU were pre-dose trough samples. No post-dose PK samples were collected for pediatric participants at Week 4.

Figure AMBU.5.1. Observed concentration-time profiles of mirikizumab in individual pediatric participants during Induction Period.

Table AMBU.5.73. Comparison of Geometric Mean (CV%) Observed Exposure Parameters at Different Weight-Based Doses

	AMBU (Induction)*			
	≤20 kg 5 mg/kg Miri IV (N=2)	20-40 kg Miri IV		>40 kg 300 mg Miri IV (N=11)
		5 mg/kg (N=8)	10 mg/kg (N=5)	
C_{max} (µg/mL)	107.9**	102.1 (33)	211.3 (23)	133 (18)
C_{trough} (µg/mL)	9.0 (93)***	5.2 (100)	9.9 (96)	4.0 (84)

Abbreviations: C_{max} = maximum serum concentration; C_{trough} = trough serum concentration; CV = coefficient of variation; IV = intravenous; MIRI = mirikizumab; N = number of participants; n = number of participants with concentration datapoints available from the 5mg/kg IV dose group in the <=20kg group; PK = pharmacokinetics.

Notes:

* Observed concentration data from Week 8 was implemented for C_{max} calculation and observed concentration data from Week 4, 8 and 12 were implemented for C_{trough} calculation.

** A single concentration datapoint for Week 8 was available from 1 participant.

*** Concentration datapoints for Week 4 (n=2), Week 8 (n=1) and Week 12 (n=2) were available from 2 participants.

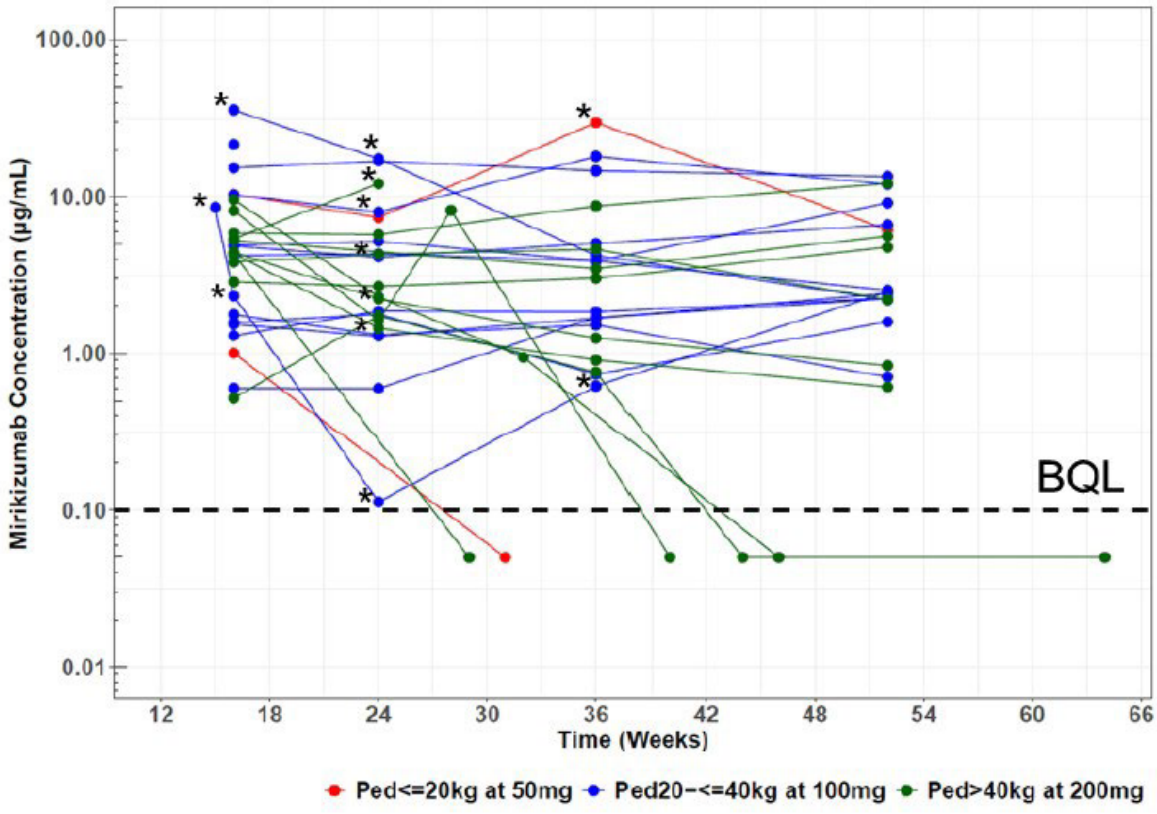
The values are summarized using estimated geometric mean (CV%).

In each of the dosing cohorts, the first sample was collected within 2 hours of completion of the first dose, and subsequent samples were collected at 4, 8, or 12 weeks prior to dose and represent Ctrough. At Week 8, a sample was also collected within 2 hours of completion of the dose and was considered a Cmax.

No participants had concentrations below BQL at the trough collection timepoints.

Summary of Observed Mirikizumab Concentration During Maintenance

Figure AMBU.5.2 shows observed individual concentration-time profiles during maintenance.



Abbreviations: BQL = lower limit of quantification of the LY3074828 (mirikizumab) bioanalytical assay; IV= intravenous; Ped = Pediatric population.
Note: Samples that were BQL were plotted at concentration of 0.05 µg/mL to allow visualization of the plot. Asterix represents the IV rescue dose injected for the individual. All the participants with BQL data had their last dose before the BQL data observation.

Figure AMBU.5.2. Observed concentration-time profiles of mirikizumab in individual pediatric participants during Maintenance Period.

In each of the dosing cohorts, samples collected at Weeks 16, 24, 36, and 52 were obtained prior to dose administration and represent trough concentrations.

As noted in Figure AMBU.5.2, several participants had concentrations BQL at the trough collection timepoints. All the participants who had below BQL data observation had their mirikizumab dosing discontinued at the previous dosing cycle.

Population PK Model Development

A previously developed 2-compartment model with first-order absorption based on data from the adult Studies AMAN and AMBG with allometric relationship incorporated for clearance and volume of distribution was used for PK modelling for AMBU. The use of fixed versus estimated exponent was considered. The population PK model with fixed allometric scaling of 0.8 for clearance and 1.0 for volume of distribution was selected as the Final Base Model as shown in PK Insert 1 in Appendix 2.

After the Final Base Model was selected, a covariate search using Stepwise Covariate Modelling approach was conducted for relevant covariates included in the Population PK Analysis Plan of Study AMBU. The key covariate selection criteria are described in the analysis plan.

Table 4.1. Covariates Assessed in the Population PK Model for Study AMBU

Age	Baseline body weight	Baseline bilirubin
Gender	Baseline body mass index	Baseline Cockcroft-Gault creatinine clearance
Race	Baseline body surface area	Baseline MMS
Ethnic origin	Baseline and time-varying serum albumin	Baseline SF/RB/EFS
Concomitant corticosteroid or immunomodulator use at baseline	Baseline and time-varying C-reactive protein	Immunogenicity (ADA +/-, TE-ADA+/-, ADA titer, neutralizing ADA +/-)
Prior biologic treatment status[a]	Baseline and time-varying fecal calprotectin	

Abbreviations: ADA = anti-drug antibody; AMBU = I6T-MC-AMBU; EFS = endoscopic finding by Mayo subscore; MMS = modified Mayo Score; PK = pharmacokinetic; RB = rectal bleeding by Mayo subscore; SF = stool frequency by Mayo subscore; TE-ADA = treatment emergent anti-drug antibody.

[a] Biologic failed or not-biologic-failed

The only covariate identified during the Stepwise Covariate Modelling step was time-varying serum albumin effect on clearance. The effect size of population PK model-estimated clearance versus albumin concentration was described in Figure AMBU.5.3. of the Study AMBU CSR (See below).

Summary of Population PK Analyses

A total of 232 serum mirikizumab concentration samples collected from 26 participants in induction and maintenance periods were included in the PK analysis. These concentration data were analyzed using population PK methods. A previously developed 2-compartment model with first-order absorption for the SC maintenance doses based on data from the adult Phase 3 studies (AMAN and AMBG) with allometric relationship incorporated for clearance and volume (central and peripheral volume) parameters was applied to the PK data in this study. Exponents of 0.8 for clearance and 1 for volume of distribution were used in the model to account for the weight effect.

A total of 6 samples (2.59%) were below the lower limit of quantification of the mirikizumab assay (0.1 µg/mL). Excluding these samples was compared to standard imputation or conditional estimation methods in the PK modeling, and no impact on the estimated PK parameters was noted, so the final analysis excluded the samples. The estimated PK parameters are shown in Table AMBU.5.74.

The model estimated systemic clearance and subcutaneous bioavailability of mirikizumab was 0.0209 L/hr and 49.8%, respectively. These results were consistent with the adult UC Phase 2 Study AMAC and UC Phase 3 Studies AMAN and AMBG. The estimated systemic volume of distribution of mirikizumab was 0.069 L/kg, which was also consistent with the adult UC Phase 2 and 3 studies.

Table AMBU.5.74. Summary of Population Pharmacometric Model-Estimated Parameters for Mirikizumab in AMBU Study

Parameter Description	Population Estimate (95% CI, %SEE)	Inter-Individual Variability[a] (95% CI, %SEE)
Rate of Absorption		
Parameter for K_a (hr^{-1})[b]	0.00706 (FIXED)	---
Clearance		
Parameter for CL (L/hr)	0.0209 (0.0178 – 0.0240, 7.51)	37.1% (23.9% – 47.1%, 28.8)
Weight effect on CL[c]	0.8 (FIXED)	---
Albumin effect on CL[c]	-0.0218 (-0.0315 – -0.0121, 22.8)	---
Parameter for Q (L/hr)[b]	0.0087 (FIXED)	---
Volume of Distribution		
Parameter for V_2 (L)	3.48 (3.22 – 3.75, 3.88)	---
Weight effect on V_2/V_3[d]	1.0 (FIXED)	---
Parameter for V_3	1.40 (1.19 – 1.61, 7.5)	---
Bioavailability		
Parameter for F_1[e]	49.8% (40.6% – 59.1%, 9.48)	77.6% (24.7% – 119.0%, 44.6)
Residual Error		
Proportional (%)	28.8% (25.7% – 32.0%, 5.59)	

Abbreviations: AMAN = I6T-MC-AMAN; AMBG = I6T-MC-AMBG; AMBU = I6T-MC-AMBU; CI = confidence interval; CL =clearance; CV = coefficient of variation; F_1 = bioavailability; K_a = absorption rate constant; PK = pharmacokinetic(s); Q = intercompartmental 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] Interindividual variability (IIV) was calculated using the following equation for log-normal distributions of the random effects for % = $100 \times \sqrt{(eOMEGAN - 1)}$, where OMEGAN is the variance of the parameter.

[b] The K_a and Q parameters were fixed to the parameter estimates of the Phase 3 AMAN/AMBG Study due to limited number of pediatric participants to estimate the parameter value.

[c] The table provides the population estimate. To obtain individual clearance estimates, use the following equation: CL,individual=CL*(BodyWeight/70.7)0.8* (1 + (-0.0218) * (Albumin−45)).

[d] The table provides the population estimate. To obtain individual central/peripheral volume of distribution estimates, use the following equations:

$$V_{2,individual}=V_2*(\text{Body Weight}/70.7)^{1.0}$$
$$V_{3,individual}=V_3*(\text{Body Weight}/70.7)^{1.0}$$

[e] Estimate is on the logit parameter for bioavailability. Using the individual post hoc estimates of participants in Study AMBU, the geometric mean (CV%) are 47.5% (27.9%) for the given population PK model.

The exposure parameters were estimated based on individual post hoc PK parameter values from the final PK model and were summarized in Table AMBU.5.75 at the various doses studied for the induction and maintenance treatment.

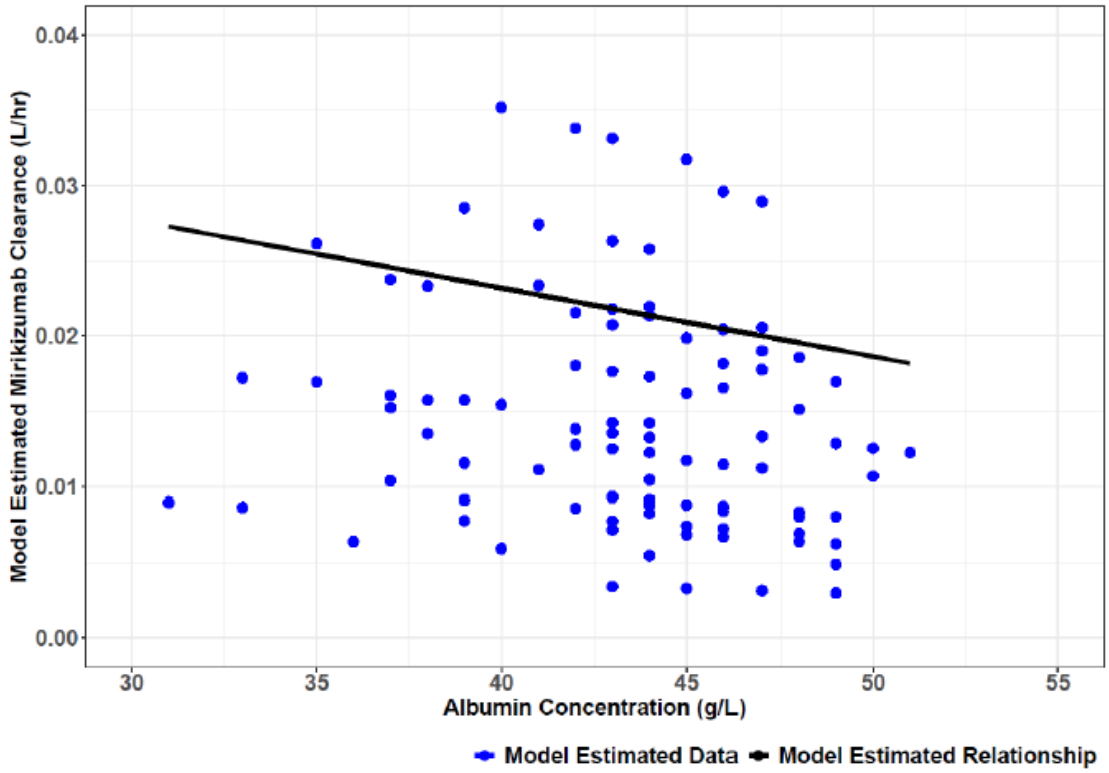
Table AMBU.5.75. Geometric Mean (CV%) Population Pharmacokinetic Model-Estimated Exposure Parameters for induction and maintenance treatment for Pediatric Participants with Ulcerative Colitis

	Induction						Maintenance					
	n	Dose (IV Q4W mg)	$AUC_{tau,ss}$ (µg·day/mL)	$C_{avg,ss}$ (µg/mL)	$C_{max,ss}$ (µg/mL)	$C_{trough,ss}$ (µg/mL)	n	Dose (SC Q4W mg)	$AUC_{tau,ss}$ (µg·day/mL)	$C_{avg,ss}$ (µg/mL)	$C_{max,ss}$ (µg/mL)	$C_{trough,ss}$ (µg/mL)
>40 kg	11	300 mg	657 (32)	23.8 (31)	117 (23)	3.14 (64)	11	200 mg	225 (45)	8.03 (45)	14.1 (42)	2.35 (59)
>20 to ≤40 kg	8	5 mg/kg	597 (45)	21.6 (44)	105 (4)	2.77 (172)	13	100 mg	164 (83)	5.84 (83)	10.2 (63)	1.69 (171)
	5	10 mg/kg	1160 (66)	42.2 (65)	212 (5)	4.9 (423)						
≤20 kg	2	5 mg/kg	272, 1066	10.0, 38.3	101, 113	0.2, 12.6	2	50 mg	120, 262	4.3, 9.3	9.9, 13.2	0.5, 4.7

Abbreviations: $C_{avg,ss}$ = time-averaged drug concentration during 1 dosing interval at steady state; ; $C_{trough,ss}$ = trough drug concentration during 1 dosing interval at steady state; $AUC_{tau,ss}$ = area under the concentration versus time curve during 1 dosing interval at steady state; $C_{max,ss}$ = maximum observed drug concentration during 1 dosing interval at steady state; CV% = geometric percent coefficient of variation; IV = intravenous; n = number of participants; PK = pharmacokinetics; Q4W = once every 4 weeks; SC = subcutaneous; UC = ulcerative colitis.

The population PK model was used to evaluate the impact of the following covariates: age, gender, BMI, body weight, ethnic origin, baseline albumin, time-varying albumin, baseline CRP, time-varying CRP, baseline fecal calprotectin, time-varying fecal calprotectin, baseline MMS, concomitant corticosteroid or immunomodulator use at baseline, prior biologic status, and immunogenicity (ADA+/-, TE-ADA+/-, ADA titer, neutralizing ADA+/-). Because weight was incorporated in the model structure, with the assumed allometric relationship, the only other factor that was found to have a statistically significant impact was time-varying albumin on clearance.

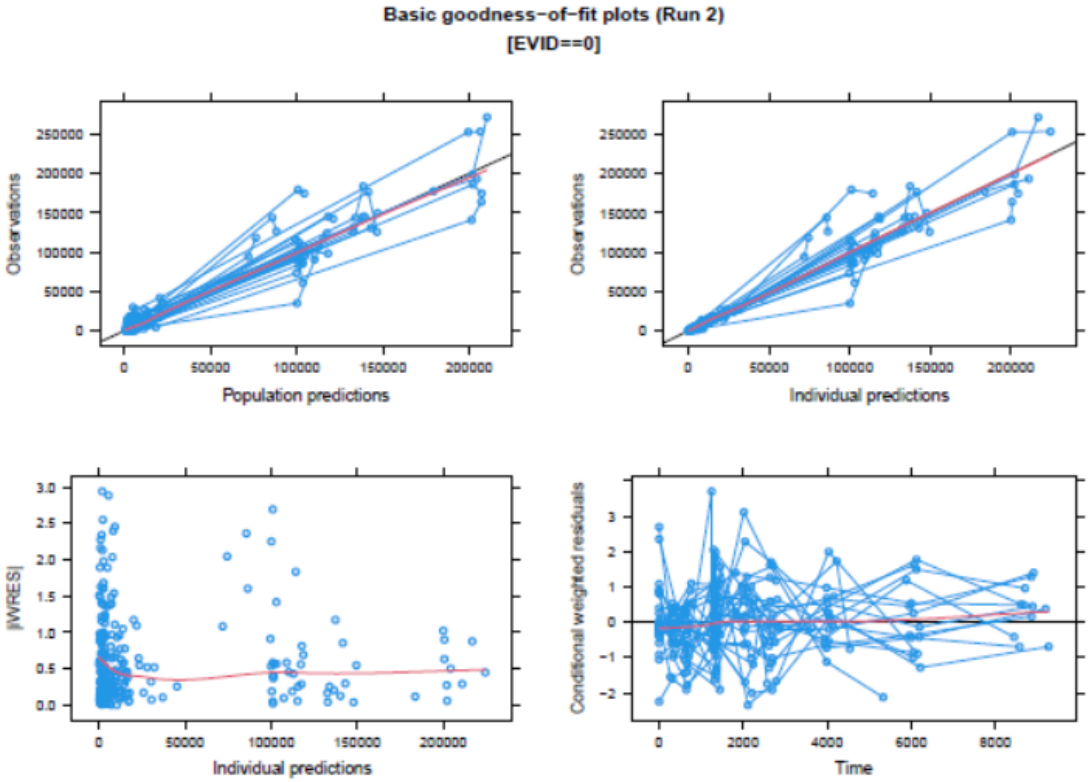
Participants with a lower albumin level tended to have higher apparent clearance (Figure AMBU.5.3). Although albumin had a statistically significant relationship with clearance, the magnitude of the model-estimated typical change in clearance for a participant with an albumin level of 30 g/L was only 33% higher than for a participant with an albumin level at the observed baseline median of 45 g/L, which is a small difference relative to the overall variation in clearance across participants. Including albumin in the population PK model reduced the estimated between-participant random variability in clearance only by 5% (41.9% to 37.1% inter-individual variability in CL). These results indicate that albumin didn't have a clinically relevant impact on the clearance of mirikizumab.



Note: To obtain individual clearance estimates, use the following equation:
$CL,individual = CL*(BodyWeight/70.7)^{0.8} * (1 + (-0.0218) * (Albumin–45))$

Figure AMBU.5.3. Population pharmacokinetic model-estimated clearance versus albumin concentration.

Goodness-of-Fit Plots for the Final Study AMBU Population Pharmacokinetic Model for Intravenous and Subcutaneous Administration Samples



Assessor comments

Full details on the PopPK model and its parameters were not provided in the originally submitted dossier and additional information was requested. The MAH subsequently submitted additional information including Control Stream and Summary of the NONMEM Output for the base and final models,, the covariate analysis and goodness-of-fit plots for the final model. The methods used for model development are acceptable. The provided goodness-of-fit plots suggest that the model describes the data reasonably well. Visual predictive checks of the final model were not provided. Therefore, the predictive performance of the model could not be assessed.

The MAH also confirmed that the same bioanalytical methods were used as in the adult studies AMAN and AMBG.

A summary of the provided pharmacokinetic results as presented in the CSR is outlined below.

Subject samples for mirikizumab concentration were collected at defined time points in both the induction and maintenance phases. In induction, the first sample was collected within 2 hours of completion of the first dose, and subsequent samples were collected at 4, 8, or 12 weeks prior to dose and represent Ctrough. At Week 8, a sample was also collected within 2 hours of completion of the dose and was considered a Cmax. In maintenance, samples were collected at Weeks 16, 24, 36, and 52 prior to dose administration and represent trough concentrations.

A PK model was developed using the 232 serum mirikizumab concentration samples collected from 26 participants in induction and maintenance periods. A previously developed 2-compartment model with first-order absorption for the SC maintenance doses based on data from the adult Phase 3 studies (AMAN and AMBG) with allometric relationship incorporated for clearance and volume (central and peripheral volume) parameters was applied to the paediatric PK data from this study

AMBU. Exponents of 0.8 for clearance and 1 for volume of distribution were used in the model to account for the weight effect.

Acknowledging the low number of subjects in each group, AUC, Cmax, Ctrough, Cavg values at steady state were almost twice as high in the 10mg/kg IV induction dose in 20-40kg group. The clinical relevance of this was not discussed in the report. The selected doses were expected to provide comparable exposure to adults. For paediatric participants less than or equal to 40 kg, participants were expected to provide comparable systemic exposures to Study AMAC and Phase 3 Studies I6T-MC-AMAN (AMAN) and I6T-MC-AMBG (AMBG), where

☐ 5 mg/kg IV was planned for the Induction Period dose, and

☐ 10 mg/kg IV was evaluated as dosing comparable to a 600 mg IV dose. The induction dose authorised in adults is 300mg by intravenous infusion at weeks 0, 4 and 8. Therefore the higher observed values at the 10mg/kg IV dose which would be comparable to the 600mg IV dose in adults is understood.

Pharmacodynamics

Observed Exposure-Response Relationships in Study AMBU for the Induction Period

Due to the narrow exposure range evaluated in this study, model-based analysis for the exposure/response (E/R) relationship was not conducted. The E/R relationship was explored using the observed efficacy endpoints and PK model estimated exposure parameters.

The relationship between the change from baseline value of MMS at Week 12 versus average mirikizumab concentration (Cavg) during induction is summarized in Figure AMBU.5.4. Mirikizumab induction treatment appeared to result in a decrease in MMS score from baseline and reached plateau at an average concentration around 40 ug/mL.

The E/R relationships between the binary clinical efficacy endpoints are shown in Figure AMBU.5.5 and Figure AMBU.5.6. These figures show the Week 12 clinical response, clinical remission and endoscopic response achieved relative to Cavg during the induction period. The Cavg values for individual participants were divided into Cavg quartiles and the efficacy rates were summarized for each quartile. No clear pattern was identified in these figures. The observations for the binary efficacy endpoints should be interpreted with caution due to the relatively small sample size.

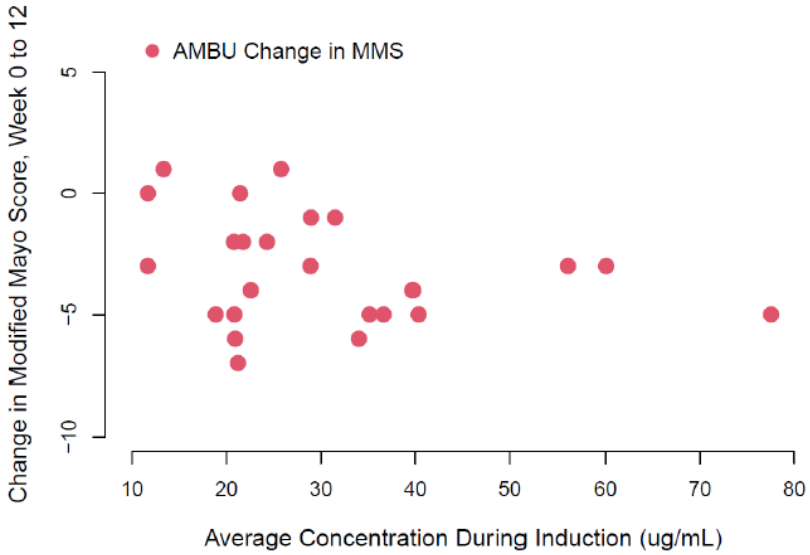
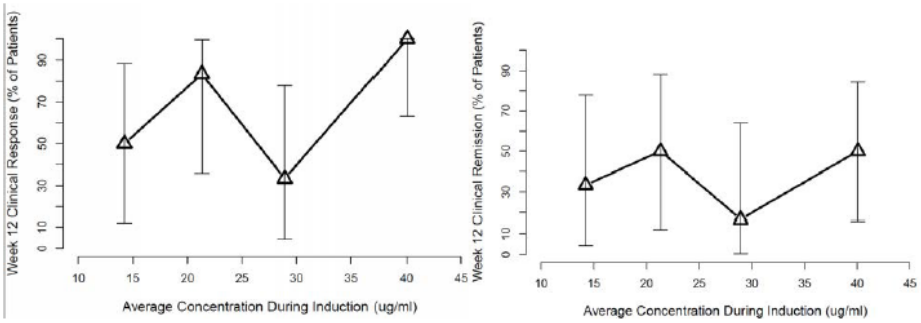
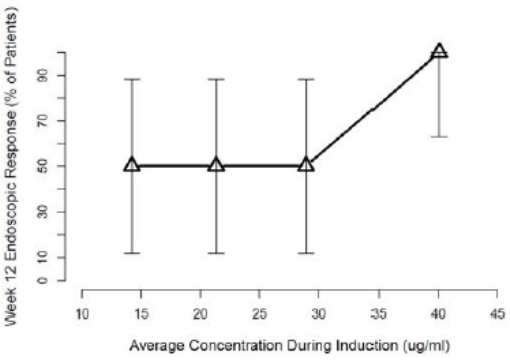


Figure AMBU.5.4. **Relationship between mirikizumab average concentration during induction and Week 12 change in modified mayo score in Study AMBU.**



Abbreviations: C_{avg} = average mirikizumab concentration during 1 dosing interval; N = number of participants.
Note: The data points represent the percentage of participants that achieved clinical response (left) and clinical remission (right) who received either 300-mg mirikizumab (>40kg), 5mg/kg mirikizumab (<20kg and 20 to ≤40kg) and 10 mg/kg mirikizumab (20 to ≤40kg) subdivided into C_{avg} quartiles (N=6,6,6,8 for Q1–Q4, respectively). The points are plotted along the x-axis at the median C_{avg} for each quartile. Error bars represent 95% confidence intervals.

Figure AMBU.5.5. **Relationship between mirikizumab average concentration during induction and Week 12 clinical response and clinical remission in randomized cohorts in post-hoc grouping by C_{avg} quartile.**



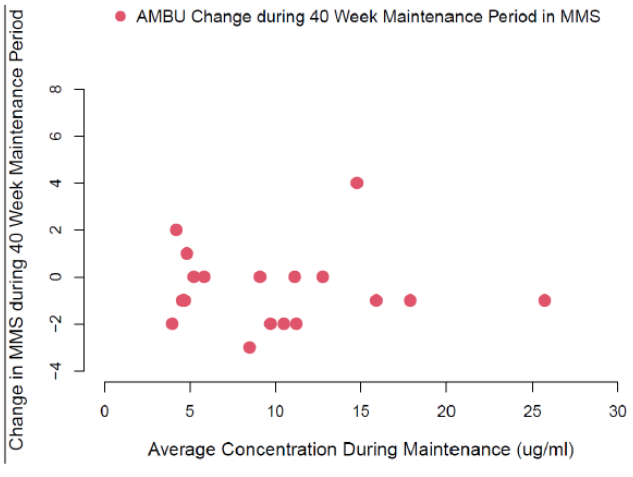
Abbreviations: C_{avg} = average mirikizumab concentration during 1 dosing interval; N = number of participants.
Note: The data points represent the percentage of participants that achieved endoscopic response who received either 300-mg mirikizumab (>40kg), 5mg/kg mirikizumab (<20kg and 20 to ≤40kg) and 10 mg/kg mirikizumab (20 to ≤40kg) subdivided into C_{avg} quartiles (N=6,6,6,8 for Q1–Q4, respectively). The points are plotted along the x-axis at the median C_{avg} for each quartile. Error bars represent 95% confidence intervals.

Figure AMBU.5.6. Relationship between mirikizumab average concentration during induction and Week 12 endoscopic response in post-hoc grouping by C_{avg} quartile.

Observed Exposure-Response Relationships in Study AMBU for the Maintenance Period

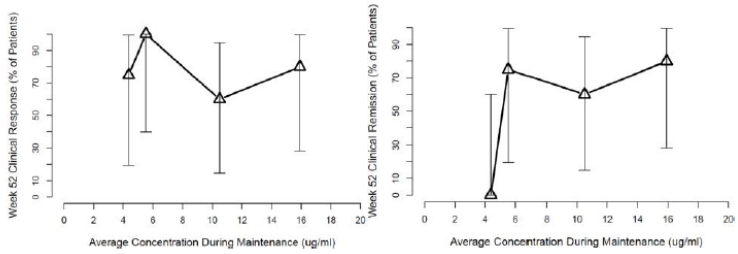
The E/R relationship between the change in MMS following the 40-week maintenance period versus Cavg is summarized for all pediatric participants who completed the Week 52 MMS assessment in Figure AMBU.5.7. No trend for greater decreases in the change in MMS with increasing exposure was observed.

The E/R relationships between the binary clinical efficacy endpoints were assessed and are shown in Figure AMBU.5.8 and Figure AMBU.5.9. These figures show the Week 52 clinical response, clinical remission and endoscopic response achieved relative to Cavg during the maintenance period. No clear E/R relationship was observed for any of these efficacy endpoints.



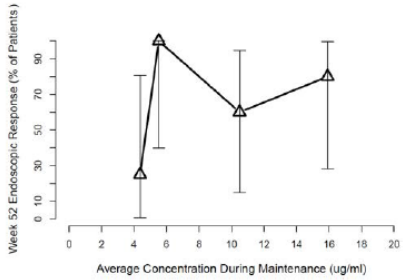
Abbreviations: AMBU = I6T-MC-AMBU; MMS = Modified Mayo Score.

Figure AMBU.5.7. Relationship between mirikizumab average concentration during maintenance and change in Modified Mayo Score during 40-week maintenance period.



Abbreviation: AMBU = I6T-MC-AMBU; C_{avg} = average mirikizumab concentration during 1 dosing interval; N =number of participants; SC = subcutaneous.
Note: The data points represent the percentage of participants that achieved clinical response (left) and clinical remission (right) who received either 200 mg SC mirikizumab (>40 kg), 100 mg SC mirikizumab (20–40 kg) and 50 mg mirikizumab (<20 kg) subdivided into C_{avg} quartiles (N=4,4,5,5 for Q1–Q4, respectively) The points are plotted along the x-axis at the median C_{avg} for each quartile. Error bars represent 95% confidence intervals.

Figure AMBU.5.8. **Relationship between mirikizumab average concentration during maintenance and Week 52 clinical response and clinical remission in cohorts in post-hoc grouping by Cavg quartile in Study AMBU.**



Abbreviation: AMBU = I6T-MC-AMBU; C_{avg} = average mirikizumab concentration during 1 dosing interval; N =number of participants; SC = subcutaneous.
Note: The data points represent the percentage of participants that achieved endoscopic response who received either 200 mg SC mirikizumab (>40 kg), 100 mg SC mirikizumab (20–40 kg) and 50 mg mirikizumab (<20 kg) subdivided into C_{avg} quartiles (N=4,4,5,5 for Q1–Q4, respectively) The points are plotted along the x-axis at the median C_{avg} for each quartile. Error bars represent 95% confidence intervals.

Figure AMBU.5.9. **Relationship between mirikizumab average concentration during maintenance and Week 52 endoscopic response in randomized cohorts in post-hoc grouping by Cavg quartile in Study AMBU.**

Assessor comments

Given the narrow exposure range evaluated in this study, model-based analysis for the exposure/response (E/R) relationship was not conducted and instead the E/R relationship was explored using observed efficacy endpoints and PK model estimated exposure parameters.

Full assessment of the PK/PD endpoints will be conducted following submission of the outstanding documents.

Acknowledging the low number of subjects enrolled, no clear E/R relationship was observed for mirikizumab in paediatric subjects with UC.

Pharmacokinetics Conclusions

The model estimated systemic clearance and subcutaneous bioavailability of mirikizumab was 0.0209 L/hr and 49.8%, respectively. These results were consistent with the adult UC Phase 2 Study AMAC and UC Phase 3 Studies AMAN and AMBG. The estimated systemic volume of distribution of mirikizumab was 0.069 L/kg, which was also consistent with the adult UC Phase 2 and 3 studies.

The only factor, in addition to weight, found to have a statistically significant impact on mirikizumab PK was serum albumin concentration. However, the magnitude of the impact was not considered clinically meaningful.

ADA was not identified to be a significant covariate on the PK of mirikizumab based on the population PK analysis.

The PK exposure estimates of mirikizumab were consistent between 300 mg induction for the >40 kg group and 5 mg/kg induction for the <40 kg group. They were also consistent in all weight groups for the maintenance treatment. These support the dosing strategy of weight group divided treatment of pediatric participants with UC.

Assessor comments

Overall, it is agreed that the exposure estimates appeared similar between the weight-based 5mg/kg mirikizumab IV and fixed dose 300mg mirikizumab IV in induction. The MAH confirmed that the Study AMBU 5 mg/kg mirikizumab IV Q4W dosing regimen was selected for use in Phase 3 for participants weighing less than or equal to 40 kg in

☐ Study I6T-MC-AMBA (AMBA) as induction dosing, and

☐ Long-term extension Study I6T-MC-AMAZ (AMAZ) ISA #1 as rescue dosing.

In Studies AMBA and AMAZ ISA #1, a 300 mg mirikizumab IV Q4W dosing regimen is used for participants weighing more than 40 kg for induction and rescue dosing, respectively.

Efficacy results

Compliance with Intervention

Overall compliance with therapy is defined as having at least 80% treatment compliant visits (i.e., received planned infusion/SC doses as per eCRF) before treatment discontinuation. All the participants (N = 26) were compliant to the study treatment.

Efficacy endpoints

Efficacy endpoints were secondary endpoints within this study. The main secondary efficacy endpoints were assessed for the induction period at Week 12 and for the maintenance period at Week 52.

For each of these endpoints, subgroup analysis by biologic failed and biologic not failed status was performed.

1. PUCAI Clinical Remission
2. PUCAI Clinical Response
3. Modified Mayo Score (MMS) Clinical Remission
4. Modified Mayo Score (MMS) Clinical Response
5. Endoscopic Remission
6. Endoscopic Subscore = 0
7. Symptomatic Remission by visit
8. Histologic- Endoscopic Mucosal Improvement

9. Histologic- Endoscopic Mucosal Remission

10. Improvement in patient-reported outcome endpoints

Results following induction at Week 12

During the Induction Period, participants received the following at Week 0, 4, and 8:

• Participants weighing >40 kg (300 mg mirikizumab IV)

• Participants weighing ≤40 kg (5 or 10 mg/kg mirikizumab IV).

PUCAI: The PUCAI is a 6-dimensional non-invasive tool, rating the severity of the following symptoms/disease characteristics of UC in children: abdominal pain, rectal bleeding, stool consistency, stool frequency, nocturnal stools, and assessment of limitations of activity of the patient. The sum of the score ranges from 0-85. The established cut-off scores for the PUCAI defined severity stages (<10 points=remission; 10-34 mild disease; 35-64 moderate disease; ≥65 severe disease). A reduction in PUCAI baseline score of >/=20 points was considered Clinical Response. PUCAI clinical remission is defined as a PUCAI score of <10 points.

1. PUCAI Clinical Remission at Week 12

The NRI analysis showed a total of 10 (38.5%) participants achieving PUCAI clinical remission at Week 12.

Table AMBU.5.1. PUCAI Clinical Remission at Week 12 (NRI; mITT Population)

	≤40 kg 5 mg/kg Miri IV (N = 10)	≤40 kg 10 mg/kg Miri IV (N = 5)	>40 kg 300 mg Miri IV (N = 11)	Total (N = 26)
Response, n (%)	6 (60.0)	0 (0.0)	4 (36.4)	10 (38.5)
95% CI[a]	(31.3, 83.2)	(0.0, 43.4)	(15.2, 64.6)	(22.4, 57.5)

Abbreviations: CI = confidence interval; IV = intravenous; mITT = modified intent-to-treat; Miri = mirikizumab; N = number of participants in the mITT Population; n = number of participants within each specific category; NRI = nonresponder imputation; PUCAI = Pediatric Ulcerative Colitis Activity Index.

[a] Response confidence intervals are constructed using Wilson method, without continuity correction.

Source: Table AMBU.8.15

A total of 29.4% of participants among the biologic failed subgroup and 55.6% of participants among the biologic not failed subgroup achieved PUCAI clinical remission at Week 12. All of the biologic not failed participants were biologic naive.

Table AMBU.5.2. PUCAI Clinical Remission at Week 12 by Biologic Failed and Biologic Not Failed Subgroups (NRI; mITT Population)

	≤40 kg 5 mg/kg Miri IV (N = 10)	≤40 kg 10 mg/kg Miri IV (N = 5)	>40 kg 300 mg Miri IV (N = 11)	Total (N = 26)
Failed (Ns)	**5**	**4**	**8**	**17**
Response, n (%)[a]	2 (40.0)	0 (0.0)	3 (37.5)	5 (29.4)
95% CI[b]	(11.8, 76.9)	(0.0, 49.0)	(13.7, 69.4)	(13.3, 53.1)
Not Failed (Ns)	**5**	**1**	**3**	**9**
Response, n (%)[a]	4 (80.0)	0 (0.0)	1 (33.3)	5 (55.6)
95% CI[b]	(37.6, 96.4)	(0.0, 79.3)	(6.1, 79.2)	(26.7, 81.1)

Abbreviations: CI = confidence interval; IV = intravenous; Miri = mirikizumab; mITT = modified intent-to-treat; N = number of participants in the mITT Population; n = number of participants within each specific category; NRI = nonresponder imputation; Ns = number of participants in each subgroup; PUCAI = Pediatric Ulcerative Colitis Activity Index.

[a] Percentage of response is calculated by n/Ns*100%.

[b] Response confidence intervals are constructed using Wilson method, without continuity correction.

Source: Table AMBU.8.16

2. PUCAI Clinical Response at Week 12

The NRI analysis showed a total of 20 (76.9%) participants achieved PUCAI clinical response at Week 12.

Table AMBU.5.3. PUCAI Clinical Response at Week 12 (NRI; mITT Population)

	≤40 kg 5 mg/kg Miri IV (N = 10)	≤40 kg 10 mg/kg Miri IV (N = 5)	>40 kg 300 mg Miri IV (N = 11)	Total (N = 26)
Response, n (%)	9 (90.0)	4 (80.0)	7 (63.6)	20 (76.9)
95% CI[a]	(59.6, 98.2)	(37.6, 96.4)	(35.4, 84.8)	(57.9, 89.0)

Abbreviations: CI = confidence interval; IV = intravenous; Miri = mirikizumab; mITT = modified intent-to-treat; N = number of participants in the mITT Population; n = number of participants within each specific category; NRI = nonresponder imputation; PUCAI = Pediatric Ulcerative Colitis Activity Index.

[a] Response confidence intervals are constructed using Wilson method, without continuity correction.

Source: TableAMBU.8.17

A total of 64.7% of participants among the biologic failed subgroup and 100.0% of participants among the biologic not failed subgroup achieved PUCAI clinical response at Week 12.

Table AMBU.5.4. PUCAI Clinical Response at Week 12 by Biologic Failed and Biologic Not Failed Subgroups (NRI; mITT Population)

	≤40 kg 5 mg/kg Miri IV (N = 10)	≤40 kg 10 mg/kg Miri IV (N = 5)	>40 kg 300 mg Miri IV (N = 11)	Total (N = 26)
Failed (Ns)	**5**	**4**	**8**	**17**
Response, n (%)[a]	4 (80.0)	3 (75.0)	4 (50.0)	11 (64.7)
95% CI[b]	(37.6, 96.4)	(30.1, 95.4)	(21.5, 78.5)	(41.3, 82.7)
Not Failed (Ns)	**5**	**1**	**3**	**9**
Response, n (%)[a]	5 (100.0)	1 (100.0)	3 (100.0)	9 (100.0)
95% CI[b]	(56.6, 100)	(20.7, 100)	(43.9, 100)	(70.1, 100)

Abbreviations: CI = confidence interval; IV = intravenous; Miri = mirikizumab; mITT = modified intent-to-treat; N = number of participants in the mITT Population; n = number of participants within each specific category; NRI = nonresponder imputation; Ns = number of participants in each subgroup; PUCAI = Pediatric Ulcerative Colitis Activity Index.

[a] Percentage of response is calculated by n/Ns*100%.

[b] Response confidence intervals are constructed using Wilson method, without continuity correction.

Source: Table AMBU.8.18

Assessor comments

During induction 10 subjects (38.5%) achieved PUCAI clinical remission, 6 subjects in the Miri IV 5mg/kg group and 4 subjects in the Miri 300mg IV group. No subjects in the Miri IV 10mg/kg group (</=40kg) achieved clinical remission. Of these 10 subjects achieving clinical remission on PUCAI, 5 had failed prior biologics and 5 had not failed prior biologics.

During induction 20 subjects (76.9%) achieved PUCAI clinical response, 9(90%) in the 5mg/kg Miri IV group, 4(80%) in the 10mg/kg Miri IV group and 7(63.6%) in the 300mg Miri IV group. 11 subjects (65.7%) achieved PUCAI clinical response in the biologic failed group and all 9 subjects (100%) achieved PUCAI clinical response in the biologic not failed group.

3. Modified Mayo Score (MMS) Clinical Remission at Week 12

The NRI analysis showed a total of 10 (38.5%) participants achieved clinical remission at Week 12.

Table AMBU.5.5. Clinical Remission at Week 12 (NRI; mITT Population)

	≤40 kg 5 mg/kg Miri IV (N = 10)	≤40 kg 10 mg/kg Miri IV (N = 5)	>40 kg 300 mg Miri IV (N = 11)	Total (N = 26)
Response, n (%)	5 (50.0)	1 (20.0)	4 (36.4)	10 (38.5)
95% CI[a]	(23.7, 76.3)	(3.6, 62.4)	(15.2, 64.6)	(22.4, 57.5)

Abbreviations: CI = confidence interval; IV = intravenous; Miri = mirikizumab; mITT = modified intent-to-treat; N = number of participants in the mITT Population; n = number of participants within each specific category; NRI = nonresponder imputation.

[a] Response confidence intervals are constructed using Wilson method, without continuity correction.

Source: Table AMBU.8.19

A total of 29.4% of participants among the biologic failed subgroup and 55.6% of participants among the biologic not failed subgroup achieved clinical remission at Week 12.

Table AMBU.5.6. Clinical Remission at Week 12 by Biologic Failed and Biologic Not Failed Subgroups (NRI; mITT Population)

	≤40 kg 5 mg/kg Miri IV (N = 10)	≤40 kg 10 mg/kg Miri IV (N = 5)	>40 kg 300 mg Miri IV (N = 11)	Total (N = 26)
Failed (Ns)	**5**	**4**	**8**	**17**
Response, n (%)[a]	2 (40.0)	1 (25.0)	2 (25.0)	5 (29.4)
95% CI[b]	(11.8, 76.9)	(4.6, 69.9)	(7.1, 59.1)	(13.3, 53.1)
Not Failed (Ns)	**5**	**1**	**3**	**9**
Response, n (%)[a]	3 (60.0)	0 (0.0)	2 (66.7)	5 (55.6)
95% CI[b]	(23.1, 88.2)	(0.0, 79.3)	(20.8, 93.9)	(26.7, 81.1)

Abbreviations: CI = confidence interval; IV = intravenous; Miri = mirikizumab; mITT = modified intent-to-treat; N = number of participants in the mITT Population; n = number of participants within each specific category; NRI = nonresponder imputation; Ns = number of participants in each subgroup

[a] Percentage of response is calculated by n/Ns*100%.

[b] Response confidence intervals are constructed using Wilson method, without continuity correction.

Source: Table AMBU.8.20

4. Modified Mayo Score (MMS) Clinical Response at Week 12

The NRI analysis showed a total of 18 (69.2%) participants achieved clinical response at Week 12.

Table AMBU.5.7. Clinical Response at Week 12 (NRI; mITT Population)

	≤40 kg 5 mg/kg Miri IV (N = 10)	≤40 kg 10 mg/kg Miri IV (N = 5)	>40 kg 300 mg Miri IV (N = 11)	Total (N = 26)
Response, n (%)	8 (80.0)	5 (100.0)	5 (45.5)	18 (69.2)
95% CI[a]	(49.0, 94.3)	(56.6, 100)	(21.3, 72.0)	(50.0, 83.5)

Abbreviations: CI = confidence interval; IV = intravenous; Miri = mirikizumab; mITT = modified intent-to-treat; N = number of participants in the mITT Population; n = number of participants within each specific category; NRI = nonresponder imputation.

[a] Response confidence intervals are constructed using Wilson method, without continuity correction.

Source: Table AMBU.8.21

A total of 64.7% of participants among the biologic failed subgroup and 77.8% of participants among the biologic not failed subgroup achieved clinical response at Week 12.

Table AMBU.5.8. Clinical Response at Week 12 by Biologic Failed and Biologic Not Failed Subgroups (NRI; mITT Population)

	≤40 kg 5 mg/kg Miri IV (N = 10)	≤40 kg 10 mg/kg Miri IV (N = 5)	>40 kg 300 mg Miri IV (N = 11)	Total (N = 26)
Failed (Ns)	**5**	**4**	**8**	**17**
Response, n (%)[a]	4 (80.0)	4 (100.0)	3 (37.5)	11 (64.7)
95% CI[b]	(37.6, 96.4)	(51.0, 100)	(13.7, 69.4)	(41.3, 82.7)
Not Failed (Ns)	**5**	**1**	**3**	**9**
Response, n (%)[a]	4 (80.0)	1 (100.0)	2 (66.7)	7 (77.8)
95% CI[b]	(37.6, 96.4)	(20.7, 100)	(20.8, 93.9)	(45.3, 93.7)

Abbreviations: CI = confidence interval; IV = intravenous; Miri = mirikizumab; mITT = modified intent-to-treat; N = number of participants in the mITT Population; n = number of participants within each specific category; NRI = nonresponder imputation; Ns = number of participants in each subgroup.

a Percentage of response is calculated by n/Ns*100%.

b Response confidence intervals are constructed using Wilson method, without continuity correction.

Source: Table AMBU.8.22

Assessor comments

During induction, 10 subjects (38.5%) achieved clinical remission on MMS at Week 12, 5 had failed prior biologics and 5 had not failed prior biologics.

18 subjects (69.2%) achieved clinical response on MMS at Week 12, 11 had failed prior biologics and 7 had not failed prior biologics.

5. Endoscopic Remission at Week 12

The NRI analysis showed a total of 14 (53.8%) participants achieved endoscopic remission at Week 12.

Table AMBU.5.9. Endoscopic Remission at Week 12 (NRI; mITT Population)

	≤40 kg 5 mg/kg Miri IV (N = 10)	≤40 kg 10 mg/kg Miri IV (N = 5)	>40 kg 300 mg Miri IV (N = 11)	Total (N = 26)
Response, n (%)	6 (60.0)	3 (60.0)	5 (45.5)	14 (53.8)
95% CI[a]	(31.3, 83.2)	(23.1, 88.2)	(21.3, 72.0)	(35.5, 71.2)

Abbreviations: CI = confidence interval; IV = intravenous; Miri = mirikizumab; mITT = modified intent-to-treat; N = number of participants in the mITT Population; n = number of participants within each specific category; NRI = nonresponder imputation.

a Response confidence intervals are constructed using Wilson method, without continuity correction.

Source: Table AMBU.8.23

A total of 52.9% of participants among the biologic failed subgroup and 55.6% of participants among the biologic not failed subgroup achieved endoscopic remission at Week 12.

Table AMBU.5.10. Endoscopic Remission at Week 12 by Biologic Failed and Biologic Not Failed Subgroups (NRI; mITT Population)

	≤40 kg 5 mg/kg Miri IV (N = 10)	≤40 kg 10 mg/kg Miri IV (N = 5)	>40 kg 300 mg Miri IV (N = 11)	Total (N = 26)
Failed (Ns)	**5**	**4**	**8**	**17**
Response, n (%)[a]	3 (60.0)	3 (75.0)	3 (37.5)	9 (52.9)
95% CI[b]	(23.1, 88.2)	(30.1, 95.4)	(13.7, 69.4)	(31.0, 73.8)
Not Failed (Ns)	**5**	**1**	**3**	**9**
Response, n (%)[a]	3 (60.0)	0 (0.0)	2 (66.7)	5 (55.6)
95% CI[b]	(23.1, 88.2)	(0.0, 79.3)	(20.8, 93.9)	(26.7, 81.1)

Abbreviations: CI = confidence interval; IV = intravenous; Miri = mirikizumab; mITT = modified intent-to-treat; N = number of participants in the mITT Population; n = number of participants within each specific category; NRI = nonresponder imputation; Ns = number of participants in each subgroup.

a Percentage of response is calculated by n/Ns*100%.

b Response confidence intervals are constructed using Wilson method, without continuity correction.

Source: Table AMBU.8.24

6. Endoscopic Subscore = 0 at Week 12

None of the participants in either of the biologic failed and not failed subgroup achieved endoscopic subscore of 0 at Week 12.

Assessor comments

14 subjects (53.8%) achieved endoscopic remission at Week 12, with similar proportion in both the biologic failed and not failed groups, 52.9% and 55.6%respectively.

No subjects achieved endoscopic subscore of 0 by week 12.

7. Symptomatic Remission by visit

The proportion of participants in symptomatic remission at applicable study visits increased from baseline at Weeks 2, 4 and 8. The NRI analysis showed that a total of 12 (46.2%) participants were in symptomatic remission at Week 8 and the proportion of participants achieving symptomatic remission remained relatively stable at Week 12.

Table AMBU.5.11. Symptomatic Remission by Visit (NRI; mITT Population)

		≤40 kg 5 mg/kg Miri IV (N = 10)	≤40 kg 10 mg/kg Miri IV (N = 5)	>40 kg 300 mg Miri IV (N = 11)	Total (N = 26)
Week 2	*Response, n (%)*	2 (20.0)	0 (0.0)	0 (0.0)	2 (7.7)
	95% CI[a]	(5.7, 51.0)	(0.0, 43.4)	(0.0, 25.9)	(2.1, 24.1)
Week 4	*Response, n (%)*	3 (30.0)	0 (0.0)	2 (18.2)	5 (19.2)
	95% CI[a]	(10.8, 60.3)	(0.0, 43.4)	(5.1, 47.7)	(8.5, 37.9)
Week 8	*Response, n (%)*	6 (60.0)	1 (20.0)	5 (45.5)	12 (46.2)
	95% CI[a]	(31.3, 83.2)	(3.6, 62.4)	(21.3, 72.0)	(28.8, 64.5)
Week 12	*Response, n (%)*	6 (60.0)	2 (40.0)	4 (36.4)	12 (46.2)
	95% CI[a]	(31.3, 83.2)	(11.8, 76.9)	(15.2, 64.6)	(28.8, 64.5)

Abbreviations: CI = confidence interval; IV = intravenous; Miri = mirikizumab; mITT = modified intent-to-treat; N = number of participants in the mITT Population; n = number of participants within each specific category; NRI = nonresponder imputation.

[a] Response confidence intervals are constructed using Wilson method, without continuity correction.

Source: Table AMBU.8.27

The proportion of participants among the biologic failed and biologic not failed subgroups in symptomatic remission increased from baseline at Weeks 4 and 8 and remained relatively stable at Week 12.

Table AMBU.5.12. Symptomatic Remission at Each Visit by Biologic Failed and Biologic Not Failed Subgroups (NRI; mITT Population)

		≤40 kg 5 mg/kg Miri IV (N=10)	≤40 kg 10 mg/kg Miri IV (N=5)	>40 kg 300 mg Miri IV (N=11)	Total (N=26)
Week 2	*Failed (Ns)*	**5**	**4**	**8**	**17**
	Response, n (%)[a]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	95% CI[b]	(0.0, 43.4)	(0.0, 49.0)	(0.0, 32.4)	(0.0, 18.4)
	Not Failed (Ns)	**5**	**1**	**3**	**9**
	Response, n (%)[a]	2 (40.0)	0 (0.0)	0 (0.0)	2 (22.2)
	95% CI[b]	(11.8, 76.9)	(0.0, 79.3)	(0.0, 56.1)	(6.3, 54.7)

Week 4	*Failed (Ns)*	**5**	**4**	**8**	**17**
	Response, n (%)[a]	1 (20.0)	0 (0.0)	1 (12.5)	2 (11.8)
	95% CI[b]	(3.6, 62.4)	(0.0, 49.0)	(2.2, 47.1)	(3.3, 34.3)
	Not Failed (Ns)	**5**	**1**	**3**	**9**
	Response, n (%)[a]	2 (40.0)	0 (0.0)	1 (33.3)	3 (33.3)
	95% CI[b]	(11.8, 76.9)	(0.0, 79.3)	(6.1, 79.2)	(12.1, 64.6)
Week 8	*Failed (Ns)*	**5**	**4**	**8**	**17**
	Response, n (%)[a]	2 (40.0)	1 (25.0)	3 (37.5)	6 (35.3)
	95% CI[b]	(11.8, 76.9)	(4.6, 69.9)	(13.7, 69.4)	(17.3, 58.7)
	Not Failed (Ns)	**5**	**1**	**3**	**9**
	Response, n (%)[a]	4 (80.0)	0 (0.0)	2 (66.7)	6 (66.7)
	95% CI[b]	(37.6, 96.4)	(0.0, 79.3)	(20.8, 93.9)	(35.4, 87.9)
Week 12	*Failed (Ns)*	**5**	**4**	**8**	**17**
	Response, n (%)[a]	2 (40.0)	1 (25.0)	3 (37.5)	6 (35.3)
	95% CI[b]	(11.8, 76.9)	(4.6, 69.9)	(13.7, 69.4)	(17.3, 58.7)
	Not Failed (Ns)	**5**	**1**	**3**	**9**
	Response, n (%)[a]	4 (80.0)	1 (100.0)	1 (33.3)	6 (66.7)
	95% CI[b]	(37.6, 96.4)	(20.7, 100)	(6.1, 79.2)	(35.4, 87.9)

Abbreviations: CI = confidence interval; IV = intravenous; Miri = mirikizumab; mITT = modified intent-to-treat; N = number of participants in the mITT Population; n = number of participants within each specific category; NRI = nonresponder imputation; Ns = number of participants in each subgroup

[a] Percentage of response is calculated by n/Ns*100%.

[b] Response confidence intervals are constructed using Wilson method, without continuity correction.

Source: Table AMBU.8.28

Assessor comments

The proportion of subjects in symptomatic remission increased from baseline at Weeks 2, 4 and 8. At week 8, 12 subjects (46.2%) were in symptomatic remission which remained stable at Week 12. The proportion in symptomatic remission at Week 12 was higher in the biologic not failed group.

8. Histologic- Endoscopic Mucosal Improvement at Week 12

HEMI was not a protocol-defined endpoint for this study, however, the endpoint was included in the SAP. HEMI was reported in the adult program and is also clinically relevant for pediatric gastroenterologists. The NRI analysis showed 4 (15.4%) participants achieving histologic-endoscopic mucosal improvement at Week 12, three (17.6%) participants in the biologic failed and only 1 (11.1%) participant in the not failed subgroup.

Table AMBU.5.13. Histologic-Endoscopic Mucosal Improvement at Week 12 (NRI; mITT Population)

	≤40 kg 5 mg/kg Miri IV (N = 10)	≤40 kg 10 mg/kg Miri IV (N = 5)	>40 kg 300 mg Miri IV (N = 11)	Total (N = 26)
Response, n (%)	1 (10.0)	1 (20.0)	2 (18.2)	4 (15.4)
95% CI[a]	(1.8, 40.4)	(3.6, 62.4)	(5.1, 47.7)	(6.2, 33.5)

Abbreviations: CI = confidence interval; IV = intravenous; Miri = mirikizumab; mITT = modified intent-to-treat; N = number of participants in the mITT Population; n = number of participants within each specific category; NRI = nonresponder imputation.

[a] Response confidence intervals are constructed using Wilson method, without continuity correction.

Source: Table AMBU.8.29

Table AMBU.5.14. Histologic-Endoscopic Mucosal Improvement at Week 12 by Biologic Failed and Biologic Not Failed Subgroups (NRI; mITT Population)

	≤40 kg 5 mg/kg Miri IV (N = 10)	≤40 kg 10 mg/kg Miri IV (N = 5)	>40 kg 300 mg Miri IV (N = 11)	Total (N = 26)
Failed (Ns)	5	4	8	17
Response, n (%)[a]	1 (20.0)	1 (25.0)	1 (12.5)	3 (17.6)
95% CI[b]	(3.6, 62.4)	(4.6, 69.9)	(2.2, 47.1)	(6.2, 41.0)
Not Failed (Ns)	5	1	3	9
Response, n (%)[a]	0 (0.0)	0 (0.0)	1 (33.3)	1 (11.1)
95% CI[b]	(0.0, 43.4)	(0.0, 79.3)	(6.1, 79.2)	(2.0, 43.5)

Abbreviations: CI = confidence interval; IV = intravenous; Miri = mirikizumab; mITT = modified intent-to-treat; N = number of participants in the mITT Population; n = number of participants within each specific category; NRI = nonresponder imputation; Ns = number of participants in each subgroup.

[a] Percentage of response is calculated by n/Ns*100%.

[b] Response confidence intervals are constructed using Wilson method, without continuity correction.

Source: Table AMBU.8.30

9. Histologic- Endoscopic Mucosal Remission at Week 12

One (3.8%) participant (biologic not failed) achieved histologic-endoscopic mucosal remission at Week 12.

Assessor comments

4 (15.4%) participants achieving histologic-endoscopic mucosal improvement at Week 12 and 1 subject achieved histologic-endoscopic- mucosal remission at Week 12.

10. Improvement in patient-reported outcome endpoints at Week 12

Urgency NRS Score

A negative Urgency NRS score indicates improvement from baseline in the participant's Urgency NRS score. Across all age groups, participants had a reduction (improvement) from baseline in Urgency NRS scores at Week 12.

Table AMBU.5.17. Urgency NRS Subscore at Week 12 (Change from baseline) by Age Group (mITT Population)

	≤40 kg 5 mg/kg Miri Q4W (N = 10)	≤40 kg 10 mg/kg Miri Q4W (N = 5)	>40 kg 300 mg Miri Q4W (N = 11)	Total (N = 26)
Change from Baseline (mBOCF) *Mean (SD)*				
2 to <8 years[a]	-3 (3.6)	N/A	N/A	-3 (3.6)
8 to <12 years[a]	-3 (1.4)	-1	N/A	-2 (1.5)
12 to <18 years[a]	-3 (3.1)	-2 (1.0)	-1 (2.9)	-2 (2.7)

Abbreviations: mBOCF = modified baseline carried forward; miri = mirikizumab; mITT = modified intent-to-treat; N = number of participants in the analysis population; NRS = numeric rating score; ObsRO = observer-reported outcomes; Q4W = every 4 weeks; SD = standard deviation.

Note: N/A denotes there were no participants assigned to the corresponding dose group.

[a] Version of Urgency NRS scale used for each age group: Urgency NRS ObsRO version 0-10 scale (2 to <8 years), Urgency NRS Pediatric version 0-5 scale (8 to <12 years), Urgency NRS Adolescent version 0-10 scale (12 to <18 years).

Source: Table AMBU.8.33

Abdominal Pain NRS Score

A negative Abdominal Pain NRS score indicates improvement from baseline in the participant's Abdominal Pain NRS score. Across all age groups, participants had a reduction (improvement) from baseline in Abdominal Pain NRS scores at Week 12.

Table AMBU.5.18. Abdominal Pain NRS Subscore at Week 12 (Change from Baseline) by Age Group (mITT Population)

	≤40 kg 5 mg/kg Miri Q4W (N = 10)	≤40 kg 10 mg/kg Miri Q4W (N = 5)	>40 kg 300 mg Miri Q4W (N = 11)	Total (N = 26)
Change from Baseline (mBOCF) *Mean (SD)*				
2 to <8 years[a]	-3 (2.1)	N/A	N/A	-3 (2.1)
8 to <12 years[a]	-3 (2.1)	-2	N/A	-2 (1.5)
12 to <18 years[a]	-4 (2.7)	-2 (1.5)	-1 (2.8)	-2 (2.7)

Abbreviations: mBOCF = modified baseline carried forward; miri = mirikizumab; mITT = modified intent-to-treat; N = number of participants in the analysis population; NRS = numeric rating score; ObsRO = observer-reported outcomes; Q4W = every 4 weeks; SD = standard deviation.

Note: N/A denotes there were no participants assigned to the corresponding dose group.

[a] Version of Urgency NRS scale used for each age group: Urgency NRS ObsRO version 0-10 scale (2 to <8 years), Urgency NRS Pediatric version 0-5 scale (8 to <12 years), Urgency NRS Adolescent version 0-10 scale (12 to <18 years).

Source: Table AMBU.8.34

Assessor comments

Across all age groups subjects had a mean decrease in Urgency and Abdominal Pain NRS subscores at Week 12.

Maintenance period

Participants who met the clinical response criteria at Week 12 were defined as Clinical Responders and entered the Maintenance Period receiving the following from Weeks 12 to 48:

• Participants weighing >40 kg (200 mg mirikizumab SC Q4W)

• Participants weighing >20 kg to ≤40 kg (100 mg mirikizumab SC Q4W), or

• Participants weighing ≤20 kg (50 mg mirikizumab SC Q4W)

Results following maintenance at Week 52

1. PUCAI Clinical Remission at Week 52

The NRI analysis showed a total of 13 (50.0%) participants achieved PUCAI clinical remission at Week 52.

Table AMBU.5.23. PUCAI Clinical Remission at Week 52 (NRI; mITT Population)

	≤20 kg 50 mg Miri SC (N = 1)	>20 kg and ≤40 kg 100 mg Miri SC (N = 8)	>40 kg 200 mg Miri SC (N = 9)	≤20 kg 10 mg/kg Miri IV/50 mg Miri SC non-responder (N = 1)	>20 kg and ≤40 kg 10 mg/kg Miri IV/ 100 mg Miri SC non-responder (N = 1)	>40 kg 300 mg Miri IV/ 200 mg Miri SC non-responder (N = 6)	Total (N = 26)
Response, n (%)	0 (0.0)	6 (75.0)	7 (77.8)	0 (0.0)	0 (0.0)	0 (0.0)	13 (50.0)
95% CI[a]	(0.0, 79.3)	(40.9, 92.9)	(45.3, 93.7)	(0.0, 79.3)	(0.0, 79.3)	(0.0, 39.0)	(32.1, 67.9)

Abbreviations: CI = confidence interval; IV = intravenous; Miri = mirikizumab; mITT = modified intent-to-treat; N = number of participants in the mITT Population; n = number of participants within each specific category; NRI = nonresponder imputation; PUCAI = Pediatric Ulcerative Colitis Activity Index; SC = subcutaneous.

[a] Response confidence intervals are constructed using Wilson method, without continuity correction.

Source: Table AMBU.8.45

A total of 35.3% of participants among the biologic failed subgroup and 77.8% of participants among the biologic not failed subgroup achieved clinical remission at Week 52.

Table AMBU.5.24. PUCAI Clinical Remission at Week 52 by Biologic Failed and Biologic Not Failed Subgroups (NRI; mITT Population)

	≤20 kg 50 mg Miri SC (N = 1)	>20 kg and ≤40 kg 100 mg Miri SC (N = 8)	>40 kg 200 mg Miri SC (N = 9)	≤20 kg 10 mg/kg Miri IV/ 50 mg Miri SC non-responder (N = 1)	>20 kg and ≤40 kg 10 mg/kg Miri IV/ 100 mg Miri SC non-responder (N = 1)	>40 kg 300 mg Miri IV/ 200 mg Miri SC non-responder (N = 6)	Total (N = 26)
Failed (Ns)	**1**	**5**	**5**	**1**	**0**	**5**	**17**
Response, n (%)[a]	0 (0.0)	3 (60.0)	3 (60.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (35.3)
95% CI[b]	(0.0, 79.3)	(23.1, 88.2)	(23.1, 88.2)	(0.0, 79.3)	(0.0, 0.0)	(0.0, 43.4)	(17.3, 58.7)
Not Failed (Ns)	**0**	**3**	**4**	**0**	**1**	**1**	**9**
Response, n (%)[a]	0 (0.0)	3 (100.0)	4(100)	0 (0.0)	0 (0.0)	0 (0.0)	7(77.8)
95% CI[b]	(0.0, 0.0)	(43.9, 100)	(51.0, 100)	(0.0, 0.0)	(0.0, 79.3)	(0.0, 79.3)	(45.3, 93.7)

Abbreviations: CI = confidence interval; IV = intravenous; Miri = mirikizumab; mITT = modified intent-to-treat; N = number of participnts in the mITT Population; n = number of participants within each specific category; NRI = nonresponder imputation; Ns = number of participants in each subgroup; PUCAI = Pediatric Ulcerative Colitis Activity Index; SC = subcutaneous.

[a] Percentage of response is calculated by n/Ns*100%

[b] Response confidence intervals are constructed using Wilson method, without continuity correction.

Source: Table AMBU.8.46

PUCAI Clinical Remission at Week 52 among the Induction PUCAI Remitters

Participants who achieved PUCAI remission at Week 12 were defined as induction PUCAI remitters. The NRI analysis showed a total of 8 (80.0%) participants (induction PUCAI remitters [n=10]) achieved PUCAI clinical remission at Week 52.

Table AMBU.5.25. PUCAI Clinical Remission at Week 52 (NRI; mITT Population Induction PUCAI Remitters)

	≤20 kg 50 mg Miri SC (N = 1)	>20 kg and ≤40 kg 100 mg Miri SC (N = 3)	>40 kg 200 mg Miri SC (N = 6)	≤20 kg 10 mg/kg Miri IV/ 50 mg Miri SC non-responder (N = 0)	>20 kg and ≤40 kg 10 mg/kg Miri IV/ 100 mg Miri SC non-responder (N = 0)	>40 kg 300 mg Miri IV/ 200 mg Miri SC non-responder (N = 0)	Total (N = 10)
Response, n (%)	0 (0.0)	3 (100.0)	5 (83.3)	0 (N/A)	0 (N/A)	0 (N/A)	8 (80.0)
95% CI[a]	(0.0, 79.3)	(43.9, 100)	(43.6, 97.0)	N/A	N/A	N/A	(49.0, 94.3)

Abbreviations: CI = confidence interval; IV = intravenous; Miri = mirikizumab; mITT = modified intent-to-treat; N = number of participants in the mITT Population; n = number of participants within each specific category; NRI = nonresponder imputation; PUCAI = Pediatric Ulcerative Colitis Activity Index; SC = subcutaneous.

[a] Response confidence intervals are constructed using Wilson method, without continuity correction.

Source: Table AMBU.8.47

Table AMBU.5.26. PUCAI Clinical Remission at Week 52 by Biologic Failed and Biologic Not Failed Subgroups (NRI; mITT Population; Induction PUCAI Remitters)

	≤20 kg 50 mg Miri SC (N = 1)	>20 kg and ≤40 kg 100 mg Miri SC (N = 3)	>40 kg 200 mg Miri SC (N = 6)	≤20 kg 10 mg/kg Miri IV/ 50 mg Miri SC non-responder (N = 0)	>20 kg and ≤40 kg 10 mg/kg Miri IV/ 100 mg Miri SC non-responder (N = 0)	>40 kg 300 mg Miri IV/ 200 mg Miri SC non-responder (N = 0)	Total (N = 10)
Failed (Ns)	**1**	**0**	**4**	**0**	**0**	**0**	**5**
Response, n (%)[a]	0 (0.0)	0 (0.0)	3 (75.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (60.0)
95% CI[b]	(0.0, 79.3)	(0.0, 0.0)	(30.1, 95.4)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)	(23.1, 88.2)
Not Failed (Ns)	**0**	**3**	**2**	**0**	**0**	**0**	**5**
Response, n (%)[a]	0 (0.0)	3 (100.0)	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (100.0)
95% CI[b]	(0.0, 0.0)	(43.9, 100)	(34.2, 100)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)	(56.6, 100)

Abbreviations: CI = confidence interval; miri = mirikizumab; mITT = modified intent-to-treat; N = number of participants in the analysis population; n = number of participants in the specified category; NRI = nonresponder imputation; Ns = number of participants in each subgroup; PUCAI = Pediatric Ulcerative Colitis Activity Index; SC = subcutaneous.

[a] Percentage of response is calculated by n/Ns*100%

[b] Response confidence intervals are constructed using Wilson method, without continuity correction.

Source: Table AMBU.8.48

Table AMBU.5.27. PUCAI Clinical Remission at Week 52 (NRI; mITT Population Induction PUCAI Responders)

	≤20 kg 50 mg Miri SC (N = 1)	>20 kg and ≤40kg 100 mg Miri SC (N = 7)	>40 kg 200 mg Miri SC (N = 9)	≤20 kg 10 mg/kg Miri IV/ 50 mg Miri SC non-responder (N = 0)	>20kg and ≤40kg 10 mg/kg Miri IV/ 100 mg Miri SC non-responder (N = 1)	>40 kg 300 mg Miri IV/ 200 mg Miri SC non-responder (N = 2)	Total (N = 20)
Response, n (%)	0 (0.0)	6 (85.7)	7 (77.8)	0 (N/A)	0 (0.0)	0 (0.0)	13 (65.0)
95% CI[a]	(0.0, 79.3)	(48.7, 97.4)	(45.3, 93.7)	N/A	(0.0, 79.3)	(0.0, 65.8)	(43.3, 81.9)

Abbreviations: CI = confidence interval; IV = intravenous; miri = mirikizumab; mITT = modified intent-to-treat; N = number of participants in the analysis population; n = number of participants in the specified category; N/A = not applicable; NRI = nonresponder imputation; PUCAI = Pediatric Ulcerative Colitis Activity Index; SC = subcutaneous.

[a] Response confidence intervals are constructed using Wilson method, without continuity correction.

Source: Table AMBU.8.49

Table AMBU.5.28. PUCAI Clinical Remission at Week 52 by Biologic Failed and Biologic Not Failed Subgroups (NRI; mITT Population; Induction PUCAI Responders)

	≤20 kg 50 mg Miri SC (N = 1)	>20 kg and ≤40 kg 100 mg Miri SC (N = 7)	>40 kg 200 mg Miri SC (N = 9)	≤20 kg 10 mg/kg Miri IV/ 50 mg Miri SC non-responder (N = 0)	>20 kg and ≤40 kg 10 mg/kg Miri IV/ 100 mg Miri SC non-responder (N = 1)	>40 kg 300 mg Miri IV/ 200 mg Miri SC non-responder (N = 2)	Total (N = 20)
Failed (Ns)	1	4	5	0	0	1	11
Response, n (%)[a]	0 (0.0)	3 (75.0)	3 (60.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (54.5)
95% CI[b]	(0.0, 79.3)	(30.1, 95.4)	(23.1, 88.2)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 79.3)	(28.0, 78.7)
Not Failed (Ns)	0	3	4	0	1	1	9
Response, n (%)[a]	0 (0.0)	3 (100.0)	4 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (77.8)
95% CI[b]	(0.0, 0.0)	(43.9, 100)	(51.0, 100)	(0.0, 0.0)	(0.0, 79.3)	(0.0, 79.3)	(45.3, 93.7)

Abbreviations: CI = confidence interval; IV = intravenous; miri = mirikizumab; mITT = modified intent-to-treat; N = number of participants in the analysis population; n = number of participants in the specified category; NRI = nonresponder imputation; Ns = number of participants in each subgroup; PUCAI = Pediatric Ulcerative Colitis Activity Index; SC = subcutaneous.

[a] Percentage of response is calculated by n/Ns*100%

[b] Response confidence intervals are constructed using Wilson method, without continuity correction.

Source: Table AMBU.8.50.

Assessor comments

At 52 weeks, 13 subjects (50%) achieved PUCAI clinical remission at Week 52, with a higher proportion in the biologic not failed subgroup.

Of the 10 subjects who achieved PUCAI clinical remission at Week 12 (PUCAI induction remitters), 8 subject achieved PUCAI clinical remission also at Week 52, again with higher proportion in the biologic not failed.

Of the 20 subjects who achieved PUCAI clinical response at Week 12 (PUCAI induction responders), 13 subjects achieved PUCAI clinical remission also at Week 52, again with higher proportion in the biologic not failed.

2. PUCAI Clinical Response

The NRI analysis showed a total of 14 (53.8%) participants achieved PUCAI clinical response at Week 52.

Table AMBU.5.29. PUCAI Clinical Response at Week 52 (NRI; mITT Population)

	≤20 kg 50 mg Miri SC (N = 1)	>20 kg and ≤40 kg 100 mg Miri SC (N = 8)	>40 kg 200 mg Miri SC (N = 9)	≤20 kg 10 mg/kg Miri IV/ 50 mg Miri SC non-responder (N = 1)	>20 kg and ≤40 kg 10 mg/kg Miri IV/ 100 mg Miri SC non-responder (N = 1)	>40 kg 300 mg Miri IV/ 200 mg Miri SC non-responder (N = 6)	Total (N = 26)
Response, n (%)	0 (0.0)	6 (75.0)	8 (88.9)	0 (0.0)	0 (0.0)	0 (0.0)	14 (53.8)
95% CI[a]	(0.0, 79.3)	(40.9, 92.9)	(56.5, 98.0)	(0.0, 79.3)	(0.0, 79.3)	(0.0, 39.0)	(35.5, 71.2)

Abbreviations: CI = confidence interval; IV = intravenous; Miri = mirikizumab; mITT = modified intent-to-treat; N = number of participants in the mITT Population; n = number of participants within each specific category; NRI = nonresponder imputation; PUCAI = Pediatric Ulcerative Colitis Activity Index; SC = subcutaneous.

[a] Response confidence intervals are constructed using Wilson method, without continuity correction.

Source: Table AMBU.8.51

Table AMBU.5.30. PUCAI Clinical Response at Week 52 by Biologic Failed and Biologic Not Failed Subgroups (NRI; mITT Population)

	≤20 kg 50 mg Miri SC (N = 1)	>20 kg and ≤40 kg 100 mg Miri SC (N = 8)	>40 kg 200 mg Miri SC (N = 9)	≤20 kg 10 mg/kg Miri IV/ 50 mg Miri SC non-responder (N = 1)	>20 kg and ≤40 kg 10 mg/kg Miri IV/ 100 mg Miri SC non-responder (N = 1)	>40 kg 300 mg Miri IV/ 200 mg Miri SC non-responder (N = 6)	Total (N = 26)
Failed (Ns)	**1**	**5**	**5**	**1**	**0**	**5**	**17**
Response, n (%)[a]	0 (0.0)	3 (60.0)	4 (80.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (41.2)
95% CI[b]	(0.0, 79.3)	(23.1, 88.2)	(37.6, 96.4)	(0.0, 79.3)	(0.0, 0.0)	(0.0, 43.4)	(21.6, 64.0)
Not Failed (Ns)	**0**	**3**	**4**	**0**	**1**	**1**	**9**
Response, n (%)[a]	0 (0.0)	3 (100.0)	4 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (77.8)
95% CI[b]	(0.0, 0.0)	(43.9, 100)	(51.0, 100)	(0.0, 0.0)	(0.0, 79.3)	(0.0, 79.3)	(45.3, 93.7)

Abbreviations: CI = confidence interval; IV = intravenous; Miri = mirikizumab; mITT = modified intent-to-treat; N = number of participants in the mITT Population; n = number of participants within each specific category; NRI = nonresponder imputation; Ns = number of participants in each subgroup; PUCAI = Pediatric Ulcerative Colitis Activity Index; SC = subcutaneous.

[a] Percentage of response is calculated by n/Ns*100%.

[b] Response confidence intervals are constructed using Wilson method, without continuity correction.

Source: Table AMBU.8.52

PUCAI Clinical Response at Week 52 among the Induction PUCAI Responders

Among the Induction PUCAI Responders (n=20), the NRI analysis showed a total of 14 (70.0%) participants achieved PUCAI clinical response at Week 52.

Table AMBU.5.31. PUCAI Clinical Response at Week 52 (NRI; mITT Population Induction PUCAI Responders)

	≤20 kg 50 mg Miri SC (N = 1)	>20 kg and ≤40 kg 100 mg Miri SC (N = 7)	>40 kg 200 mg Miri SC (N = 9)	≤20 kg 10 mg/kg Miri IV/ 50 mg Miri SC non-responder (N = 0)	>20 kg and ≤40 kg 10 mg/kg Miri IV/ 100 mg Miri SC non-responder (N = 1)	>40 kg 300 mg Miri IV/ 200 mg Miri SC non-responder (N = 2)	Total (N = 20)
Response, n (%)	0 (0.0)	6 (85.7)	8 (88.9)	0 (N/A)	0 (0.0)	0 (0.0)	14 (70.0)
95% CI[a]	(0.0, 79.3)	(48.7, 97.4)	(56.5, 98.0)	N/A	(0.0, 79.3)	(0.0, 65.8)	(48.1, 85.5)

Abbreviations: CI = confidence interval; IV = intravenous; Miri = mirikizumab; mITT = modified intent-to-treat; N = number of participants in the analysis population; n = number of participants in the specified category; N/A = not applicable; NRI = nonresponder imputation; Nx = number of participants with non-missing values; PUCAI = Pediatric Ulcerative Colitis Activity Index; SC = subcutaneous.

[a] Response confidence intervals are constructed using Wilson method, without continuity correction.

Source: Table AMBU.8.53

PUCAI Clinical Response at Week 52 among the Induction PUCAI Responders by Biologic Failed and Biologic Not Failed Subgroups

Among the induction PUCAI responders (n=20), a total of 63.6% of participants among the biologic failed subgroup and 77.8% of participants among the biologic not failed subgroup achieved PUCAI clinical response at Week 52.

Table AMBU.5.32. PUCAI Clinical Response at Week 52 by Biologic Failed and Biologic Not Failed Subgroups (NRI; mITT Population - Induction PUCAI Responders)

	≤20 kg 50 mg Miri SC (N = 1)	>20 kg and ≤40 kg 100 mg Miri SC (N = 7)	>40 kg 200 mg Miri SC (N = 9)	≤20 kg 10 mg/kg Miri IV/ 50 mg Miri SC non-responder (N = 0)	>20 kg and ≤40 kg 10 mg/kg Miri IV/ 100 mg Miri SC non-responder (N = 1)	>40 kg 300 mg Miri IV/ 200 mg Miri SC non-responder (N = 2)	Total (N = 20)
Failed (Ns)	1	4	5	0	0	1	11
Response, n (%)[a]	0 (0.0)	3 (75.0)	4 (80.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (63.6)
95% CI[b]	(0.0, 79.3)	(30.1, 95.4)	(37.6, 96.4)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 79.3)	(35.4, 84.8)
Not Failed (Ns)	0	3	4	0	1	1	9
Response, n (%)[a]	0 (0.0)	3 (100.0)	4 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (77.8)
95% CI[b]	(0.0, 0.0)	(43.9, 100)	(51.0, 100)	(0.0, 0.0)	(0.0, 79.3)	(0.0, 79.3)	(45.3, 93.7)

Abbreviations: CI = confidence interval; IV = intravenous; miri = mirikizumab; mITT = modified intent-to-treat; N = number of participants in the analysis population; n = number of participants in the specified category; NRI = nonresponder imputation; Ns = number of participants in each subgroup; PUCAI = Pediatric Ulcerative Colitis Activity Index; SC = subcutaneous.

[a] Percentage of response is calculated by n/Ns*100%.

[b] Response confidence intervals are constructed using Wilson method, without continuity correction.

Source: Table AMBU.8.54

PUCAI Clinical Response and Clinical Remission – Week 12 MMS Responders

At Week 52, PUCAI response and PUCAI remission rates for Week 12 MMS clinical responders were 77.8% and 72.2%, respectively.

3. Modified Mayo Score (MMS) Clinical Remission

The NRI analysis showed a total of 10 (38.5%) participants achieved clinical remission at Week 52.

Table AMBU.5.33. Clinical Remission at Week 52 (NRI; mITT Population)

	≤20 kg 50 mg Miri SC (N = 1)	>20 kg and ≤40 kg 100 mg Miri SC (N = 8)	>40 kg 200 mg Miri SC (N = 9)	≤20 kg 10 mg/kg Miri IV/ 50 mg Miri SC non-responder (N = 1)	>20 kg and ≤40 kg 10 mg/kg Miri IV/ 100 mg Miri SC non-responder (N = 1)	>40 kg 300 mg Miri IV/ 200 mg Miri SC non-responder (N = 6)	Total (N = 26)
Response, n (%)	0 (0.0)	5 (62.5)	5 (55.6)	0 (0.0)	0 (0.0)	0 (0.0)	10 (38.5)
95% CI[a]	(0.0, 79.3)	(30.6, 86.3)	(26.7, 81.1)	(0.0, 79.3)	(0.0, 79.3)	(0.0, 39.0)	(22.4, 57.5)

Abbreviations: CI = confidence interval; IV = intravenous; Miri = mirikizumab; mITT = modified intent-to-treat; N = number of participants in the mITT Population; n = number of participants within each specific category; NRI = nonresponder imputation; SC = subcutaneous.

[a] Response confidence intervals are constructed using Wilson method, without continuity correction.

Source: Table AMBU.8.55

Clinical Remission by Biologic Failed and Biologic Not Failed Subgroups

A total of 29.4% of participants among the biologic failed subgroup and 55.6% of participants among the biologic not failed subgroup achieved clinical remission at Week 52

Table AMBU.5.34. Clinical Remission at Week 52 by Subgroup (NRI; mITT Population)

	≤20 kg 50 mg Miri SC (N = 1)	>20 kg and ≤40 kg 100 mg Miri SC (N = 8)	>40 kg 200 mg Miri SC (N = 9)	≤20 kg 10 mg/kg Miri IV/ 50 mg Miri SC non-responder (N = 1)	>20 kg and ≤40 kg 10 mg/kg Miri IV/ 100 mg Miri SC non-responder (N = 1)	>40 kg 300 mg Miri IV/ 200 mg Miri SC non-responder (N = 6)	Total (N = 26)
Failed (Ns)	**1**	**5**	**5**	**1**	**0**	**5**	**17**
Response, n (%)[a]	0 (0.0)	3 (60.0)	2 (40.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (29.4)
95% CI[b]	(0.0, 79.3)	(23.1, 88.2)	(11.8, 76.9)	(0.0, 79.3)	(0.0, 0.0)	(0.0, 43.4)	(13.3, 53.1)
Not Failed (Ns)	**0**	**3**	**4**	**0**	**1**	**1**	**9**
Response, n (%)[a]	0 (0.0)	2 (66.7)	3 (75.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (55.6)
95% CI[b]	(0.0, 0.0)	(20.8, 93.9)	(30.1, 95.4)	(0.0, 0.0)	(0.0, 79.3)	(0.0, 79.3)	(26.7, 81.1)

Abbreviations: CI = confidence interval; IV = intravenous; Miri = mirikizumab; mITT = modified intent-to-treat; N = number of participants in the mITT Population; n = number of participants within each specific category; NRI = nonresponder imputation; Ns = number of participants in each subgroup; SC = subcutaneous.

[a] Percentage of response is calculated by n/Ns*100%.

[b] Response confidence intervals are constructed using Wilson method, without continuity correction.

Source: Table AMBU.8.56

Clinical Remission at Week 52 among the Induction Clinical Remitters

Participants who achieved clinical remission at Week 12 were defined as induction clinical remitters. The NRI analysis showed a total of 7 (70.0%) participants (induction clinical remitters [n=10]) achieved clinical remission at Week 52.

Table AMBU.5.35. Clinical Remission at Week 52 (NRI; mITT Population Induction Clinical Remitters)

	≤20 kg 50 mg Miri SC (N = 0)	>20 kg and ≤40 kg 100 mg Miri SC (N = 4)	>40 kg 200 mg Miri SC (N = 6)	Total (N = 10)
Response, n (%)	N/A	2 (50.0)	5 (83.3)	7 (70.0)
95% CI[a]	N/A	(15.0, 85.0)	(43.6, 97.0)	(39.7, 89.2)

Abbreviations: CI = confidence interval; Miri = mirikizumab; mITT = modified intent-to-treat; N = number of participants in the mITT Population; n = number of participants within each specific category; NRI = nonresponder imputation; SC = subcutaneous.

Note: N/A denotes there were no participants assigned to the corresponding dose group.

[a] Response confidence intervals are constructed using Wilson method, without continuity correction.

Source: Table AMBU.8.57

Clinical Remission at Week 52 among the Induction Clinical Remitters by Biologic Failed and Biologic Not Failed Subgroups

Among the Induction Clinical Remitters (n=10), a total of 60.0% of participants among the biologic failed subgroup and 80.0% of participants among the biologic not failed subgroup achieved clinical remission at Week 52.

Table AMBU.5.36. Clinical Remission at Week 52 by Biologic Failed and Biologic Not Failed Subgroups (NRI; mITT Population Induction Clinical Remitters)

	≤20 kg 50 mg Miri SC (N = 0)	>20 kg and ≤40 kg 100 mg Miri SC (N = 4)	>40 kg 200 mg Miri SC (N = 6)	Total (N = 10)
Failed (Ns)	**0**	**2**	**3**	**5**
Response, n (%)	0 (0.0)	1 (50.0)	2 (66.7)	3 (60.0)
95% CI[a]	(0.0, 0.0)	(9.5, 90.5)	(20.8, 93.9)	(23.1, 88.2)
Not Failed (Ns)	**0**	**2**	**3**	**5**
Response, n (%)	0 (0.0)	1 (50.0)	3 (100.0)	4 (80.0)
95% CI[a]	(0.0, 0.0)	(9.5, 90.5)	(43.9, 100)	(37.6, 96.4)

Abbreviations; CI = confidence interval; Miri = mirikizumab; mITT = modified intent-to-treat; N = number of participants in the analysis population; n = number of participants in the specified category; NRI = nonresponder imputation; Ns = number of participants in each subgroup; SC = subcutaneous.

[a] Percentage of response is calculated by n/Ns*100%.

[b] Response confidence intervals are constructed using Wilson method, without continuity correction.

Source: Table AMBU.8.58

Clinical Remission at Week 52 among the Induction Clinical Responders

The NRI analysis showed a total of 10 (55.6%) participants (induction clinical responders [n=18]) achieved clinical remission at Week 52.

Table AMBU.5.37. Clinical Remission at Week 52 (NRI; mITT Population Induction Clinical Responders)

	≤20 kg 50 mg Miri SC (N = 1)	>20 kg and ≤40 kg 100 mg Miri SC (N = 8)	>40 kg 200 mg Miri SC (N = 9)	Total (N = 18)
Response, n (%)	0 (0.0)	5 (62.5)	5 (55.6)	10 (55.6)
95% CI[a]	(0.0, 79.3)	(30.6, 86.3)	(26.7, 81.1)	(33.7, 75.4)

Abbreviations: CI = confidence interval; Miri = mirikizumab; mITT = modified intent-to-treat; N = number of participants in the analysis population; n = number of participants in the specified category; NRI = nonresponder imputation; Nx = number of participants with non-missing values; SC = subcutaneous.

[a] Response confidence intervals are constructed using Wilson method, without continuity correction.

Source: Table AMBU.8.59

Clinical Remission at Week 52 among the Induction Clinical Responders by Biologic Failed and Biologic Not Failed Subgroups

Among the induction clinical responders (n=18), a total of 45.5% of participants among the biologic failed subgroup and 71.4% of participants among the biologic not failed subgroup achieved clinical remission at Week 52.

Table AMBU.5.38. Clinical Remission at Week 52 by Biologic Failed and Biologic Not Failed Subgroups (NRI; mITT Population Induction Clinical Responders)

	≤20 kg 50 mg Miri SC (N = 1)	>20 kg and ≤40 kg 100 mg Miri SC (N = 8)	>40 kg 200 mg Miri SC (N = 9)	Total (N = 18)
Failed (Ns)	**1**	**5**	**5**	**11**
Response, n (%)[a]	0 (0.0)	3 (60.0)	2 (40.0)	5 (45.5)
95% CI[b]	(0.0, 79.3)	(23.1, 88.2)	(11.8, 76.9)	(21.3, 72.0)
Not Failed (Ns)	**0**	**3**	**4**	**7**
Response, n (%)[a]	0 (0.0)	2 (66.7)	3 (75.0)	5 (71.4)
95% CI[b]	(0.0, 0.0)	(20.8, 93.9)	(30.1, 95.4)	(35.9, 91.8)

Abbreviations: CI = confidence interval; miri = mirikizumab; mITT = modified intent-to-treat; N = number of participants in the analysis population; n = number of participants in the specified category; NRI = nonresponder imputation; Ns = number of participants in each subgroup; SC = subcutaneous.

[a] Percentage of response is calculated by n/Ns*100%.

[b] Response confidence intervals are constructed using Wilson method, without continuity correction.

Source: Table AMBU.8.60

4. Modified Mayo Score (MMS) Clinical Response

The NRI analysis showed a total of 14 (53.8%) participants achieved clinical response at Week 52.

Table AMBU.5.39. Clinical Response at Week 52 (NRI; mITT Population)

	≤20 kg 50 mg Miri SC (N = 1)	>20 kg and ≤40 kg 100 mg Miri SC (N = 8)	>40 kg 200 mg Miri SC (N = 9)	≤20 kg 10 mg/kg Miri IV/ 50 mg Miri SC non-responder (N = 1)	>20 kg and ≤40 kg 10 mg/kg Miri IV/ 100 mg Miri SC non-responder (N = 1)	>40 kg 300 mg miri IV/ 200 mg Miri SC non-responder (N = 6)	Total (N = 26)
Response, n (%)	0 (0.0)	6 (75.0)	8 (88.9)	0 (0.0)	0 (0.0)	0 (0.0)	14 (53.8)
95% CI[a]	(0.0, 79.3)	(40.9, 92.9)	(56.5, 98.0)	(0.0, 79.3)	(0.0, 79.3)	(0.0, 39.0)	(35.5, 71.2)

Abbreviations: CI = confidence interval; IV = intravenous; Miri = mirikizumab; mITT = modified intent-to-treat; N = number of participants in the mITT Population; n = number of participants within each specific category; NRI = nonresponder imputation; Ns = number of participants in each subgroup; SC = subcutaneous.

[a] Response confidence intervals are constructed using Wilson method, without continuity correction.

Source: Table AMBU.8.65

Clinical Response by Biologic Failed and Biologic Not Failed Subgroups

A total of 41.2% of participants among the biologic failed subgroup and 77.8% of participants among the biologic not failed subgroup achieved clinical response at Week 52.

Table AMBU.5.40. Clinical Response at Week 52 by Subgroup (NRI; mITT Population)

	≤20 kg 50 mg Miri SC (N = 1)	>20 kg and ≤40 kg 100 mg Miri SC (N = 8)	>40 kg 200 mg Miri SC (N = 9)	≤20 kg 10 mg/kg Miri IV/ 50 mg Miri SC non-responder (N = 1)	>20 kg and ≤40 kg 10 mg/kg Miri IV/ 100 mg Miri SC non-responder (N = 1)	>40 kg 300 mg Miri IV/ 200 mg Miri SC non-responder (N = 6)	Total (N = 26)
Failed (Ns)	**1**	**5**	**5**	**1**	**0**	**5**	**17**
Response, n (%)[a]	0 (0.0)	3 (60.0)	4 (80.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (41.2)
95% CI[b]	(0.0, 79.3)	(23.1, 88.2)	(37.6, 96.4)	(0.0, 79.3)	(0.0, 0.0)	(0.0, 43.4)	(21.6, 64.0)
Not Failed (Ns)	**0**	**3**	**4**	**0**	**1**	**1**	**9**
Response, n (%)[a]	0 (0.0)	3 (100.0)	4 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (77.8)
95% CI[b]	(0.0, 0.0)	(43.9, 100)	(51.0, 100)	(0.0, 0.0)	(0.0, 79.3)	(0.0, 79.3)	(45.3, 93.7)

Abbreviations: CI = confidence interval; IV = intravenous; Miri = mirikizumab; mITT = modified intent-to-treat; N = number of participants in the mITT Population; n = number of participants within each specific category; NRI = nonresponder imputation; Ns = number of participants in each subgroup; SC = subcutaneous.

[a] Percentage of response is calculated by n/Ns*100%.

[b] Response confidence intervals are constructed using Wilson method, without continuity correction.

Source: Table AMBU.8.66

Clinical Response at Week 52 among Induction Clinical Responders

The NRI analysis showed a total of 14 (77.8%) participants (induction clinical responders [n=18]) achieved clinical response at Week 52.

Table AMBU.5.41. Clinical Response at Week 52 (NRI; mITT Population Induction Clinical Responders)

	≤20 kg 50 mg Miri SC (N = 1)	>20 kg and ≤40 kg 100 mg Miri SC (N = 8)	>40 kg 200 mg Miri SC (N = 9)	Total (N = 18)
Response, n (%)	0 (0.0)	6 (75.0)	8 (88.9)	14 (77.8)
95% CI[a]	(0.0, 79.3)	(40.9, 92.9)	(56.5, 98.0)	(54.8, 91.0)

Abbreviations: CI = confidence interval; Miri = mirikizumab; mITT = modified intent-to-treat; N = number of participants in the analysis population; n = number of participants in the specified category; NRI = nonresponder imputation; Nx = number of participants with non-missing values; SC = subcutaneous.

[a] Response confidence intervals are constructed using Wilson method, without continuity correction.

Source: Table AMBU.8.67

Clinical Response at Week 52 among Induction Clinical Responders by Biologic Failed and Biologic Not Failed Subgroups

Among the induction clinical responders (n=18), a total of 63.6% of participants among the biologic failed subgroup and 100.0% of participants among the biologic not failed subgroup achieved clinical response at Week 52.

Table AMBU.5.42. Clinical Response at Week 52 by Biologic Failed and Biologic Not Failed Subgroups (NRI; mITT Population Induction Clinical Responders)

	≤20 kg 50 mg Miri SC (N = 1)	>20 kg and ≤40kg 100 mg Miri SC (N = 8)	>40 kg 200 mg Miri SC (N = 9)	Total (N = 18)
Failed (Ns)	**1**	**5**	**5**	**11**
Response, n (%)[a]	0 (0.0)	3 (60.0)	4 (80.0)	7 (63.6)
95% CI[b]	(0.0, 79.3)	(23.1, 88.2)	(37.6, 96.4)	(35.4, 84.8)
Not Failed (Ns)	**0**	**3**	**4**	**7**
Response, n (%)[a]	0 (0.0)	3 (100.0)	4 (100.0)	7 (100.0)
95% CI[b]	(0.0, 0.0)	(43.9, 100)	(51.0, 100)	(64.6, 100)

Abbreviations: CI = confidence interval; Miri = mirikizumab; mITT = modified intent-to-treat; N = number of participants in the analysis population; n = number of participants in the specified category; NRI = nonresponder imputation; Ns = number of participants in each subgroup; SC = subcutaneous.

[a] Percentage of response is calculated by n/Ns*100%.

[b] Response confidence intervals are constructed using Wilson method, without continuity correction.

Source: Table AMBU.8.68.

Assessor comments

10 subjects (38.5%) achieved clinical remission on MMS at Week 52. Of the 10 who achieved clinical remission on MMS at Week 12 (induction clinical remitters), 7 achieved clinical remission at week 52. Of the 18 subjects who achieved clinical response on MMS at week 12, 10 subjects (55.6%) achieved clinical remission at Week 52. 14 subjects (53.8%) achieved clinical response on MMS at Week 52.

5. Corticosteroid-Free Remission at Week 52

Corticosteroid-Free Remission

The NRI analysis showed a total of 10 (38.5%) participants achieved corticosteroid-free clinical remission at Week 52. Corticosteroid-free remission is defined as clinical remission at Week 52, and no corticosteroid use or UC-related surgery for ≥12 weeks prior to Week 52.

Table AMBU.5.43. Corticosteroid-Free Remission at Week 52 (NRI; mITT Population)

	≤20 kg 50 mg Miri SC (N = 1)	>20 kg and ≤40 kg 100 mg Miri SC (N = 8)	>40 kg 200 mg Miri SC (N = 9)	≤20 kg 10 mg/kg Miri IV/ 50 mg Miri SC non-responder (N = 1)	>20 kg and ≤40 kg 10 mg/kg Miri IV/ 100 mg Miri SC non-responder (N = 1)	>40 kg 300 mg Miri IV/ 200 mg Miri SC non-responder (N = 6)	Total (N = 26)
Response, n (%)	0 (0.0)	5 (62.5)	5 (55.6)	0 (0.0)	0 (0.0)	0 (0.0)	10 (38.5)
95% CI[a]	(0.0, 79.3)	(30.6, 86.3)	(26.7, 81.1)	(0.0, 79.3)	(0.0, 79.3)	(0.0, 39.0)	(22.4, 57.5)

Abbreviations: CI = confidence interval; IV = intravenous; Miri = mirikizumab; mITT = modified intent-to-treat; N = number of participants in the analysis population; n = number of participants in the specified category; NRI = nonresponder imputation; Ns = number of participants in each subgroup; SC = subcutaneous.

[a] Response confidence intervals are constructed using Wilson method, without continuity correction.

Source: Table AMBU.8.69

Corticosteroid-Free Remission by Biologic Failed and Biologic Not Failed Subgroups

A total of 29.4% of participants among the biologic failed subgroup and 55.6% of participants among the biologic not failed subgroup achieved corticosteroid-free clinical remission at Week 52.

Table AMBU.5.44. Corticosteroid-Free Remission at Week 52 by Biologic Failed and Biologic Not Failed Subgroups (NRI; mITT Population)

	≤20 kg 50 mg Miri SC (N = 1)	>20 kg and ≤40 kg 100 mg Miri SC (N = 8)	>40 kg 200 mg Miri SC (N = 9)	≤20 kg 10 mg/kg Miri IV/ 50 mg Miri SC non-responder (N = 1)	>20kg and ≤40 kg 10 mg/kg Miri IV/ 100 mg Miri SC non-responder (N = 1)	>40 kg 300 mg Miri IV/ 200 mg Miri SC non-responder (N = 6)	Total (N = 26)
Failed (Ns)	**1**	**5**	**5**	**1**	**0**	**5**	**17**
Response, n (%)[a]	0 (0.0)	3 (60.0)	2 (40.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (29.4)
95% CI[b]	(0.0, 79.3)	(23.1, 88.2)	(11.8, 76.9)	(0.0, 79.3)	(0.0, 0.0)	(0.0, 43.4)	(13.3, 53.1)
Not Failed (Ns)	**0**	**3**	**4**	**0**	**1**	**1**	**9**
Response, n (%)[a]	0 (0.0)	2 (66.7)	3 (75.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (55.6)
95% CI[b]	(0.0, 0.0)	(20.8, 93.9)	(30.1, 95.4)	(0.0, 0.0)	(0.0, 79.3)	(0.0, 79.3)	(26.7, 81.1)

Abbreviations: CI = confidence interval; IV = intravenous; Miri = mirikizumab; mITT = modified intent-to-treat; N = number of participants in the analysis population; n = number of participants in the specified category; NRI = nonresponder imputation; Ns = number of participants in each subgroup; SC = subcutaneous.

[a] Percentage of response is calculated by n/Ns*100%.

[b] Response confidence intervals are constructed using Wilson method, without continuity correction.

Source: Table AMBU.8.70

Assessor comments

14 subjects (53.8%) achieved clinical response on MMS at Week 52. Of the 18 induction clinical responders on MMS, 14 (77.8%) achieved clinical response on MMS at Week 52.

10 subjects (38.5%) achieved corticosteroid-free clinical remission at Week 52.

6. Endoscopic Remission

The NRI analysis showed a total of 10 (38.5%) participants achieved endoscopic remission at Week 52.

Table AMBU.5.45. Endoscopic Remission at Week 52 (NRI; mITT Population)

	≤20 kg 50 mg Miri SC (N = 1)	>20 kg and ≤40 kg 100 mg Miri SC (N = 8)	>40 kg 200 mg Miri SC (N = 9)	≤20 kg 10 mg/kg Miri IV/ 50 mg Miri SC non-responder (N = 1)	>20 kg and ≤40 kg 10 mg/kg Miri IV/ 100 mg Miri SC non-responder (N = 1)	>40 kg 300 mg Miri IV/ 200 mg Miri SC non-responder (N = 6)	Total (N = 26)
Response, n (%)	0 (0.0)	5 (62.5)	5 (55.6)	0 (0.0)	0 (0.0)	0 (0.0)	10 (38.5)
95% CI[a]	(0.0, 79.3)	(30.6, 86.3)	(26.7, 81.1)	(0.0, 79.3)	(0.0, 79.3)	(0.0, 39.0)	(22.4, 57.5)

Abbreviations: CI = confidence interval; IV = intravenous; Miri = mirikizumab; mITT = modified intent-to-treat; N = number of participants in the analysis population; n = number of participants in the specified category; NRI = nonresponder imputation; SC = subcutaneous.

[a] Response confidence intervals are constructed using Wilson method, without continuity correction.

Source: Table AMBU.8.71

Endoscopic Remission by Biologic Failed and Biologic Not Failed Subgroups

A total of 29.4% of participants among the biologic failed subgroup and 55.6% of participants among the biologic not failed subgroup achieved endoscopic remission at Week 52.

Table AMBU.5.46. Endoscopic Remission at Week 52 by Biologic Failed and Biologic Not Failed Subgroups (NRI; mITT Population)

	≤20 kg 50 mg Miri SC (N = 1)	>20 kg and ≤40 kg 100 mg Miri SC (N = 8)	>40 kg 200 mg Miri SC (N = 9)	≤20 kg 10 mg/kg Miri IV/ 50 mg Miri SC non-responder (N = 1)	>20 kg and ≤40 kg 10 mg/kg Miri IV/ 100 mg Miri SC non-responder (N = 1)	>40 kg 300 mg Miri IV/ 200 mg Miri SC non-responder (N = 6)	Total (N = 26)
Failed (Ns)	1	5	5	1	0	5	17
Response, n (%)[a]	0 (0.0)	3 (60.0)	2 (40.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (29.4)
95% CI[b]	(0.0, 79.3)	(23.1, 88.2)	(11.8, 76.9)	(0.0, 79.3)	(0.0, 0.0)	(0.0, 43.4)	(13.3, 53.1)
Not Failed (Ns)	0	3	4	0	1	1	9
Response, n (%)[a]	0 (0.0)	2 (66.7)	3 (75.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (55.6)
95% CI[b]	(0.0, 0.0)	(20.8, 93.9)	(30.1, 95.4)	(0.0, 0.0)	(0.0, 79.3)	(0.0, 79.3)	(26.7, 81.1)

Abbreviations: CI = confidence interval; IV = intravenous; Miri = mirikizumab; mITT = modified intent-to-treat; N = number of participants in the analysis population; n = number of participants in the specified category; NRI = nonresponder imputation; Ns = number of participants in each subgroup; SC = subcutaneous.

[a] Percentage of response is calculated by n/Ns*100%.

[b] Response confidence intervals are constructed using Wilson method, without continuity correction.

Source: Table AMBU.8.72

Endoscopic Remission at Week 52 among the Induction Endoscopic Remitters

The NRI analysis showed a total of 9 (64.3%) participants (induction endoscopic remitters) achieved endoscopic remission at Week 52

Table AMBU.5.47. Endoscopic Remission at Week 52 (NRI; mITT Population Induction Endoscopic Remitters)

	≤20 kg 50 mg Miri SC (N = 1)	>20 kg and ≤40 kg 100 mg Miri SC (N = 6)	>40 kg 200 mg Miri SC (N = 6)	≤20 kg 10 mg/kg Miri IV/ 50 mg Miri SC non-responder (N = 0)	>20 kg and ≤40 kg 10 mg/kg Miri IV/ 100 mg Miri SC non-responder (N = 0)	>40 kg 300 mg Miri IV/ 200 mg Miri SC non-responder (N = 1)	Total (N = 14)
Response, n (%)	0 (0.0)	4 (66.7)	5 (83.3)	N/A	N/A	0 (0.0)	9 (64.3)
95% CI[a]	(0.0, 79.3)	(30.0, 90.3)	(43.6, 97.0)	N/A	N/A	(0.0, 79.3)	(38.8, 83.7)

Abbreviations: CI = confidence interval; IV = intravenous; Miri = mirikizumab; mITT = modified intent-to-treat; N = number of participants in the analysis population; n = number of participants in the specified category; N/A = not applicable; NRI = nonresponder imputation; SC = subcutaneous.

[a] Response confidence intervals are constructed using Wilson method, without continuity correction.

Source: Table AMBU.8.73

Endoscopic Remission at Week 52 among the Induction Endoscopic Remitters by Biologic Failed and Biologic Not Failed Subgroups

Among the induction endoscopic remitters (n=14), a total of 55.6% of participants among the biologic failed subgroup and 80.0% of participants among the biologic not failed subgroup achieved endoscopic remission at Week 52.

Table AMBU.5.48. Endoscopic Remission at Week 52 by Biologic Failed and Biologic Not Failed Subgroups (NRI; mITT Population - Induction Endoscopic Remitters)

	≤20 kg 50 mg Miri SC (N = 1)	>20 kg and ≤40 kg 100 mg Miri SC (N = 6)	>40 kg 200 mg Miri SC (N = 6)	≤20 kg 10 mg/kg Miri IV/ 50 mg Miri SC non-responder (N = 0)	>20 kg and ≤40 kg 10 mg/kg Miri IV/ 100 mg Miri SC non-responder (N = 0)	>40 kg 300 mg Miri IV/ 200 mg Miri SC non-responder (N = 1)	Total (N = 14)
Failed (Ns)	**1**	**4**	**3**	**0**	**0**	**1**	**9**
Response, n (%)[a]	0 (0.0)	3 (75.0)	2 (66.7)	0 (0.0)	0 (0.0)	0 (0.0)	5 (55.6)
95% CI[b]	(0.0, 79.3)	(30.1, 95.4)	(20.8, 93.9)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 79.3)	(26.7, 81.1)
Not Failed (Ns)	**0**	**2**	**3**	**0**	**0**	**0**	**5**
Response, n (%)[a]	0 (0.0)	1 (50.0)	3 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (80.0)
95% CI[b]	(0.0, 0.0)	(9.5, 90.5)	(43.9, 100)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)	(37.6, 96.4)

Abbreviations: CI = confidence interval; IV = intravenous; Miri = mirikizumab; mITT = modified intent-to-treat; N = number of participants in the analysis population; n = number of participants in the specified category; NRI = nonresponder imputation; Ns = number of participants in each subgroup; SC = subcutaneous.

[a] Percentage of response is calculated by n/Ns*100%.

[b] Response confidence intervals are constructed using Wilson method, without continuity correction.

Source: Table AMBU.8.74

Endoscopic Remission at Week 52 among the Induction Clinical Responders

The NRI analysis showed a total of 10 (55.6%) participants (induction clinical responders) achieved endoscopic remission at Week 52.

Table AMBU.5.49. Endoscopic Remission at Week 52 (NRI; mITT Population Induction Clinical Responders)

	≤20 kg 50 mg Miri SC (N = 1)	>20 kg and ≤40 kg 100 mg Miri SC (N = 8)	>40 kg 200 mg Miri SC (N = 9)	Total (N = 18)
Response, n (%)	0 (0.0)	5 (62.5)	5 (55.6)	10 (55.6)
95% CI[a]	(0.0, 79.3)	(30.6, 86.3)	(26.7, 81.1)	(33.7, 75.4)

Abbreviations: CI = confidence interval; IV = intravenous; Miri = mirikizumab; mITT = modified intent-to-treat; N = number of participants in the analysis population; n = number of participants in the specified category; NRI = nonresponder imputation; SC = subcutaneous.

[a] Response confidence intervals are constructed using Wilson method, without continuity correction.

Source: Table AMBU.8.75

Endoscopic Remission at Week 52 among the Induction Clinical Responders by Biologic Failed and Biologic Not Failed Subgroups

Among the induction clinical responders (n=18), a total of 45.5% of participants among the biologic failed subgroup and 71.4% of participants among the biologic not failed subgroup achieved endoscopic remission at Week 52.

Table AMBU.5.50. Endoscopic Remission at Week 52 by Biologic Failed and Biologic Not Failed Subgroups (NRI; mITT Population - Induction Clinical Responders)

	≤20 kg 50 mg Miri SC (N = 1)	>20 kg and ≤40 kg 100 mg Miri SC (N = 8)	>40 kg 200 mg Miri SC (N = 9)	Total (N = 18)
Failed (Ns)	**1**	**5**	**5**	**11**
Response, n (%)[a]	0 (0.0)	3 (60.0)	2 (40.0)	5 (45.5)
95% CI[b]	(0.0, 79.3)	(23.1, 88.2)	(11.8, 76.9)	(21.3, 72.0)
Not Failed (Ns)	**0**	**3**	**4**	**7**
Response, n (%)[a]	0 (0.0)	2 (66.7)	3 (75.0)	5 (71.4)
95% CI[b]	(0.0, 0.0)	(20.8, 93.9)	(30.1, 95.4)	(35.9, 91.8)

Abbreviations: CI = confidence interval; Miri = mirikizumab; mITT = modified intent-to-treat; N = number of participants in the analysis population; n = number of participants in the specified category; NRI = nonresponder imputation; Ns = number of participants in each subgroup; SC = subcutaneous.

[a] Percentage of response is calculated by n/Ns*100%.

[b] Response confidence intervals are constructed using Wilson method, without continuity correction.

Source: Table AMBU.8.76

7. Endoscopic Subscore = 0

The NRI analysis showed a total of 6 (23.1%) participants achieved endoscopic subscore of 0 at Week 52.

Table AMBU.5.51. Endoscopic Subscore 0 at Week 52 (NRI; mITT Population)

	≤20 kg 50 mg Miri SC (N = 1)	>20 kg and ≤40 kg 100 mg Miri SC (N = 8)	>40 kg 200 mg Miri SC (N = 9)	≤20 kg 10 mg/kg Miri IV/ 50 mg Miri SC non-responder (N = 1)	>20 kg and ≤40 kg 10 mg/kg Miri IV/ 100 mg Miri SC non-responder (N = 1)	>40 kg 300 mg Miri IV/ 200 mg Miri SC non-responder (N = 6)	Total (N = 26)
Response, n (%)	0 (0.0)	4 (50.0)	2 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	6 (23.1)
95% CI[a]	(0.0, 79.3)	(21.5, 78.5)	(6.3, 54.7)	(0.0, 79.3)	(0.0, 79.3)	(0.0, 39.0)	(11.0, 42.1)

Abbreviations: CI = confidence interval; Miri = mirikizumab; mITT = modified intent-to-treat; N = number of participants in the analysis population; n = number of participants in the specified category; NRI = nonresponder imputation; SC = subcutaneous.

a Response confidence intervals are constructed using Wilson method, without continuity correction.

Source: Table AMBU.8.77

Assessor comments

10 subjects (38.5%) achieved endoscopic remission at Week 52. Of the induction endoscopic remitters, 9 (64.3%) subjects achieved endoscopic remission at Week 52. Of the induction clinical responders, 10 subjects (55.6%) achieved endoscopic remission at week 52. 6 subjects (23.1%) achieved endoscopic subscore of 0 at Week 52.

8. Symptomatic Remission by visit

Symptomatic Remission at Week 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52

Proportion of participants in symptomatic remission at applicable study visits increased from baseline at all applicable visits during the maintenance period. The NRI analysis showed that a total of 14 (53.8%) participants were in symptomatic remission at Week 20 and the proportion of participants achieving symptomatic remission remained relatively stable at all the following applicable visits. A total of 12 (46.2%) participants were in symptomatic remission at Week 52.

Symptomatic Remission at Week 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52 by Biologic Failed and Biologic Not Failed Subgroups

Proportion of participants among the biologic failed subgroup in symptomatic remission increased from baseline at all applicable visits and remained relatively stable from Week 16 until Week 52 (n=6 [35.3%]). The proportion of participants among the biologic not failed subgroup in symptomatic remission increased from baseline at all applicable visits and remained relatively stable from Week 16 until Week 52 (n=6 [66.7%]).

9. Histologic- Endoscopic Mucosal Improvement

Nine (34.6%) participants achieved histologic-endoscopic mucosal improvement at Week 52.

Histologic-Endoscopic Mucosal Improvement by Biologic Failed and Biologic Not Failed Subgroups

Five (29.4%) participants among the biologic failed subgroup and 4 (44.4%) participants in the not failed subgroup achieved histologic-endoscopic mucosal improvement at Week 52.

10. Histologic- Endoscopic Mucosal Remission

The NRI analysis showed a total of 9 (34.6%) participants achieved histologic-endoscopic mucosal remission at Week 52.

Histologic-Endoscopic Mucosal Remission by Biologic Failed and Biologic Not Failed Subgroups

A total of 29.4% of participants among the biologic failed subgroup and 44.4% of participants among the biologic not failed subgroup achieved histologic-endoscopic mucosal remission at Week 52.

Assessor comments

The highest proportion of subjects in symptomatic remission was at Week 20, 14 subjects (53.8%). A total of 12 subjects (46.2%) were in symptomatic remission at Week 52.

Nine subjects (34.6%) achieved histologic endoscopic mucosal improvement and nine subjects (34.6%) achieved histologic endoscopic mucosal remission.

11. Improvement in patient-reported outcome endpoints

Urgency NRS score

Across all age groups, participants had a reduction (improvement) from baseline in Urgency NRS scores at Week 52.

Table AMBU.5.59. Urgency NRS Score at Week 52 (Change from baseline) by Age Group (mITT Population)

	≤20 kg 50 mg Miri SC (N = 1)	>20 kg and ≤40 kg 100 mg Miri SC (N = 8)	>40 kg 200 mg Miri SC (N = 9)	≤20 kg 10 mg/kg Miri IV/ 50 mg Miri SC non-responder (N = 1)	>20 kg and ≤40 kg 10 mg/kg Miri IV/ 100 mg Miri SC non-responder (N = 1)	>40 kg 300 mg Miri IV/ 200 mg Miri SC non-responder (N = 6)	Total (N = 26)
Change from Baseline (mBOCF) *Nx* *Mean (SD)*							
2 to <8 years	1 -1	1 -7	N/A	1 -1	N/A	N/A	3 -3 (3.5)
8 to <12 years	N/A	3 -2 (1.5)	N/A	N/A	N/A	N/A	3 -2 (1.5)
12 to <18 years	N/A	3 -5 (2.3)	8 -4 (2.1)	N/A	6 -3	1 -1 (1.9)	18 -3 (2.5)

Abbreviations: mBOCF = modified baseline carried forward; CI = confidence interval; IV = intravenous; Miri = mirikizumab; mITT = modified intent-to-treat; N = number of participants in the analysis population; n = number of participants in the specified category; Nx = number of patients in specified age category and treatment group; SC = subcutaneous; SD = standard deviation.
Note: N/A denotes there were no participants assigned to the corresponding dose group.
Source: Table AMBU.8.85

Change from baseline in 7-day average of Abdominal Pain (in past 24 hours) NRS score at Week 52

Across all age groups, participants had a reduction (improvement) from baseline in Abdominal Pain NRS scores at Week 52.

Table AMBU.5.60. Abdominal Pain NRS Score at Week 52 (Change from baseline) by Age Group (mITT Population)

	≤20 kg 50 mg Miri SC (N = 1)	>20 kg and ≤40 kg 100 mg Miri SC (N = 8)	>40 kg 200 mg Miri SC (N = 9)	≤20 kg 10 mg/kg Miri IV/ 50 mg Miri SC non-responder (N = 1)	>20 kg and ≤40 kg 10 mg/kg Miri IV/ 100 mg Miri SC non-responder (N = 1)	>40 kg 300 mg Miri IV/200 mg Miri SC non-responder (N = 6)	Total (N = 26)
Change from Baseline (mBOCF) *Nx* *Mean (SD)*							
2 to <8 years	1 -2	1 -6	N/A	N/A	N/A	N/A	2 -3 (3.1)
8 to <12 years	N/A	3 -2 (1.0)	N/A	N/A	N/A	N/A	3 -2 (1.0)
12 to <18 years	N/A	3 -5 (3.1)	8 -4 (2.4)	N/A	1 -3	6 0	18 -3 (3.0)

Abbreviations: mBOCF = modified baseline carried forward; CI = confidence interval; IV = intravenous; Miri = mirikizumab; mITT = modified intent-to-treat; N = number of participants in the analysis population; n = number of participants in the specified category; NRI = nonresponder imputation; Nx = number of patients in specified age category and treatment group; SC = subcutaneous; SD = standard deviation.
Note: N/A denotes there were no participants assigned to the corresponding dose group.
Source: Table AMBU.8.86

Assessor comments

Across all age groups, subjects had a reduction (improvement) from baseline in mean Urgency and Abdominal pain NRS scores at Week 52.

Additional Efficacy Analyses

Extended Induction Treatment in Week 12 Nonresponders

Eight participants were non-responders at Week 12 and entered extended induction treatment, and of these 8 participants, 5 (62.5%) later discontinued the study.

Table AMBU.5.62. Week 52 Efficacy Endpoint Data in Participants who received Extended Induction Treatment at Week 12 (NRI; mITT Population)

Endpoint	≤20 kg 10 mg/kg Miri IV/50 mg Miri SC non-responder (N =1)	>20 kg and ≤40 kg 10 mg/kg Miri IV/ 100 mg Miri SC non-responder (N =1)	>40 kg 300 mg Miri IV/200 mg Miri SC non-responder (N =6)	Total (N = 8)
MMS Clinical Response	0	1 (100%)	2 (33.3%)	3 (37.5%)
MMS Clinical Remission	0	0	0	0
MMS Alternate Clinical Remission	0	0	0	0
Endoscopic Remission	0	1 (100%)	1 (16.7%)	2 (25%)
ES = 0	0	0	0	0
PUCAI Response	0	1 (100%)	2 (33.3%)	3 (37.5%)
PUCAI Remission	0	1 (100%)	2 (33.3%)	3 (37.5%)
Symptomatic Remission	0	0	0	0
Corticosteroid-Free Remission	0	0	0	0
Histologic-Endoscopic Improvement	0	0	1 (16.7%)	1 (12.5%)
Histologic-Endoscopic Remission	0	0	1 (16.7%)	1 (12.5%)

Abbreviations: ES = Endoscopic subscore; IV = intravenous; Miri = mirikizumab; mITT = modified intent-to-treat; MMS = modified Mayo score; N = number of participants in the analysis population; n = number of participants in the specified category; NRI = nonresponder imputation; PUCAI = Pediatric Ulcerative Colitis Activity Index; SC = subcutaneous.

Note: Missing data are imputed as non-responder at Week 52.

n represents number of participants achieved efficacy endpoint at Week 52, among week 12 non-responders.

% represents: proportion which is calculated under each treatment group.

Source: Table AMBU.8.89

Assessor comments

8 subjects were non-responders at Week 12 and entered extended induction treatment. At Week 52, 3 of these had MMS clinical response (37.5%), 2 (25%) had endoscopic remission and 3(37.5%) had PUCAI response and 3 (37.5%) PUCAI remission, suggesting a role in some subjects for extended induction.

Loss of Response in Maintenance

During the maintenance period, 3 participants met the loss of response criteria and received 3 IV doses of mirikizumab once a month based on their current weight. All 3 participants completed the study and continued into the long-term extension study.

Exploratory endpoints

Fecal Calprotectin

Table AMBU.5.20. Fecal calprotectin at Week 12 (Change from baseline; mBOCF) (mITT Population)

	≤40 kg 5 mg/kg Miri Q4W (N = 10)	≤40 kg 10 mg/kg Miri Q4W (N = 5)	>40 kg 300 mg Miri Q4W (N = 11)	Total (N = 26)
Number of participants	7	4	7	18
Mean (SD)	-3885.86 (6133.19)	-1549.75 (1229.22)	-4147.57 (6987.15)	-3468.50 (5648.14)

Abbreviations: mBOCF = modified baseline carried forward; miri = mirikizumab; mITT = modified intent-to-treat N = number of participants in the analysis population; Q4W = every 4 weeks; SD = standard deviation.
Source: Table AMBU.8.39

Table AMBU.5.63. Fecal calprotectin at Week 52 (Change from baseline; mBOCF) (mITT Population)

	≤20 kg 50 mg Miri SC (N = 1)	>20 kg and ≤40 kg 100 mg Miri SC (N = 8)	>40 kg 200 mg Miri SC (N = 9)	≤20 kg 10 mg/kg Miri IV/ 50 mg Miri SC non-responder (N = 1)	>20 kg and ≤40 kg 10 mg/kg Miri IV/ 100 mg Miri SC non-responder (N = 1)	>40 kg 300 mg Miri IV/ 200 mg Miri SC non-responder (N = 6)	Total (N = 26)
Number of participants	0	8	9	1	1	5	24
Mean (SD)	N/A	-3939.50 (5437.16)	-4177.22 (5706.83)	1367.00 (-)	-8281.00 (-)	-1343.20 (2320.13)	-3447.54 (4953.81)

Abbreviations: IV = intravenous; mBOCF = modified baseline carried forward; miri = mirikizumab; mITT = modified intent-to-treat; N = number of participants in the analysis population; N/A = not applicable; SC = subcutaneous; SD = standard deviation.
Source: Table AMBU.8.90

CRP

Table AMBU.5.21. CRP at Week 12 (Change from Baseline; mBOCF) (mITT Population)

	≤40 kg 5 mg/kg Miri Q4W (N = 10)	≤40 kg 10 mg/kg Miri Q4W (N = 5)	>40 kg 300 mg Miri Q4W (N = 11)	Total (N = 26)
Number of participants	10	5	11	26
Mean (SD)	-2.13 (4.86)	2.35 (17.01)	-3.10 (3.59)	-1.68 (8.01)

Abbreviations: miri = mirikizumab; mBOCF = modified baseline carried forward; N = number of participants in the analysis population; Q4W = every 4 weeks; SD = standard deviation; mITT = modified intent-to-treat
Source: Table AMBU.8.40

Table AMBU.5.64. CRP at Week 52 (Change from baseline; mBOCF) (mITT Population)

	≤20 kg 50 mg Miri SC (N = 1)	>20 kg and ≤40 kg 100 mg Miri SC (N = 8)	>40 kg 200 mg Miri SC (N = 9)	≤20 kg 10 mg/kg Miri IV/ 50 mg Miri SC non-responder (N = 1)	>20 kg and ≤40 kg 10 mg/kg Miri IV/ 100 mg Miri SC non-responder (N = 1)	>40 kg 300 mg Miri IV/ 200 mg Miri SC non-responder (N = 6)	Total (N = 26)
Number of participants	1	8	9	1	1	6	26
Mean (SD)	0.00 (-)	-1.32 (2.30)	-4.98 (7.63)	0.01 (-)	0.42 (-)	-2.35 (2.93)	-2.65 (5.03)

Proportion of patients who had UC related emergency room visits or hospitalizations

One participant reported an UC related emergency room visit or hospitalization during the maintenance period identified as the SAE Colitis ulcerative event.

Proportion of patients who had UC related surgeries

None of the participants had any UC related surgery during the trial.

Additional Exploratory endpoints

A number of additional exploratory endpoints were assessed but do not impact on the overall study results.

Safety results

An overview of AEs reported during the induction period is summarized in Table AMBU.8.101 below. There were 18 (69.2%) participants in the induction period who reported at least 1 TEAE. TEAEs reported were mild or moderate in severity. No participant discontinued from study treatment due to AEs during the induction period.

Table AMBU.8.101. Overview of Adverse Events
Safety Population
16T-MC-AMBU – Induction Period

Category	<=40 kg 5mg/kg miri IV (N=10) n (%)	<=40 kg 10mg/kg miri IV (N=5) n (%)	>40 kg 300mg miri IV (N=11) n (%)	Total (N=26) n (%)
Treatment-emergent adverse event (TEAE)	8 (80.0)	2 (40.0)	8 (72.7)	18 (69.2)
TEAE by severity *a				
Mild	5 (50.0)	2 (40.0)	7 (63.6)	14 (53.8)
Moderate	3 (30.0)	0	1 (9.1)	4 (15.4)
Severe	0	0	0	0
Death	0	0	0	0
Serious adverse event	0	0	0	0
Discontinuation from study treatment due to adverse event (including death)	0	0	0	0

Abbreviations:miri = mirikizumab; IV = intravenous; TEAE = treatment emergent adverse event; N = number of subjects in the analysis population; n = number of subjects in the specified category.
Patients with multiple occurrences of these categories are counted once for each category. Patients may be counted in more than one category. Deaths are also included as serious adverse events and discontinuations due to adverse events.

An overview of AEs reported for the combined induction and maintenance periods is presented in Table AMBU.5.66. There were 25 (96.2%) participants who reported at least 1 TEAE. Most TEAEs were mild or moderate in severity. 1 (3.8%) participant discontinued from study treatment due to AEs during the maintenance period.

No deaths were reported during the study.

Table AMBU.5.66. Overview of Adverse Events for the Combined Induction and Maintenance Periods

Category	≤40 kg 5 mg/kg Miri IV (N = 10) n (%)	≤40 kg 10 mg/kg Miri IV (N = 5) n (%)	>40 kg 300 mg Miri IV (N = 11) n (%)	Total (N = 26) n (%)
All TEAEs	9 (90.0)	5 (100.0)	11 (100.0)	25 (96.2)
TEAE by severity[a]				
Mild	4 (40.0)	1 (20.0)	8 (72.7)	13 (50.0)
Moderate	5 (50.0)	4 (80.0)	2 (18.2)	11 (42.3)
Severe	0	0	1 (9.1)	1 (3.8)
Death	0	0	0	0
SAE	0	2 (40.0)	1 (9.1)	3 (11.5)
AEs leading to discontinuation from study treatment	0	0	1 (9.1)	1 (3.8)

Abbreviations: AE = adverse event; IV = intravenous; Miri = mirikizumab; N = number of participants in the analysis population; n = number of participants in the specified category; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] Participants with multiple occurrences of the same event are counted under the highest severity.

Source: Table AMBU.8.102

Frequency of all TEAEs

Headache (15.4% [n=4]) and Pyrexia (11.5% [n=3]) were the most frequently reported TEAEs in the induction period. No severe TEAEs were reported.

For the combined induction and maintenance periods, the most frequently reported TEAEs were:

- COVID-19 (23.1% [n=6])
- Injection site pain (23.1% [n=6])
- Headache (19.2% [n=5])
- Pyrexia (15.4% [n=4])
- Rash (15.4% [n=4])
- Viral upper respiratory infection (15.4% [n=4])

The frequency of participants with at least 1 severe TEAE was 3.8% (n=1; Abdominal Pain Upper).

Frequency of TEAEs by SOC and PT

TEAEs reported in mirikizumab treated participants by SOC and PT for the combined induction and maintenance periods are summarised below. For the combined periods, AEs were most frequently reported in the Infections and infestations SOC, General disorders and administration site conditions SOC, and the Gastrointestinal disorders SOC.

Table AMBU.5.67. Summary of TEAEs Reported in the Infections and infestations SOC, General Disorders and Administration Site Conditions SOC, and the Gastrointestinal disorders SOC for the Combined Induction and Maintenance Periods

System Organ Class *Preferred Term*	≤40 kg 5 mg/kg Miri IV (N = 10) n (%)	≤40 kg 10 mg/kg Miri IV (N = 5) n (%)	>40 kg 300 mg Miri IV (N = 11) n (%)	Total (N = 26) n (%)
Infections and infestations	8 (80.0)	3 (60.0)	6 (54.5)	17 (65.4)
COVID-19	2 (20.0)	2 (40.0)	2 (18.2)	6 (23.1)
Viral upper respiratory tract infection	2 (20.0)	1 (20.0)	1 (9.1)	4 (15.4)
Asymptomatic COVID-19	1 (10.0)	0	2 (18.2)	3 (11.5)
Upper respiratory tract infection	1 (10.0)	0	1 (9.1)	2 (7.7)
Gastroenteritis	1 (10.0)	0	0	1 (3.8)
General disorders and administration site conditions	5 (50.0)	3 (60.0)	6 (54.5)	14 (53.8)
Injection site pain	2 (20.0)	1 (20.0)	3 (27.3)	6 (23.1)
Pyrexia	2 (20.0)	0	2 (18.2)	4 (15.4)
Fatigue	1 (10.0)	0	1 (9.1)	2 (7.7)
Injection site erythema	1 (10.0)	1 (20.0)	0	2 (7.7)
Injection site pruritus	1 (10.0)	1 (20.0)	0	2 (7.7)
Gastrointestinal disorders	5 (50.0)	2 (40.0)	5 (45.5)	12 (46.2)
Nausea	1 (10.0)	0	2 (18.2)	3 (11.5)
Vomiting	2 (20.0)	0	1 (9.1)	3 (11.5)
Abdominal pain upper	1 (10.0)	0	1 (9.1)	2 (7.7)
Constipation	1 (10.0)	0	1 (9.1)	2 (7.7)
Abdominal discomfort	1 (10.0)	0	0	1 (3.8)

Abbreviations: COVID-19 = coronavirus disease 2019; IV = intravenous; Miri = mirikizumab; N = number of participants in the analysis population; n = number of participants in the specified category; SOC = System Organ Class; TEAE = treatment-emergent adverse event.

Source: Table AMBU.8.104

Serious Adverse Events

No SAEs were reported during the induction period.

Table AMBU.5.68 provides SAEs reported by SOC and PT for the combined induction and maintenance periods. No single SAE was reported by more than 1 participant.

The SAE of Colitis ulcerative was assessed as related to the treatment by the investigator and led to study discontinuation.

Table AMBU.5.68. Summary of SAEs by SOC and PT for the Combined Induction and Maintenance Periods

System Organ Class *Preferred Term*	≤40 kg 5 mg/kg Miri IV (N = 10) n (%)	≤40 kg 10 mg/kg Miri IV (N = 5) n (%)	>40 kg 300 mg Miri IV (N = 11) n (%)	Total (N = 26) n (%)
Participants with at least 1 SAE	**0**	**2 (40.0)**	**1 (9.1)**	**3 (11.5)**
Gastrointestinal disorders	0	1 (20.0)	1 (9.1)	2 (7.7)
Appendicitis noninfective	0	1 (20.0)	0	1 (3.8)
Colitis ulcerative	0	0	1 (9.1)	1 (3.8)
Musculoskeletal and connective tissue disorders	0	1 (20.0)	0	1 (3.8)
Pseudarthrosis	0	1 (20.0)	0	1 (3.8)

Abbreviations: IV = intravenous; miri = mirikizumab; N = number of participants in the analysis population; n = number of participants in the specified category; PT = Preferred Term; SAE = serious adverse event; SOC = System Organ Class.
Source: Table AMBU.8.110

Trial Intervention Discontinuations due to Adverse Events

No AEs were reported that led to discontinuation from the study treatment during the induction period.

Table AMBU.5.69. shows AEs reported by participants leading to discontinuation from the study treatment for the combined induction and maintenance periods. One participant discontinued the study treatment due to an AE of Colitis ulcerative.

Table AMBU.5.69. Summary of AEs Leading to Discontinuation from Study Treatment for the Combined Induction and Maintenance Periods

System Organ Class *Preferred Term*	≤40 kg 5 mg/kg Miri IV (N = 10) n (%)	≤40 kg 10 mg/kg Miri IV (N = 5) n (%)	>40 kg 300 mg Miri IV (N = 11) n (%)	Total (N = 26) n (%)
Gastrointestinal disorders	0	0	1 (9.1)	1 (3.8)
Colitis ulcerative	0	0	1 (9.1)	1 (3.8)

Abbreviations: AE = adverse event; IV = intravenous; Miri = mirikizumab; N = number of participants in the analysis population; n = number of participants in the specified category.
Source: Table AMBU.8.113

Adverse Events of Special Interest

Study AMBU predetermined the following topics as AESIs:

- hepatic safety
- infections, including opportunistic infections and serious infections
- hypersensitivity
- infusion/injection site reaction
- cerebro-cardiovascular and peripheral vascular events
- malignancies
- suicidal ideation/behaviour and depression

- immunogenicity

Hepatic safety

For the induction period and the combined induction and maintenance periods, the frequency of participants reporting treatment-emergent hepatic disorders SMQ (narrow terms) was 3.8% (n=1). The specified SMQ was liver related investigations, signs and symptoms. One participant in the ≤40 kg 5 mg/kg treatment group reported TEAEs of increased ALT and increased AST in the Induction Period, based on local and central laboratory results. The ALT and AST elevations did not reach ≥3 × ULN and were not reported as an SAE. Study drug was not changed and the participant enrolled into the long-term extension study.

No cases meeting hepatocellular or cholestatic drug-induced liver injury criteria have been reported.

Infections, including opportunistic infections and serious infections

The frequency of participants reporting treatment-emergent infections during the induction period was 3.8% (n=1). No opportunistic infections were reported. No infection SAEs were reported.

All infection TEAEs that occurred during the combined induction and maintenance periods were mild or moderate in severity. The frequency of participants reporting treatment-emergent infections was 65.4% (n=17). The most frequently reported infections were COVID-19 (23.1%, n=6) and Viral upper respiratory infection (15.4%, n=4). No opportunistic infections were reported. No serious infections were reported.

Hypersensitivity

The frequencies of participants reporting immediate hypersensitivity reactions (broad and narrow terms) during the induction period was 3.8% (n=1).

An Infusion related reaction (narrow term) was initially reported for 1 participant in the >40 kg 300 mg/kg treatment group, but follow up from the site clarified that this event was not a true hypersensitivity reaction.

There were no reports of immediate anaphylactic reaction or immediate angioedema.

There were no additional reports of hypersensitivity during the combined induction and maintenance periods. There were no reports of immediate anaphylactic reaction or immediate angioedema.

Infusion/injection site reaction

The frequency of participants who reported at least 1 infusion site reaction (HLT) during the induction period was 3.8% (n=1).

The frequency of participants who reported at least 1 injection site reaction (HLT) during the maintenance period was 34.6% (n=9). The most frequently reported was Injection site pain (23.1% [n=6]).

Other AESIs

In the induction period and the combined induction and maintenance periods, no reports were identified for cerebro-cardiovascular events, major adverse cardiovascular events, or venous thromboembolic events, malignancies, or depression, suicidal ideation or behaviour.

Assessor comments

Overall, the drug was well tolerated in the paediatric population enrolled to this study.

Immunogenicity results

Development of ADA

Of the 26 evaluable participants, 3 (11.5%) mirikizumab-treated participants had treatment-emergent ADA detected postbaseline. Of these, all 3 (11.5%) participants had neutralizing antibodies detected (Table AMBU.5.76). The data showed no meaningful differences in immunogenicity between the treatment groups.

Table AMBU.5.76. Summary of TE-ADA and NAb

Category	≤40 kg 5 mg/kg Miri IV (N=10)	≤40 kg 10 mg/kg Miri IV (N=5)	>40 kg 300 mg Miri IV (N=11)	Total (N=26)
TE-ADA negative, n (%)	8 (80.0%)	5[a] (100.0%)	10 (90.9%)	23 (84.6%)
TE-ADA positive, n (%)	2 (20.0%)	0	1 (9.1%)	3 (11.5%)
NAb to mirikizumab positive, n (%)	2 (20.0%)	0	1 (9.1%)	3 (11.5%)

Abbreviations: ADA = anti-drug antibody; NAb = neutralizing antibodies; TE = treatment emergent.
Source: Table AMBU.8.143.

[a] A baseline sample for one study participant was taken post-dosing and had very high drug level, making the ADA result inconclusive. All subsequent samples were negative for this participant; therefore this participant is considered to be TE ADA negative

Analyses of TE-ADA on PK

Based on the PopPK analysis, ADA was not identified as a significant covariate on the clearance of mirikizumab.

During the induction period, TE-ADA had a minimal impact on mirikizumab concentration. One participant who developed TE-ADA with a titer of 1:160 at Week 12 appeared to have a slight decrease in mirikizumab concentration at Week 12. In the maintenance period, visual assessment of the mirikizumab concentration for participants with TE-ADA did not reveal any effect of TE-ADA on mirikizumab concentration.

Analyses of TE-ADA on Efficacy

No association of TE-ADA status with reduced efficacy (MMS Clinical remission status) was observed.

Analyses of TE-ADA on Safety

Two of the 3 TE-ADA positive participants experienced either an infusion site reaction and/or an injection site reaction. However, in both cases the reactions occurred prior to the development of the TE-ADA. Further, 7 of the 9 participants that experienced injection-site reactions did not develop TE-ADA at any time. Based on this, no apparent association was observed between select AEs (infusion-site reactions, infusion-related reactions, and hypersensitivity events) and TE-ADA status.

Clinical Laboratory Evaluation

Among the mirikizumab treated participants, treatment-emergent abnormal values were noted in fewer than 2 participants in the following serum or whole blood analytes: sodium, chloride, potassium, protein, direct bilirubin, AST, Blood urea nitrogen, creatinine, urate, haemoglobin, erythrocytes, neutrophils (absolute), basophils, platelets, faecal calprotectin, and CRP.

Treatment emergent abnormal low laboratory values in 2 or more participants were observed for the following serum or whole blood analytes: bicarbonate (n = 11), bilirubin (n=5), calcium(n = 3), ALP (n = 2), ALT (n = 2), glucose (n = 4 non-fasting and 2 fasting), cholesterol (n = 3), haematocrit (n = 3), mean red cell volume (n = 7), mean hemoglobin concentration (n = 3), leukocytes (n = 8), lymphocytes (n = 4), and monocytes (n = 6).

Treatment emergent abnormal high laboratory values in 2 or more participants were observed for the following serum or whole blood analytes: ALP (n = 2), ALT (n = 2), calcium (n = 2), albumin (n = 11), creatine kinase (n = 5), haematocrit (n = 2), leukocytes (n = 2), eosinophils(n = 6) and CRP (n=3).

One participant reported elevated ALT and AST as TEAEs. The AST elevation was not associated with an elevated central lab value or flag listed above, the site reported it based on a local lab value. None of the other laboratory changes from baseline were reported as TEAEs.

Of the 26 enrolled participants, 8 (30.7%) presented low bicarbonate values at screening or baseline. Postbaseline, 11 (42.3%) participants presented treatment emergent bicarbonate shifts to low. Majority of the observed shifts to low were very mild and not clinically meaningful. This shifts to low were observed sporadically and there was no consistent trend to low along the 52-weeks of the treatment period.

Vital Signs

Treatment emergent vital sign changes during the Induction and Maintenance Period were not meaningful and were consistent with the overall safety profile of mirikizumab to date.

Height

Participants in the ≤40 kg weight class that received the 5 mg/kg induction dose showed an increase in height percentile and height z-score change at Week 24 that continued to increase at Week 52, indicating growth moving towards the mean of a normal population. Participants in the 10 mg/kg and 300 mg induction dose groups showed more variability and small changes over the treatment period indicating these participants maintained growth at a rate consistent with their baseline percentile.

Weight

Participants in the ≤40 kg weight class showed an increase in weight percentile and weight z-score change at Week 24 that continued to increase at Week 52, indicating participants gained weight generally increasing in percentile moving towards the mean of a normal population. Participants in the >40kg weight class showed a weight percentile increase at Week 12, however at Week 24 and Week 52 this increase in mean weight percentile was not maintained indicating these participants as a group maintained a growth rate consistent with their baseline percentile

Overall, all female groups and male participants in the ≤40 kg group who received the 5 mg/kg induction dose gained weight starting at Week 4 which continued through the treatment period. Male participants in the >40kg weight group maintained their baseline weight or showed slight reductions at the group level through Week 24 but showed an increase from baseline by Week 52. The slight reductions in the group means were likely due to weight loss experienced by 1 participant (☒☒☒☒) who discontinued the study due to disease flare.

Hormone levels

Hormone levels were collected at baseline, Weeks 12, 36 and 52 in study participants who had not reached puberty in an effort to evaluate pubertal development. Given the low numbers of female participants who had not reached puberty (n=5) and variability of the data, no conclusions can be drawn on female pubertal development.

Testosterone data was collected in 8 male participants. Throughout the study, testosterone levels increased over time except for 2 participants in 10 mg/kg dose group, where levels remained undetectable at baseline and throughout the treatment period.

Assessor comments

3 participants developed ADAs during the clinical trial. The applicant states that there were no associations seen between the emergence of TE-ADAs and any PK, efficacy, or safety outcome. While this can be accepted, it is noted that the small numbers enrolled to this study make it difficult to draw any meaningful conclusions in this regard.

No significant adverse effects were seen with regards to laboratory value changes from baseline, vital signs, height, weight, or hormone levels in treated patients.

2.3.3. Discussion on clinical aspects

The purpose of this submission was to comply with Article 46 of Regulation (EC) No 1901/2006, as amended, by submitting the clinical study report and OUS addendum for Study I6T-MC-AMBU**.**

Study AMBU, also known as SHINE-1, was a Phase 2 open label multicenter study to evaluate the safety, pharmacokinetics, pharmacodynamics and clinical response to mirikizumab and to establish the induction and maintenance doses to evaluate in Phase 3 in children and adolescents with ulcerative colitis aged 2 to less than 18 years.

Study AMBU included 12 weeks of open-label IV treatment with mirikizumab (induction period), followed by:

• 40-week open-label SC treatment with mirikizumab (maintenance period) to evaluate long-term safety and durability of clinical response and remission in participants who achieved clinical response at Week 12, or

• extended induction period (12 additional weeks of IV treatment for participants who did not achieve response at Week 12) to explore the effect of additional IV dosing on clinical response at Week 24.

Participants were also eligible for rescue treatment with mirikizumab for LOR once in the maintenance period between Weeks 16 and 40.

Approximately 60 participants with moderately to severely active UC were planned to be screened to enroll approximately 30 participants in the study.

Upon completion of the maintenance period (Week 52), participants who achieved clinical benefit were offered continued treatment in a separate 3-year long-term extension Study I6T-MC-AMAZ (AMAZ). Participants who did not meet enrollment criteria for Study AMAZ or chose not to continue into Study AMAZ entered the post-treatment follow-up period (12 weeks following SC administration or 16 weeks following IV administration).

The study population included paediatric participants with moderately to severely active UC, who had an inadequate response to, loss of response to, or were intolerant to nonbiologic therapy for UC (biologic-naive), and/or those who had been exposed to at least 1 biologic and/or JAK inhibitor therapy for UC (biologic/ JAK inhibitor-experienced).

The primary objective of the study was to evaluate the PK of mirikizumab treatment in paediatric participants. The PK of mirikizumab following induction and maintenance treatment was characterized using a population PK approach. Potential impact of participant factors on the PK of mirikizumab was evaluated. The relationship between key efficacy responses and mirikizumab exposure was also explored. The study included a large number of efficacies related secondary objectives and endpoints, focused on clinical remission and responses (MMS, PUCAI), symptomatic and endoscopic remission and response amongst others. Clinical safety and immunogenicity were also evaluated. The study objectives and endpoints are considered standard and acceptable for a Phase 2 study with intent to assess mirikizumab and establish dosing for Phase 3 in children and adolescents with ulcerative colitis. Due to the nature of the open label single arm study, no formal statistical testing was performed.

This study was conducted at 19 centers, that enrolled 26 participants in Israel, Japan, South Korea and the United States. Participants were assigned to 1 of 3 treatment groups based on current body weight. All 26 participants completed the Week 12 Induction Period.

All participants who achieved a MMS clinical response at Week 12 or Week 24 (non-responders at Week 12 who received extended IV induction dosing for 12 more weeks) were eligible for the Maintenance Period. All 26 participants entered the maintenance period and were assigned to 1 of 3 mirikizumab SC treatment groups based on current body weight. Nineteen of the 26 (73.1%) participants completed the Week 52 maintenance period and 7 (26.9%) participants discontinued the study treatment. 15 (57%) of subjects were female and mean age of subjects was 11.8 years. All subjects had received at least one prior treatment for UC, and 17 (65.4%) had prior biologic exposure.

The primary objective was to evaluate the PK of mirikizumab treatment in paediatric patients. Full details on the PopPK model and its parameters were not provided in the submitted dossier, and additional information was requested. The MAH subsequently submitted additional information including Control Stream and Summary of the NONMEM Output for the base and final models, the covariate analysis and goodness-of-fit plots for the final model. The methods used for model development are acceptable. The provided goodness-of-fit plots suggest that the model describes the

data reasonably well. Visual predictive checks of the final model were not provided. Therefore, the predictive performance of the model could not be assessed.

Only a summary of the provided pharmacokinetic results as presented in the CSR are thus outlined. A PK model was developed using the 232 serum mirikizumab concentration samples collected from 26 participants in induction and maintenance periods. A previously developed 2-compartment model with first-order absorption for the SC maintenance doses based on data from the adult Phase 3 studies (AMAN and AMBG) with allometric relationship incorporated for clearance and volume (central and peripheral volume) parameters was applied to the paediatric PK data from this study AMBU. Exponents of 0.8 for clearance and 1 for volume of distribution were used in the model to account for the weight effect. The MAH concluded that the model-estimated systemic clearance and subcutaneous bioavailability was consistent with the adult UC Phase 2 study AMAC and UC Phase 3 Studies AMAN and AMBG, and that albumin despite having a statistically significant impact on mirikizumab PK was not considered clinically meaningful. The MAH also concluded that the PK exposure estimates support the dosing strategy of weight group divided treatment of paediatric participants with UC. As stated, further information is required to evaluate the MAH conclusions regarding PK. Overall, however it is agreed that the exposure estimates appeared similar between the weight-based 5mg/kg mirikizumab IV and fixed dose 300mg mirikizumab IV in induction. The MAH confirmed thatthe 5 mg/kg mirikizumab IV Q4W dosing regimen was selected for use in Phase 3 for participants weighing less than or equal to 40 kg in

☐ Study I6T-MC-AMBA (AMBA) as induction dosing, and

☐ Long-term extension Study I6T-MC-AMAZ (AMAZ) ISA #1 as rescue dosingThe MAH evaluated a large number of secondary efficacy endpoints, including PUCAI, MMS, endoscopic and symptomatic remission. In general, the results showed demonstration of improvement across these endpoints for a proportion of subjects at Week 12 following induction and at Week 52 maintenance. At Week 52, 13 subject (50%) achieved PUCAI clinical remission, 14 subjects (53.8%) achieved PUCAI clinical response, 10 subjects (38.5%) achieved clinical remission on MMS and 14 subjects (53.8%) achieved clinical response on MMS. Thus, the efficacy results support further evaluation of mirikizumab in a randomized setting in a paediatric population with ulcerative colitis.

The medicine was generally well tolerated in the paediatric population. No significant immunogenicity was seen in the trial.

3. Rapporteur's overall conclusion and recommendation

☒ Fulfilled:

☐ Not fulfilled:

Based on the data submitted, the MAH should provide additional information and response to the clarifications as requested as part of this procedure.

See section "Request for supplementary information".

4. Request for supplementary information

Based on the data submitted, the MAH should address the following questions as part of this procedure:

The timetable is a 30-day response timetable with clock stop.

Other concerns

1. A critical expert overview statement should be provided as part of an application under Article 46. Please provide a short critical expert overview.
2. The Applicant should confirm the two pharmaceutical formulations used in this study were the approved adult formulations.
3. The rationale for the original dosing and subsequent change for subjects >20kg and </=40kg should be provided. In addition, the number of subjects who were dosed prior to and post amendment c should be provided.
4. Reasons for screen failure of 23 subjects should be provided.
5. Considering the study objectives, the Applicant should provide additional information on the dosing errors and what impact this may have had on the PK conclusions.
6. For some of the other deviations, e.g. not obtaining informed consent, not reporting SAEs within 24 hours, the MAH should confirm that site education and training were provided to address these issues and their occurrence in future studies.
7. The Applicant should provide a clear summary of concomitant UC medications received during induction and maintenance.
8. Full details on the PopPK model and its parameters were not provided in the submitted dossier, therefore additional information is required to enable full assessment of the primary PK objectives, the PK model and PK results. The Applicant is requested to submit the relevant data on PK/PD analyses and all referenced appendices stated to be included as per List of Appendices on Pg1535 of CSR.
9. The MAH should confirm if the same bioanalytical methods were used as in the adult studies AMAN and AMBG and if not details of these should be provided.
10. The MAH should confirm if the 5mg/kg mirikizumab IV induction dosing has been selected to be brought forward for subjects >20kg to </=40kg in Phase 3, with other dosing the same as that evaluated in this study.

5. MAH Response to request for supplementary information

Question 1
A critical expert overview statement should be provided as part of an application under Article 46. Please provide a short critical expert overview.

MAH Response

Lilly has provided a short critical expert overview along with this response.

Assessment of MAH Response

The MAH has now provided the critical expert overview as requested.

Conclusion

Issue resolved.

Question 2
The Applicant should confirm the two pharmaceutical formulations used in this study were the approved adult formulations.

MAH Response
Lilly confirms that the 2 pharmaceutical formulations used in Study AMBU, are the same as the OMVOH adult formulations currently authorized by the EMA for the treatment of UC (EMA product number EMEA/H/C/005122, marketing authorization issued 26 May 2023).

Assessment of MAH Response
The applicant has confirmed that the formulations used in the study are the same as the adult formulations currently authorized by the EMA for the treatment of UC.

Conclusion

Issue resolved

Question 3
The rationale for the original dosing and subsequent change for subjects >20kg and </=40kg should be provided. In addition, the number of subjects who were dosed prior to and post amendment c should be provided.

MAH Response

Protocol AMBU, AMBU(a), and AMBU(b) Section 7.1 contained the language: Subcutaneous administration of mirikizumab will be given in not more than 2 injections (maximum volume is 1 mL per injection for patients >40 kg and 0.5 mL for patients ≤40 kg).

The primary purpose of Protocol AMBU(c) was to modify dosing instructions for the ≥20-40 kg participants during the maintenance period. Amendment (c) meant that each participant would receive 1 injection of a 1 mL prefilled syringe instead of two 0.5 mL injections for SC maintenance dosing. In both cases, the total dose was 100 mg of mirikizumab.

The amendment was prompted by study site feedback indicating that injecting 1 mL SC in participants weighing 20 kg to ≤40 kg was acceptable and, importantly, avoided 2 injections in a child. Therefore, the maximum volume limitation was removed.
Three participants receiving 100 mg SC during the maintenance period were dosed with two 0.5 mL injections (prior to amendment c), and 9 participants were dosed with one 1 mL prefilled syringe after the amendment.

Assessment of MAH Response
The response of the applicant is acceptable. The Applicant clarified that the amendment to change the dosing from two 0.5 mL SC injections to one 1.0 mL SC injection was prompted by study site feedback that injecting 1 mL volume SC was acceptable to subjects weighing 20 kg to </=40kg, avoiding two

injections in a child. This rationale is understood. The Applicant also clarified 3 participants were dosed prior to amendment c with two injections and 9 participants doses after the amendment with one 1 mL PFS.

Conclusion

Issue resolved

Question 4

Reasons for screen failure of 23 subjects should be provided.

MAH Response

Of 23 participants that had screen failure, 5 were later rescreened and met all eligibility criteria to be able to enrol in the study. At the time of their initial screening, 3 of these participants did not have moderately to severely active UC as defined by an MMS of 4 to 9 with ES ≥2. The other 2 of the 5 participants had Clostridium difficile or tested positive for Clostridium difficile or other intestinal pathogens within 30 days of the screening endoscopy in the initial screening period. The remaining 18 of the 23 screen failures did not meet the eligibility criteria or consent was withdrawn prior to enrolment. The reasons for their screen failure are provided:

Reason for Discontinuation	Details	Number of Participants
Inclusion/Exclusion #3	Both the parent or legal representative and child (if capable) must agree to comply with the requirements of the protocol.	1
Inclusion/Exclusion #6	Have moderately to severely active UC as defined by a MMS of 4 to 9 with an ES ≥2 within 14 days before first dose of study treatment (baseline).	8
Inclusion/Exclusion #11	Have clinically acceptable central laboratory results or local laboratory results reviewed and approved by the sponsor medical monitor or designee during screening, as assessed by the investigator see protocol for details of specific laboratory levels).	1
Inclusion/Exclusion #13	Have a current diagnosis of CD, IBD-Unclassified, ulcerative proctitis (distal disease limited to the rectum), or primary sclerosing cholangitis.	1
Inclusion/Exclusion #20	Have failed anti-IL12p40 antibodies (for example, ustekinumab) or have ever received anti-IL-23p19 antibodies for any indication, including investigational use.	1
Inclusion/Exclusion #21	Have evidence of active TB or have past history of active TB, regardless of treatment, or have past history of latent tuberculosis infection (LTBI) and have not completed an appropriate TB treatment regimen, or are diagnosed with LTBI at screening.	1
Inclusion/Exclusion #26	Have *Clostridium difficile* or other intestinal infection within 30 days of screening endoscopy, or test positive at screening for *C. difficile* or for other intestinal pathogens.	4
Withdrawal by Parent or Guardian	Withdrawal by Parent or Guardian.	1

Abbreviations: CD = Crohn's disease; ES = endoscopy subscore; IBD = inflammatory bowel disease; LTBI = latent tuberculosis infection; MMS = modified Mayo score; TB = tuberculosis; UC = ulcerative colitis.

Assessment of MAH Response

The Applicant has now provided the reason for screen failure of subjects as requested. Five patients who had initially failed at a screening visit but who subsequently met the screening criteria were included in the trial following rescreening.

Conclusion

Issue resolved

Question 5

Considering the study objectives, the Applicant should provide additional information on the dosing errors and what impact this may have had on the PK conclusions

MAH Response

Induction

During the Induction Period, 4 participants were affected by dosing errors.

Participant…	in the group…	received…	at…	instead of…	because…
AMBU-☒☒☒☒	20-40 kg 5 mg/kg induction dose	197 mg	Visit 4	185 mg	the dosing calculation was based on the current visit weight instead of the baseline weight.
		211 mg[a]	Visit 5		
AMBU-☒☒☒☒		70 mg	Visit 4	56.5 mg	
			Visit 5		
AMBU- ☒☒☒☒		122 mg	Visit 4	117.5 mg	
		132 mg	Visit 5		
AMBU- ☒☒☒☒	20-40 kg 10 mg/kg induction dose	318 mg	Visit 4	327 mg	

[a] The dose received by participant AMBU-☒☒☒☒ is listed in this regulatory response as 211 mg at Visit 5, however the listing provided in the Study AMBU CSR appendix 18 states the dose received was 300 mg. The 211 mg is in the raw data from the electronic Case Report Form and was used in the PK analyses. The 300 mg came from a Protocol Deviation file that Lilly statistics does not edit but uses to provide details within the listing. The 300 mg was likely an error by the contract research organization clinical research associate within the Protocol Deviation file.

Maintenance

During the Maintenance Period, 1 participant was affected by a dosing error.

Participant…	in the group…	received…	at…	instead of…	because…
AMBU-☒☒☒☒	20-40 kg 100 mg maintenance dose	150 mg	Visit 7	100 mg	the study coordinator was looking at incorrect dosing information.

Corrective actions

Site 172 was the initial dosing deviation found by the site monitor during a routine monitoring visit on 07 March 2022. The dosing issue prompted a Quality Issue assessment by the Clinical Research Organization and Lilly study teams. The actions from this Quality Issue included initiating action for the Clinical Research Associate to retrain the site staff on the dosing instructions in the latest protocol amendment. The issue also prompted the study team to update the Investigational Product Pharmacy and Preparation Instructions. The new version of the Pharmacy and Preparation Instructions was completed on 31 March 2022 and was released to all investigator sites by e-mail in early April 2022. Following the initial issue, additional dosing errors were found during routine monitoring visits of Sites 105, 107, and 180. The Clinical Research Associates were able to retrain the sites with the 31 March 2022 updated Pharmacy and Preparation Instructions along with the latest protocol amendment.

Discussion

The largest differences in dosing errors were noted for
☐ Participant AMBU-☒☒☒☒ in the Induction Period received 23.9% more than expected,
and
☐ Participant AMBU-☒☒☒☒ in the Maintenance Period received 50% more than expected.

Even if the participants had received the correct dose, the PK exposures would have been readily adjusted in the population PK model. Given the linear exposure changes between dose and exposures in mirikizumab, there would be no large effect on the AUCtau,ss and Cmax,ss exposure metrics that were provided in the AMBU CSR (Table AMBU.5.75).

With no large changes expected in the population PK model parameter estimates, the geometric mean estimate of 20-40 kg 5 mg/kg for the induction group 597 ug*day/mL (CV% 45%) would be largely unchanged with the 95% CI overlapping with the adult population 543 ug*day/mL (CV% 38%). Therefore, the dosing correction is unlikely to change the PK conclusion.

In addition, the exposure-matching metrics are dependent on the steady-state measure of the maintenance dosing. Therefore, the dosing error at Visit 8, which occurred earlier during the study, is unlikely to impact the exposure metrics provided in the Study AMBU CSR (Table AMBU.5.75) and has minimal impact on PK conclusions.

Assessment of MAH Response

The MAH has provided further discussion on the dosing errors that occurred and considers that these had minimal impact on PK conclusions. In the induction period the dosing errors were due to incorrect calculation using the current visit weight rather than the baseline visit weight. The largest difference in induction was a 23.9% higher dose received. In the maintenance period, one dosing error occurred in a subject who received a 50% higher dose, 150mg instead of 100mg. In this case the reason was the investigator was looking at the incorrect study information.

The MAH highlights that given the linear exposure changes between dose and exposures in mirikizumab, there would be no large effect on the AUCtau,ss and Cmax,ss exposure metrics that were provided in the AMBU CSR based on the dosing errors. The MAH considers that as no large change is expected in population PK model parameter estimates that the geometric mean estimate of 20-50kg 5mg/kg for the induction group would be largely unchanged with the 95% CI overlapping with the adult population and therefore unlikely changing the PK conclusion.

Conclusion

Issue resolved.

Question 6

For some of the other deviations, e.g. not obtaining informed consent, not reporting SAEs within 24 hours, the MAH should confirm that site education and training were provided to address these issues and their occurrence in future studies.

MAH Response

A Protocol Deviation Management Plan was followed which included actions to be taken for each type and category of protocol deviations. For key deviations such as informed consent violations and delays in reporting serious adverse events, site re-education was performed, and documented in the protocol deviation log. In addition to documenting the study protocol deviation logs, sites were also instructed to report the deviation to their respective Institutional Review Boards and to reconsent participants correctly at the next onsite visits.

Assessment of MAH Response

The MAH confirmed that site re-education was performed and documented in the protocol deviation log for above mentioned deviations.

Conclusion

Issue resolved.

Question 7

The Applicant should provide a clear summary of concomitant UC medications received during induction and maintenance.

MAH Response

The Study AMBU CSR Section 4.5.3 states:

"Stable doses of permitted UC concomitant medications (other than oral corticosteroids) were encouraged. Participants taking oral corticosteroids were to follow the corticosteroid taper instructions described in the protocol. Summaries of concomitant medications and therapies within class (i.e, corticosteroids, immunomodulators) for the mITT Population are provided for:
☐ Induction Period (Table AMBU 8.9)
☐ Combined Induction and Maintenance Periods (Table AMBU 8.10)"

A summary of concomitant UC medications received during induction and maintenance is presented in Section 5.1.2 of the critical expert overview that is provided with this response.

Assessment of MAH Response

The MAH provide the requested summary of concomitant UC medications in the critical expert overview. The AR was updated accordingly.

Conclusion

Issue resolved.

Question 8

Full details on the PopPK model and its parameters were not provided in the submitted dossier, therefore additional information is required to enable full assessment of the primary PK objectives, the PK model and PK results. The Applicant is requested to submit the relevant data on PK/PD analyses and all referenced appendices stated to be included as per List of Appendices on Pg1535 of CSR.

MAH Response

Pharmacokinetics information

Lilly has also provided a response to an Other Concern that was present on Page 28 of the Assessment Report but was not included in the list of Other Concerns within Section 4 Request for supplementary information:

Acknowledging the low number of subjects in each group, AUC, Cmax, Ctrough, Cavg values at steady state were almost twice as high in the 10mg/kg IV induction dose in 20- 40kg group. The clinical relevance of this was not discussed in the report.

As provided in Protocol AMBU Section 5.5. Justification of Dose, dose regimens, and weight categories are based on analyses of
☐ PK
☐ exposure-response, and
☐ safety data from the Phase 2 adult Study I6T-MC-AMAC (AMAC) in participants with UC.

Based on adult data from Study AMAC, paediatric participants with a body weight greater than 40 kg were expected to have comparable PK to adults, and therefore, evaluation of an IV dose of 300 mg was planned for the Induction Period dose in participants with body weight greater than 40 kg.

For paediatric participants less than or equal to 40 kg, participants were expected to provide comparable systemic exposures to Study AMAC and Phase 3 Studies I6T-MC-AMAN (AMAN) and I6T-MC-AMBG (AMBG), where
☐ 5 mg/kg IV was planned for the Induction Period dose, and
☐ 10 mg/kg IV was evaluated as dosing comparable to a 600 mg IV dose.

These doses were not expected to produce exposures higher than those evaluated in adults in Study AMAC. The dose regimens selected for the Maintenance Period were expected to provide comparable maintenance exposures to the 200 mg SC Q4W regimen in Study AMAC, which was subsequently evaluated in the Phase 3 adult Study AMBG.
A previously developed 2-compartment model with first-order absorption based on data from the volume of distribution was used for PK modelling for AMBU. The use of fixed versus estimated exponent was considered. The population PK model with fixed allometric scaling of 0.8 for clearance and 1.0 for volume of distribution was selected as the Final Base Model as shown in PK Insert 1 in Appendix 2.
After the Final Base Model was selected, a covariate search using Stepwise Covariate Modelling approach was conducted for relevant covariates included in the Population PK Analysis Plan of Study AMBU. The key covariate selection criteria are described in the analysis plan.

Table 4.1. Covariates Assessed in the Population PK Model for Study AMBU

Age	Baseline body weight	Baseline bilirubin
Gender	Baseline body mass index	Baseline Cockcroft-Gault creatinine clearance
Race	Baseline body surface area	Baseline MMS
Ethnic origin	Baseline and time-varying serum albumin	Baseline SF/RB/EFS
Concomitant corticosteroid or immunomodulator use at baseline	Baseline and time-varying C-reactive protein	Immunogenicity (ADA +/-, TE-ADA+/-, ADA titer, neutralizing ADA +/-)
Prior biologic treatment status[a]	Baseline and time-varying fecal calprotectin	

Abbreviations: ADA = anti-drug antibody; AMBU = I6T-MC-AMBU; EFS = endoscopic finding by Mayo subscore; MMS = modified Mayo Score; PK = pharmacokinetic; RB = rectal bleeding by Mayo subscore; SF = stool frequency by Mayo subscore; TE-ADA = treatment emergent anti-drug antibody.

[a] Biologic failed or not-biologic-failed

The covariates that came up during the Stepwise Covariate Modelling step were considered for manual forward addition and backward deletion. The only covariate identified was time-varying serum albumin effect on clearance, as shown in PK Insert 1 and PK Insert 2 in Appendix 2. The effect size of population PK model-estimated clearance versus albumin concentration was described in Figure AMBU.5.3. of the Study AMBU CSR.

Study AMBU CSR appendices

Study AMBU appendices are provided along with this response.

Appendix name and link	Included	ICH appendix number	File tag
Bioanalytical report	Yes	NA	NA
Summary of COVID-19 Disruptions Impact	Yes	NA	02
Protocol and addenda	Yes	16.1.1	05

Appendix name and link	Included	ICH appendix number	File tag
• AMBU 05 Protocol • AMBU 05 Protocol amendment (a) • AMBU 05 Protocol amendment (b) • AMBU 05 Protocol amendment (c) • AMBU 05 Protocol addendum 1 – Japan • AMBU 05 Protocol addendum 1.1 – Japan			
Patient narratives	Yes	NA	04
Sample CRF	Yes	16.1.2	06
ERB list and sample ICF	Yes	16.1.3	07
Investigators' summary of training and experience and administrative information table	Yes	16.1.4	08
Investigator's signature	Yes	16.1.5	09
Batch listing	No, available upon request	16.1.6	10
Randomization	Yes	16.1.7	11
Audit certificates	Yes	16.1.8	12
Statistical methods	No, available upon request PK methods included	16.1.9	13
Interlaboratory standardization methods	Yes	16.1.10	14
Publications based on the study	No, there are currently no publications based on this study	16.1.11	15
Publications cited in the report	No, available upon request	16.1.12	16
Listing of disposition and discontinuation	Yes	16.2.1	17
Listing of protocol deviations	Yes	16.2.2	18
Listing of excluded patients	No, available upon request	16.2.3	19
Listing of demographics	Yes	16.2.4	20
Listing of compliance	Yes	16.2.5	21
Listing of individual efficacy	Yes	16.2.6	22
Listing of adverse events	Yes	16.2.7	23
Listing of individual laboratory measures	Yes	16.2.8	24

Abbreviations: AMBU = I6T-MC-AMBU; COVID-19 = coronavirus disease 2019; CRF = case report form; ERB = ethics review board; ICF = informed consent form; ICH = International Council for Harmonisation; NA = not applicable.

Assessment of Responses

The MAH provided some additional details on the covariate search in the popPK analysis, which are acceptable. The provided goodness-of-fit plots suggest that the model describes the data reasonably well. Visual predictive checks of the final model were not provided. Therefore, the predictive performance of the model could not be assessed. Study AMBU appendices were provided as requested.

Conclusion

Issue resolved.

Question 9

The MAH should confirm if the same bioanalytical methods were used as in the adult studies AMAN and AMBG and if not details of these should be provided.

MAH Response

Lilly confirms that the same bioanalytical methods were used for Study AMBU.

Assessment of Responses
It has been confirmed that the same bioanalytical methods were used for Study AMBU.

Conclusion

Issue resolved

Question 10

The MAH should confirm if the 5mg/kg mirikizumab IV induction dosing has been selected to be brought forward for subjects >20kg to </=40kg in Phase 3, with other dosing the same as that evaluated in this study.

MAH Response

Lilly confirms that the Study AMBU 5 mg/kg mirikizumab IV Q4W dosing regimen was selected for use in Phase 3 for participants weighing less than or equal to 40 kg in

☐ Study I6T-MC-AMBA (AMBA) as induction dosing, and
☐ Long-term extension Study I6T-MC-AMAZ (AMAZ) ISA #1 as rescue dosing.

In Studies AMBA and AMAZ ISA #1, a 300 mg mirikizumab IV Q4W dosing regimen is used for participants weighing more than 40 kg for induction and rescue dosing, respectively.

Assessment of MAH Response

The MAH has clarified the doses selected for use in the Phase 3 study.

Conclusion

Issue resolved.