CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761279Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

Joint Summary Clinical Review

Division of Gastroenterology
Office of Immunology and Inflammation / Office of New Drugs
Center for Drug Evaluation and Research

Application Type	BLA
Application Number(s)	761279
Priority or Standard	Standard resubmission
Submit Date(s)	May 24, 2023
Received Date(s)	May 24, 2023
PDUFA Goal Date	November 24, 2023
Division/Office	Division of Gastroenterology
Review Completion Date	October 26, 2023
Established/Proper Name	Mirikizumab-mrkz
(Proposed) Trade Name	OMVOH
Pharmacologic Class	Interleukin-23 antagonist
Code name	LY3074828
Applicant	Eli Lilly and Company
Dosage form	Injection
Applicant proposed Dosing Regimen	Induction dosage regimen: 300 mg intravenous (IV) for at least 30 minutes at Week 0, Week 4, and Week 8 Maintenance dosage regimen: 200 mg subcutaneous (SC) every 4 weeks after completion of induction dosing
Applicant Proposed Indication(s)/Population(s)	Adult patients with moderately to severely active ulcerative colitis (UC)
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	64766004 Ulcerative colitis (disorder)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Adult patients with moderately to severely active ulcerative colitis (UC)
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	64766004 Ulcerative colitis (disorder)
Recommended Dosing Regimen	Induction dosage regimen: 300 mg intravenous (IV) for at least 30 minutes at Week 0, Week 4, and Week 8

	Maintenance dosage regimen: 200 mg subcutaneous (SC) every 4 weeks after completion of induction dosing

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DMEPA=Division of Medication Error Prevention and Analysis
OPQ=Office of Pharmaceutical Quality
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology

[1] Refer to the Multi-Disciplinary Review and Evaluation (Unireview) dated March 30, 2023 (Reference ID: 5150402), for details regarding the review team of the original BLA submission.

1 Executive Summary

1.1 Product Introduction

Trade Name: OMVOH
Established Name: Mirikizumab-mrkz
Mirikizumab is a humanized immunoglobulin 4 (IgG4) monoclonal antibody that binds to the p19 subunit of interleukin 23 (IL-23), a cytokine that is a key mediator in intestinal mucosal inflammation.[2] IL-23 is a pro-inflammatory member of the IL-12 family of cytokines. It is composed of two subunits, IL-12p40, which is shared with IL-12, and IL-23p19 (the target of mirikizumab), which is specific to IL-23. IL-23 signaling has been implicated in the pathogenesis of inflammatory bowel diseases, including ulcerative colitis (UC), by genome-wide association studies.[3]

The Applicant is seeking approval of mirikizumab injection for the treatment of moderately to severely active ulcerative colitis (UC) in adult patients.

1.2 Biologic License Application (BLA) Resubmission

The Applicant resubmitted BLA 761279 to support the approval of Omvoh (mirikizumab injection) through the 351(a) regulatory pathway. This resubmission was received on May 24, 2023, in response to a Complete Response action on March 30, 2023, for the original BLA submission.

During review of the original submission of BLA 761279 (received March 30, 2022), the multidisciplinary review team determined that the analyses of the primary and multiplicity-controlled secondary endpoints provided substantial evidence of effectiveness for mirikizumab for the treatment of moderately to severely active UC in adults. The safety profile was acceptable, and the review team determine that the identified risks could be mitigated through labeling. The benefit-risk assessment based on clinical data was considered favorable to support the proposed indication. For details of the prior review, see the March 30, 2023, Multi-Disciplinary Review and Evaluation (Unireview) in DARRTS (Reference ID: 5150357).

However, the pre-approval inspection of the drug product manufacturing facility (FDA Establishment Identifier [FEI] 1819470, Eli Lilly and Company, Indianapolis, Indiana) identified significant deficiencies. Therefore, the facility was determined to be unacceptable to support the approval of BLA 761279, and a Complete Response letter was issued on March 30, 2023. The letter communicated the following deficiencies.

[2] Kobayashi, T, S Okamoto, T Hisamatsu, N Kamada, H Chinen, R Saito, MT Kitazume, A Nakazawa, A Sugita, K Koganei, K Isobe, and T Hibi, 2008, IL23 differentially regulates the Th1/Th17 balance in ulcerative colitis and Crohn's disease, Gut, 57(12):1682-1689.
[3] Duerr, RH, KD Taylor, SR Brant, JD Rioux, MS Silverberg, MJ Daly, AH Steinhart, C Abraham, M Regueiro, A Griffiths, T Dassopoulos, A Bitton, H Yang, S Targan, LW Datta, EO Kistner, LP Schumm, AT Lee, PK Gregersen, MM Barmada, JI Rotter, DL Nicolae, and JH Cho, 2006, A genome-wide association study identifies IL23R as an inflammatory bowel disease gene, Science, 314(5804):1461-1463.

Following pre-license inspection of the Eli Lilly and Company, Indianapolis, Indiana (FEI 1819470), manufacturing facility listed in this application, FDA conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

In this resubmission, the Applicant submitted data to support that the manufacture of Omvoh (mirikizumab-mrkz) is well-controlled and leads to a product that is pure and potent. Additionally, the Applicant provided a safety update in accordance with FDA recommendations communicated in the Complete Response letter.

The multidisciplinary review team recommend approval of this original BLA for Omvoh (mirikizumab-mrkz) for the treatment of moderately to severely active UC in adults.

2 Relevant Regulatory Background for Resubmission

The original submission of BLA 761279 received a complete response on March 30, 2023. On April 7, 2023, the Applicant submitted a Type A meeting request; however, this meeting request was denied because the specific questions on facility deficiencies were outside the scope of a Type A meeting with CDER (issued by FDA on April 20, 2023 [Reference ID: 5161507]). In the meeting denied letter, The Agency stated that the adequacy of the facility's response to the post-application action letter deficiencies as well as the determination regarding whether a re-inspection is necessary would be determined after the BLA is resubmitted. The current resubmission was received on May 24, 2023.

3 Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

3.1 Product Quality

On repeat inspection post-remediation, the drug product (DP) manufacturing facility (FEI 1819470, Eli Lilly and Company, Indianapolis, Indiana) was found to be satisfactory. Accordingly, the data submitted in this application are adequate to support that the manufacture of Omvoh (mirikizumab-mrkz) is well-controlled and leads to a product that is pure and potent. The OPQ review team recommended that this product be approved for human use under conditions specified in the package insert. For further information, refer to the October 26, 2023, Quality Executive Summary in DARRTS (Reference ID: 5267330).

3.2 Nonclinical Pharmacology/Toxicology

No new nonclinical/toxicology information was included in this resubmission. For details of the prior review, see the March 30, 2023, Multi-Disciplinary Review and Evaluation (Unireview) in DARRTS (Reference ID: 5150357).

3.3 Clinical Pharmacology

No new clinical pharmacology data was included in this resubmission. For details of the prior review, see the March 30, 2023, Multi-Disciplinary Review and Evaluation (Unireview) in DARRTS (Reference ID: 5150357).

4 Sources of Clinical Data and Review Strategy

4.1 Review of Effectiveness

No clinical studies were included in the BLA resubmission. Substantial evidence of effectiveness was established in the original BLA submission based on two adequate and well-controlled trials, described below.

Study I6T-MC-AMAN (AMAN) - A phase 3, multicenter, randomized, double-blind, parallel group, placebo-controlled induction trial. AMAN compared mirikizumab 300 mg IV every 4 weeks (Q4W) versus placebo for a treatment duration of 12 weeks.

Study I6T-MC-AMBG (AMBG) – A phase 3, multicenter, randomized, double-blind, parallel group, placebo-controlled maintenance trial. AMBG compared mirikizumab 200 mg SC Q4W versus placebo for a treatment duration of 40 weeks.

In both trials, mirikizumab was demonstrated to be superior to placebo for the primary endpoint of the proportion of subjects achieving clinical remission, as well as for several secondary endpoints including endoscopic response, endoscopic remission, and histologic-endoscopic mucosal improvement. Refer to the Multi-Disciplinary Review and Evaluation (Unireview) dated March 30, 2023, in DARRTS (Reference ID: 5150357) for full details regarding the data to support substantial evidence of effectiveness.

The previous Unireview contained information on disease characteristics and prior medications for the safety population, not the FDA preferred efficacy analysis population that will be presented in the prescribing information. Thus, the baseline disease characteristics and prior medications for AMAN using the FDA preferred efficacy analysis population are shown in Table 1; these were similar between AMAN and AMBG because subjects who were responders during AMAN were enrolled in AMBG. Overall, the baseline characteristics were consistent across two treatment arms for the FDA preferred efficacy analysis population.

Table 1. Baseline Disease Characteristics and Prior Medications, AMAN, 12 Week Induction Period (FDA Preferred Analysis Population)

Characteristic	Mirikizumab 300 mg IV Q4W N=795	Placebo N=267	Total N=1062
Biologic and JAKi naïve, n (%)			
Yes	450 (56.6)	155 (58.1)	605 (57.0)
No	345 (43.4)	112 (41.9)	457 (43.0)
Prior biologic or JAKi failure, n (%)			
Failed	331 (41.6)	107 (40.1)	438 (41.2)
Not failed	464 (58.4)	160 (59.9)	624 (58.8)
Prior biologic failure, n (%)			
Failed	330 (41.5)	106 (39.7)	436 (41.1)
Not failed	465 (58.5)	161 (60.3)	626 (58.9)
Prior JAKi failure, n (%)			
Yes	33 (4.2)	4 (1.5)	37 (3.5)[1]
No	762 (95.8)	263 (98.5)	1025 (96.5)
Prior exposure to biologic or JAKi without failure, n (%)			
Yes	14 (1.8)	5 (1.9)	19 (1.8)
No	781 (98.2)	262 (98.1)	1043 (98.2)
Baseline modified Mayo score category, n (%)			
Moderate [5-6]	332 (41.8)	112 (41.9)	444 (41.8)
Severe [7-9]	463 (58.2)	155 (58.1)	618 (58.2)
Baseline modified Mayo score			
Mean (SD)	6.7 (1.1)	6.7 (1.1)	6.7 (1.1)
Median (min, max)	7 (5, 9)	7 (5, 9)	7 (5, 9)
Baseline corticosteroids use, n (%)			
Yes	331 (41.6)	100 (37.5)	431 (40.6)
No	464 (58.4)	167 (62.5)	631 (59.4)
Baseline immunomodulators use, n (%)			
Yes	194 (24.4)	62 (23.2)	256 (24.1)
No	601 (75.6)	205 (76.8)	806 (75.9)
Baseline aminosalicylates use, n (%)			
Yes	594 (74.7)	199 (74.5)	793 (74.7)
No	201 (25.3)	68 (25.5)	269 (25.3)

Source: Reviewer generated table using data submitted by the Applicant in BLA 761279, dataset adsl.xpt, module 5.3.5.1
[1] The percentage is 3.48% (b) (4)
Abbreviations: N, number of subjects in treatment group; n, number of subjects with given characteristic; Q4W, once every 4 weeks; IV, intravenous; JAKi, Janus kinase inhibitor; SD, standard deviation

4.2 Review of Safety

4.2.1 Safety Review Approach

The safety review of the original BLA application focused on data from the randomized, double-blind, placebo-controlled trials I6T-MC-AMAN (the 12-week induction study) and I6T-MC-AMBG (the 40-week maintenance study). Supportive safety information included data from open-label portions of I6T-MC-AMBG, as well as other indications (i.e., CD and psoriasis).

In this resubmission, the Applicant updated the safety database to include information on adverse events reported in ongoing clinical studies in subjects with UC, as well as from CD, for the period from March 23, 2022, through December 22, 2022.

4.2.2 Safety Review

During the original submission of BLA 761279, the review team determined that the safety profile of mirikizumab for the treatment of moderately to severely active UC in adults was acceptable to support the proposed indication. For details of the prior review, see the March 30, 2023, Multi-Disciplinary Review and Evaluation (Unireview) in DARRTS (Reference ID: 5150357).

In this resubmission, the Applicant's safety update did not reveal any new safety signals regarding the use of mirikizumab. The safety profile of mirikizumab in the resubmission remains consistent with the original BLA review.

4.3 Conclusions and Recommendations

The multidisciplinary review team recommends an Approval of this BLA resubmission for the treatment of moderately to severely active UC.

The safety and effectiveness of mirikizumab for the treatment of moderately to severely active UC was demonstrated in the adequate and well-controlled trials AMAN and AMBG. This BLA resubmission addressed the deficiencies of the drug product manufacturing facility described in the Complete Response letter.

5 Pediatrics

Post marketing commitments (PMC) to conduct pediatric trials were negotiated during the previous review cycle and will be issued upon approval of the BLA 761279. During the resubmission review cycle, the PMC dates were updated. Refer to Section 7 for the description of the PMCs.

6 Prescription Drug Labeling

The labeling was negotiated during the previous cycle. During the previous review cycle, the review team identified 145 subjects with an infection. The labeling submitted with the resubmission described (b) (4) subjects with an infection; therefore, the number of subjects with an infection was updated to reflect the review team's previous analysis (i.e., 145 subjects with an infection). No other significant labeling changes were made during review of the resubmission.

7 Postmarketing Requirements and Commitment

Postmarketing requirements (PMRs) and PMCs were negotiated during the previous review cycle. The Applicant agreed to the PMRs/PMCs during this review cycle. The following PMRs will be issued upon approval of BLA 761279.

4409-1 Perform a lactation study (milk only) in lactating women who have received Omvoh (mirikizumab-mrkz), regardless of indication, to assess concentrations of

mirikizumab-mrkz in breast milk using a validated assay and to assess the effects on the breastfed infant.

Draft Protocol Submission:	06/2024
Final Protocol Submission:	12/2024
Study Completion:	12/2025
Final Report Submission:	12/2026

4409-2 Conduct a prospective, registry-based, observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to mirikizumab-containing products regardless of indication during pregnancy to an unexposed control population. The registry should be designed to detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age births, preterm births, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, neonatal deaths, and infections, will be assessed through at least the first year of life.

Draft Protocol Submission:	06/2024
Final Protocol Submission:	12/2024
Study Completion:	12/2034
Final Report Submission:	12/2035

4409-3 Conduct an additional pregnancy study that uses a different design from the prospective pregnancy registry established to fulfill postmarketing requirement 4409-2 (for example a retrospective cohort study using claims or electronic medical record data with outcome validation or a case-control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm births in women exposed to mirikizumab-containing products regardless of indication during pregnancy compared to an unexposed control population.

Draft Protocol Submission:	06/2024
Final Protocol Submission:	12/2024
Study Completion:	12/2030
Final Report Submission:	12/2031

4409-4 Conduct an observational study to assess the incidence of severe acute liver injury in adults with moderately to severely active ulcerative colitis who are exposed to Omvoh (mirikizumab-mrkz), relative to other therapies used to treat ulcerative colitis. Compare rates (per person-time) or risks (proportion of patients with a minimum amount of follow-up). Describe and justify the choice of appropriate comparator population(s). Specify concise case definition for

severe liver injury and validation of algorithm(s) to identify severe liver injury in the proposed data source. For the Omvoh (mirikizumab-mrkz)-exposed and comparator(s) cohorts, clearly define the study drug initiation period and any exclusion and inclusion criteria. Ensure that the data source allows for average follow-up for at least 1 year. Specify a minimum sample size and justify the precision of the estimate achievable with the proposed study.

Draft Protocol Submission:	06/2024
Final Protocol Submission:	12/2024
Interim Submission:	12/2030
Study Completion:	12/2036
Final Report Submission:	06/2037

The following PMCs will be issued upon approval of BLA 761279.

4409-5 Complete the ongoing phase 2 trial to evaluate the safety, pharmacokinetics (PK), pharmacodynamics (PD), and clinical response to Omvoh (mirikizumab-mrkz) in pediatric patients 2 to 17 years of age with moderately to severely active ulcerative colitis.

Final Report Submission:	01/2024

4409-6 Conduct a one-year trial to evaluate the safety, efficacy, and pharmacokinetics of Omvoh (mirikizumab-mrkz) in pediatric patients 2 to 17 years of age with moderately to severely active ulcerative colitis.

Final Protocol Submission:	04/2024
Study Completion:	04/2029
Final Report Submission:	10/2029

4409-7 Conduct a long-term extension trial to evaluate the long-term safety of Omvoh (mirikizumab-mrkz) in pediatric patients 2 to 17 years of age with moderately to severely active ulcerative colitis who participated in the postmarketing commitment 4409-6. This study can be conducted as part of the postmarketing commitment 4409-6.

Final Protocol Submission:	04/2024
Study Completion:	04/2034
Final Report Submission:	10/2034

During the previous review cycle, the Applicant agreed to conduct enhanced pharmacovigilance to monitor for postmarketing events of hepatotoxicity. The Applicant agreed to the following enhanced pharmacovigilance during this review cycle, which will be issued upon approval of BLA 761279.

1. We request that for Omvoh (mirikizumab-mrkz) you submit all serious and non-serious domestic and/or foreign cases of hepatotoxicity as 15-day "Alert reports" (described under 21 CFR 600.80(c)(1)) through the 3rd year following initial U.S. approval date.

2. We request that you provide a separate narrative summary and analysis of hepatotoxicity, apart from your required analysis of 15-day "Alert reports," as part of your required periodic safety reports [e.g., periodic adverse drug experience report (PADER) required under 21 CFR 600.80(c)(2), quarterly during the first 3 years post-approval. Your analysis should include interval and cumulative data relative to the date of approval of Omvoh (mirikizumab-mrkz). Your analysis should provide an assessment of causality, with documentation of indication, temporal association, duration of therapy, associated signs and symptoms, hepatic enzymes and liver function tests, confounders, underlying risk factors, treatment given for the event, outcome, and dechallenge/rechallenge.

8 Division Director Comments

I concur with the recommendation of the review team to approve BLA 761279 for Omvoh (mirikizumab-mrkz) injection for the treatment of moderately to severely active UC in adults. The clinical safety and efficacy data contained in the original BLA, submitted on March 30, 2022, supported a favorable benefit-risk assessment (see Multi-Disciplinary Review and Evaluation, dated March 30, 2023); however, deficiencies observed during the pre-license inspection of the drug product manufacturing facility (Eli Lilly and Company, Indianapolis, Indiana [FEI 1819470]) were determined to be unacceptable to support the approval of the BLA. Thus, a Complete Response letter was issued on March 30, 2023; satisfactory resolution of these deficiencies would be required before the application may be approved.

The resubmission, received on May 24, 2023, did not contain new clinical studies. The Applicant's safety update from open-label, long-term extension study in UC as well as other related indications did not reveal any new safety signals. The safety profile of mirikizumab in the resubmission remains unchanged, and the benefit-risk of mirikizumab for the proposed indication remains favorable.

As the deficiencies identified during prior inspection of the drug product manufacturing facility (Eli Lilly and Company, Indianapolis, Indiana [FEI 1819470]) have been adequately addressed based on re-inspection of the facility, an approval action is recommended. The postmarketing requirements and commitments that were negotiated during the previous review cycle (see Section 7 of this review) will be issued at the time of the approval. In addition, enhanced pharmacovigilance will be requested to report cases of liver injury in an expedited manner.

9 Office Director Comments

I concur with the review team's assessment and recommendation to approve BLA 761279 for Omvoh (mirikizumab-mrkz) injection for the treatment of moderately to severely active UC in adults.

The original BLA submission received a Complete Response action on March 30, 2023, because of Good Manufacturing Practice (GMP) deficiencies identified during inspection of the drug product manufacturing facility (Eli Lilly and Company, Indianapolis, Indiana [FEI 1819470]). Based on data submitted, the Office of Pharmaceutical Quality concluded, and I agree, that the data are adequate to support the conclusion that the manufacture of mirikizumab is well-controlled and leads to a product that is pure and potent and recommended that this product be approved for human use under conditions specified in the package insert.

The clinical safety and efficacy data contained in the original BLA, submitted on March 30, 2022, supported a favorable benefit-risk assessment (see Multi-Disciplinary Review and Evaluation, dated March 30, 2023). The review team concluded, and I agree, that the benefit-risk profile of mirikizumab remains favorable for the proposed indication for the treatment of moderately to severely active UC in adults.

The regulatory action for BLA 761279 is Approval with agreed upon labeling.

Postmarketing requirements (PMRs) and postmarketing commitments (PMCs) will include studies detailed in Section 7.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MATTHEW R KOWALIK
10/26/2023 11:02:59 AM

NIKOLAY P NIKOLOV
10/26/2023 11:12:42 AM

This is a corrected review that does not change the overall recommendations/conclusions of the original review dated March 30, 2023.

BLA 761279 Omvoh (mirikizumab), injection

BLA Multi-Disciplinary Review and Evaluation

Application Type	BLA
Application Number(s)	761279
Priority or Standard	Standard
Submit Date(s)	March 30, 2022
Received Date(s)	March 30, 2022
PDUFA Goal Date	March 30, 2023
Division/Office	Division of Gastroenterology
Review Completion Date	March 30, 2023
Established/Proper Name	Mirikizumab-mrkz
(Proposed) Trade Name	OMVOH
Pharmacologic Class	Interleukin-23 antagonist
Code name	LY3074828
Applicant	Eli Lilly and Company
Dosage form	Injection
Applicant proposed Dosing Regimen	Induction dosage regimen: 300 mg intravenous (IV) for at least 30 minutes at Week 0, Week 4, and Week 8 Maintenance dosage regimen: 200 mg subcutaneous (SC) every 4 weeks after completion of induction dosing
Applicant Proposed Indication(s)/Population(s)	Adult patients with moderately to severely active ulcerative colitis (UC)
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	64766004 Ulcerative colitis (disorder)
Recommendation on Regulatory Action	Complete Response
Recommended Indication(s)/Population(s) (if applicable)	Not applicable
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	Not applicable
Recommended Dosing Regimen	Not applicable

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion

OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
DCOA=Division of Clinical Outcome Assessment
PFSS=Patient-Focused Statistical Support

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity

OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Trade Name: OMVOH

Pharmacological Class: Humanized immunoglobulin 4 (IgG4) monoclonal antibody

Supplied as: 300 mg/15 mL (20 mg/mL) single-dose vial for intravenous (IV) infusion; 100 mg/mL in a single-use prefilled pen (PFP, autoinjector [AI]) for subcutaneous (SC) injection.

Mirikizumab is a humanized immunoglobulin 4 (IgG4) monoclonal antibody that binds to the p19 subunit of interleukin 23 (IL-23), a cytokine that is a key mediator in intestinal mucosal inflammation (Kobayashi et al. 2008). IL-23 is a pro-inflammatory member of the IL-12 family of cytokines. It is composed of two subunits, IL-12p40, which is shared with IL-12, and IL-23p19 (the target of mirikizumab), which is specific to IL-23. IL-23 signaling has been implicated in the pathogenesis of inflammatory bowel diseases, including ulcerative colitis (UC), by genome-wide association studies (Duerr et al. 2006). Additionally, Stelara (ustekinumab), a human monoclonal antibody that binds to the IL-12p40 subunit used by both IL-12 and IL-23 is approved for the treatment of moderately to severely active UC. Skyrizi (risankizumab), a human monoclonal antibody that binds to the IL-23p19 subunit (the target as mirikizumab), and Stelara are approved for the treatment of moderately to severely active Crohn's disease (CD).

1.2. Conclusions on the Substantial Evidence of Effectiveness

The multidisciplinary review team recommends a Complete Response for this original BLA for the treatment of moderately to severely active UC due to deficiencies observed in the manufacturing facility listed in this application. Satisfactory resolution of these deficiencies is required before this application may be approved. Therefore, this original BLA is not recommended for approval in its present form until the abovementioned facility deficiencies

are satisfactorily resolved. To support this submission, the Applicant conducted two adequate and well-controlled investigations:

1. Study I6T-MC-AMAN (AMAN)[1] - A phase 3, multicenter, randomized, double-blind, parallel group, placebo-controlled induction trial. AMAN compared mirikizumab 300 mg IV every 4 weeks (Q4W) versus placebo for a treatment duration of 12 weeks.
2. Study I6T-MC-AMBG (AMBG) – A phase 3, multicenter, randomized, double-blind, parallel group, placebo-controlled maintenance trial. AMBG compared mirikizumab 200 mg SC Q4W versus placebo for a treatment duration of 40 weeks. Subjects who were mirikizumab responders[2] during AMAN were eligible for the randomized, double-blind portion of AMBG.

The primary endpoint for AMAN and AMBG was clinical remission, which was determined using the modified (3-component) Mayo score (mMS) and defined as a stool frequency subscore (SFS) = 0 or 1 with at least a 1-point decrease from baseline; a rectal bleeding subscore (RBS) = 0; and an endoscopy subscore (ES) = 0 or 1 (excluding friability), at Weeks 12 (AMAN) or 40 (AMBG). Results from AMAN indicated that mirikizumab 300 mg IV Q4W was superior to placebo in achieving clinical remission in subjects at Week 12 (mirikizumab 23.5% vs placebo 13.9%; p=0.00057). Results from AMBG indicated that mirikizumab 200 mg SC Q4W was superior to placebo in achieving clinical remission, in subjects who were mirikizumab responders during AMAN, at Week 40 (mirikizumab 50.4% vs placebo 26.0%; p<0.001). Similar results for AMAN (mirikizumab 24.0% vs placebo 14.6%; p=0.00082) and AMBG (mirikizumab 50.7% vs placebo 26.6%; p<0.001) were observed for the "alternate clinical remission"[3] endpoint. Since the "alternate clinical remission" is aligned with the Division's preferred definition for clinical remission, this definition was the focus of the review and described in product labeling.

Results of the multiplicity-controlled secondary endpoints were also statistically significantly different compared to placebo and supported the results of the primary endpoint. The secondary endpoints that achieved statistical significance include: for induction, clinical

[1] Prior to the initiation of the phase 3 program, the Applicant discussed with the Division their plan to perform a single induction trial (AMAN). The Division communicated that the results of a single induction trial would need to be statistically significant and highly persuasive to support the demonstration of substantial evidence of effectiveness. The Applicant selected an alpha-level of 0.00125, which would provide the same amount of evidence against the null hypothesis of no treatment effect as two successful trials each tested at an alpha of 0.05, to support their plan to perform a single induction trial.

[2] Mirikizumab responders were defined as subjects who achieved clinical response (defined as a decrease in the mMS of ≥ 2 points with ≥ 30% decrease from baseline, and either a decrease of ≥ 1 point in the rectal bleeding subscore (RBS) from baseline or an RBS of 0 or 1 during the induction study AMAN.

[3] Alternate clinical remission was defined as a mMS of 0 to 2, SFS of 0 or 1, RBS of 0; and an ES of 0 or 1 (excluding friability).

response at Week 12, endoscopic improvement at Week 12, symptomatic remission at Week 12, change from baseline in bowel urgency severity at Week 12, and histologic-endoscopic mucosal improvement at Week 12; for maintenance, clinical response at Week 40, endoscopic improvement at Week 40, change from baseline in bowel urgency severity at Week 40, "urgency remission"[4] at Week 40, maintenance of clinical remission at Week 40, corticosteroid-free clinical remission at Week 40, and histologic-endoscopic mucosal improvement plus absence of neutrophils at Week 40.

(b) (4)

The results from the analyses of the primary and multiplicity-controlled secondary endpoints provide substantial evidence of effectiveness for mirikizumab for the treatment of subjects with moderately to severely active UC. Thus, the Applicant has met the evidentiary standard required by 21 Code of Federal Regulations 314.126 to support approval of mirikizumab for the proposed indication. However, following pre-license inspection of the Eli Lilly and Company, Indianapolis, Indiana (FEI 1819470), manufacturing facility listed in this application, FDA conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved. Therefore, this BLA is not recommended for approval in its present form until the abovementioned facility deficiencies are satisfactorily resolved and a Complete Response (CR) action is recommended.

[4] Urgency remission was defined as an Urgency Numeric Rating Scale (NRS) of 0 or 1 among subjects with an Urgency NRS ≥ 3 at induction baseline.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Moderately to severely active ulcerative colitis (UC) is a serious chronic disease associated with morbidity and mortality when inadequately treated. Multiple therapies are approved for the treatment of moderately to severely active UC; however, there remains a need for novel therapies as not all patients will respond or have continued response to any given treatment.

Mirikizumab demonstrated efficacy in inducing clinical remission after 12 weeks of treatment with 300 mg IV Q4W, and in maintaining clinical remission over 40 weeks of treatment with 200 mg SC Q4W. Efficacy was also demonstrated on multiple clinically relevant secondary endpoint at Week 12 and Week 40. Overall, the results from the analyses of the primary and multiplicity-controlled secondary endpoints were highly statistically persuasive and provided substantial evidence of effectiveness for mirikizumab in treating adult patients with moderately to severely active UC. Therefore, the Applicant has met the evidentiary standard required by 21 Code of Federal Regulations (CFR) 314.126 to support approval of mirikizumab for the proposed indication.

(b) (4)

(b) (4)

The safety profile of the 300 mg IV Q4W induction dosage for 12 weeks and 200 mg SC Q4W maintenance dosage for 40 weeks was acceptable

and supports approval of the induction dosing regimen limited to 12 weeks and the maintenance dosing regimen. A concern for hepatotoxicity was identified as one case of drug-induced liver injury that met Hy's Law criteria was observed in a subject who received mirikizumab. The size of the safety database was inadequate to fully assess some adverse events of special interesting (including cerebrovascular events, thrombosis, and malignancy) as these events occur infrequently. To mitigate the known safety risk of hepatotoxicity, a Warnings and Precautions section will be included in labeling to communicate the risk of hepatotoxicity. Additionally, enhanced pharmacovigilance and a postmarketing observational study will be required postapproval.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Ulcerative colitis (UC), an inflammatory bowel disease (IBD), is a chronic, relapsing disease of the colonic mucosa. The peak age of occurrence is between the ages of 30 and 40. UC may affect as many as 907,000 Americans; the annual incidence rates of UC in the United States range from 1.55 to 15.0 cases per 100,000 person-years, and the prevalence ranges from 117 to 238 cases per 100,000 persons. • Patients with UC most commonly present with bloody diarrhea, rectal bleeding, tenesmus, urgency, abdominal pain, and passage of mucus in the stool. Disease of moderate to severe activity may be associated with systemic symptoms, including fatigue, fever, anorexia, nausea, weight loss, and dehydration. Patients may also experience symptoms secondary to anemia and hypoalbuminemia, including dyspnea and peripheral edema. • UC is associated with many extraintestinal manifestations, which have been reported to affect a wide variety of organ systems, most commonly joints, skin, eyes, kidneys, and hepatobiliary tract.	• UC is a chronic, relapsing inflammatory disease of the colonic mucosa. • Patients with UC commonly present with bloody diarrhea, rectal bleeding, tenesmus, urgency, abdominal pain, and passage of mucus in the stool. Left untreated, patients may experience significant morbidity and/or mortality.
Current Treatment Options	• The overall goal in the treatment and management of UC is to reduce signs and symptoms of active disease, decrease the underlying mucosal inflammation, and prevent short-term (e.g., severe bleeding,	• Mirikizumab is the first biologic within the class of IL-23 antagonists proposed for the treatment of moderately to severely active UC. A related class, an IL-12 and IL-23

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	bowel perforation) and long-term complications (e.g., colon cancer). The choice of therapy is guided by the disease severity, extent of disease, and presence of other manifestations (i.e., extraintestinal complications, malabsorption). • Therapeutic options for treatment include 5-ASA products (e.g., mesalamine), corticosteroids, antibiotics, immunomodulators (e.g., AZA, 6-MP, MTX), biologic therapies (e.g., TNFα blockers, anti-integrin receptor blockers), S1P receptor modulators, and JAK inhibitors. Corticosteroids are not recommended for long-term use given the toxicities associated with chronic steroid use. While these medications are widely used in clinical practice, not all are FDA approved for the treatment of UC. There remains a need for novel therapies as not all patients will respond or have continued response to any given treatment.	antagonist, is approved for the treatment of moderately to severely active UC. • IL-23 antagonists offer a novel mechanism of action as compared to other approved therapies. Additional therapies are needed since many patients lose response to currently available therapies over time.
Benefit	• The efficacy of mirikizumab was demonstrated in two adequate and well-controlled trials, one 12-week induction study (AMAN) and one 40-week maintenance study (AMBG), for a total treatment duration of 52 weeks. Of note, study AMAN was designed to provide the same evidence against the null hypothesis of no treatment effect as two successful studies. • In the induction study, 1281 subjects with moderately to severely active UC (defined as a mMS of 4 to 9 with an ES of at least 2) were enrolled and randomized to receive either mirikizumab 300 mg IV or placebo. The primary analysis population consisted of 1,062 subjects with moderately to severely active UC (defined as a mMS of 5 to 9 with an ES of at least 2). ○ Efficacy was demonstrated in the primary analysis	• Substantial evidence of effectiveness was demonstrated in the induction trial for the 300 mg IV dose administered Q4W for 12 weeks and maintenance trial for the 200 mg SC dose administered Q4W for 40 weeks (total treatment period of 52 weeks). (b) (4)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	population on the primary endpoint of clinical remission (defined as a mMS SFS = 0 or 1 with a ≥1-point decrease from baseline, a RBS = 0, and ES = 0 or 1 [excluding friability]). Efficacy was also demonstrated in subjects with the Division's preferred definition of clinical remission (i.e., "alternate clinical remission," defined as a mMS of 0 to 2, with a SFS of 0 or 1, RBS of 0, and ES of 0 or 1 [excluding friability]). ▪ The treatment difference in mMS clinical remission rates between mirikizumab and placebo was 9.9% (p=0.00057). ▪ The treatment difference in the Division's preferred definition of clinical remission rates between mirikizumab and placebo was 9.7% (p=0.00082). ▪ The treatment difference between mirikizumab and placebo was statistically significant for all the multiplicity controlled secondary endpoints, except for "symptomatic remission" at Week 4. • In the maintenance study, 544 subjects who were mirikizumab induction responders (defined as a decrease in the mMS of ≥2 points and ≥30% decrease from baseline, and a decrease of ≥1 point in the RBS from baseline or a RBS of 0 or 1) were re-randomized to receive either mirikizumab 200 mg SC or placebo. The primary analysis population for the maintenance study consisted of 506 subjects (defined as a mMS of 5 to 9 with an ES of at least 2 at enrollment into the induction study). ○ Efficacy was demonstrated in the primary analysis	(b) (4) • Subgroup analyses of subjects with prior biologic exposure support that these subjects, who are typically more refractory to treatment than biologic-naïve subjects, also derived benefit from treatment with mirikizumab.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	population on the primary endpoint of clinical remission. Efficacy was also demonstrated in subjects with the Division's preferred definition of clinical remission. ▪ The treatment difference in mMS clinical remission rates between mirikizumab and placebo was 22.7% (p<0.001). ▪ The treatment difference in the Division's preferred definition of clinical remission rates between mirikizumab and placebo was 22.4% (p<0.001). ▪ The treatment difference between mirikizumab and placebo was statistically significant for all multiplicity controlled secondary endpoints.	
Risk and Risk Management	• The safety of mirikizumab was evaluated in in two adequate and well-controlled trials, one 12-week induction study (AMAN) and one 40-week maintenance study (AMBG), for a total treatment duration of 52 weeks. Additional safety information in subjects with UC was provided from a phase 2 study (AMAC) and an open-label extension study (AMAP) for subjects who completed AMAN or AMBG. Safety information in subjects with Crohn's disease (CD) and psoriasis were also included; however, mirikizumab is not approved for these indications. • The following safety issues were identified: ○ Hypersensitivity reactions - Serious hypersensitivity reactions were reported in subjects who received mirikizumab, including anaphylaxis; however, anaphylaxis was reported in 2 subjects with CD and was not reported in subjects with UC.	• The safety profile of mirikizumab for the treatment of moderately to severely active UC was appropriately characterized within the UC development program and supports approval of this original BLA. • The observed drug-induced liver injury may be attributed to the longer induction regimen than recommended that was received by the subject. Additionally, the subject recovered after discontinuation of mirikizumab. Overall, AEs related to liver enzyme elevations were generally similar between mirikizumab and placebo.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	○ Infections – Infections were reported in subjects who received mirikizumab more frequently than placebo for both AMAN and AMBG. ○ Tuberculosis – Subjects were excluded if they had evidence of active TB, a past history of active TB, or were diagnosed with latent TB at screening. Based on the mechanism of action, there may be an increased risk of serious TB infection. ○ Hepatotoxicity - A case of drug-induced liver injury (alanine aminotransferase [ALT] 18x the upper limit of normal (ULN), aspartate aminotransferase [AST] 10x ULN, and total bilirubin 2.4x ULN) in conjunction with pruritis was reported one subject who received open-label extended induction mirikizumab. After mirikizumab was discontinued, the liver test abnormalities eventually returned to baseline. ○ Immunizations – Based on the mechanism of action, use of live vaccines in patients treated with mirikizumab should be avoided. • The most common adverse reactions (≥2%) during induction were upper respiratory tract infections and arthralgia. The most common adverse reactions during maintenance were upper respiratory tract infections, injection site reactions, arthralgia, headache, and rash. • Similar safety results were observed for AMAC and AMAP. • Safety results were generally similar for the open-label extended induction cohort and the open-label loss of response rescue therapy cohort; however, a case of drug-induced liver injury was reported in one subject who received open-label extended induction	• The known and anticipated risks will be managed through labeling, including the following: ○ Warnings and Precautions section will include Hepatotoxicity, Hypersensitivity Reactions, Infections, Tuberculosis, and Immunizations to inform patients and prescribers of the potential risks of mirikizumab. ○ Section 6.1 Clinical Trial Experience will include "Infections" and "Hepatic Enzyme Elevations" as an adverse reaction. ○ The following Procedures Prior to Treatment Initiation will be included in Section 2.1 of the label: ▪ Evaluate patients for TB infection ▪ Obtain liver enzymes and bilirubin levels ▪ Complete all age-appropriate vaccinations

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	mirikizumab. After mirikizumab was discontinued, the liver test abnormalities eventually returned to baseline. • The size of the safety database was inadequate to fully assess some adverse events of special interest (including cerebrovascular events, thrombosis, and malignancy) as these events occur infrequently. • The available data are insufficient to inform mirikizumab-associated risk during pregnancy and lactation.	• The following postmarketing requirements will be issued under 505(o): ○ An observational study to assess DILI in adult patients with UC ○ A lactation trial ○ Pregnancy registry, both prospective and retrospective studies. • Postapproval enhanced pharmacovigilance for DILI with expedited reporting of liver injury using detailed questionnaire for follow-up for the reported cases will be requested. • Postapproval commitments will be issued to conduct a safety and efficacy trial as well as a long-term extension study to evaluate the long-term safety of mirikizumab in pediatric patients 2 to 17 years of age with moderately to severely active UC. • Following pre-license inspection of the Eli Lilly and Company, Indianapolis, Indiana (FEI 1819470), manufacturing facility listed in this application, FDA

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved. Therefore, from an OPQ perspective, this BLA is not recommended for approval in its present form until the abovementioned facility deficiencies are satisfactorily resolved, and OPQ recommends a Complete Response (CR) action.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	Sections 8.1, 16.4, 16.5, 16.6
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	X	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		Section 16.4
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	X	Other: Literature review, Study of a Prospective Adult Research Cohort with IBD (SPARC IBD)		Section 16.4
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			

	□	Input informed from participation in meetings with patient stakeholders	
	□	Patient-focused drug development or other stakeholder meeting summary reports	
	□	Observational survey studies designed to capture patient experience data	
	□	Other: (Please specify):	
□	**Patient experience data was not submitted as part of this application.**		

2. Therapeutic Context

2.1. Analysis of Condition

Ulcerative colitis (UC) is a chronic, relapsing, and remitting inflammatory bowel disease characterized by diffuse mucosal inflammation of the colon and rectum.

The etiology of UC is not well understood but it is a multifactorial disorder. Genetic predisposition, epithelial barrier defects, dysregulated immune responses and environmental factors play a role in its pathogenesis (Ungaro et al. 2017).

UC may affect any age group, with the peak age of diagnosis ranging from 30 to 40 years of age, and is more common in men (Cosnes et al. 2011). The annual incidence rates of UC in the United States range from 1.55 to 15.0 cases per 100,000 person-years, and the prevalence ranges from 117 to 238 cases per 100,000 persons. UC may affect as many as 907,000 Americans. Globally, the prevalence of UC continues to rise, particularly in North America and Europe, and is expected to increase in newly industrialized countries in Africa, Asia, and South America (Ng et al. 2017).

Clinical manifestations of active disease include bloody diarrhea (with or without mucus), urgency, tenesmus, abdominal pain, weight loss, fever, and malaise. In patients with extensive or severe inflammation, acute complications may occur such as severe bleeding and toxic megacolon, which can lead to colon perforation. Almost half of patients experience a UC-related hospitalization at some point during the disease course. Patients may also experience symptoms from anemia and hypoalbuminemia, including dyspnea and peripheral edema and are at an increased risk of perforated bowel, toxic megacolon, and colorectal cancer. The estimated risk of colorectal cancer is approximately 2% after 10 years, 5% to 10% after 20 years, and 12% to 30% after 30 to 35 years of UC (Bernstein et al. 2001; Eaden et al. 2001; Feuerstein and Cheifetz 2014).

UC is associated with many extraintestinal manifestations, which have been reported to affect a wide variety of organ systems, most commonly joints, skin, eyes, kidneys, and hepatobiliary tract (Ungaro et al. 2017).

Ulcerative colitis is associated with high morbidity, with high rates of fatigue, lower health-related quality of life, and high disability (Fumery et al. 2018). Additionally, childhood-onset UC has been associated with an increased risk of all-cause mortality (Olén et al. 2019).

2.2. Analysis of Current Treatment Options

The goals of UC treatment include reducing signs and symptoms of active disease, decreasing the underlying mucosal inflammation, and preventing short-term (e.g., severe bleeding, bowel perforation) and long-term complications (e.g., colon cancer).

Treatment of UC is challenging due to its multifactorial nature and incompletely understood pathogenesis. UC is also a chronic disease, in general, most drugs that are initiated for induction of remission are continued as maintenance therapy, if they are effective (Feuerstein et al. 2020).

Therapeutic options for the treatment of moderately to severely active UC include a variety of pharmacologic therapies such as tumor necrosis factor (TNF)-α antagonists (infliximab, adalimumab, golimumab), anti-integrin agents (vedolizumab), Janus kinase (JAK) inhibitors (tofacitinib, upadacitinib), interleukin (IL) 12/23 antagonist (ustekinumab), sphingosine 1-phosphate (S1P) receptor modulator (ozanimod), and other immunomodulators (thiopurines, methotrexate). However, a proportion of patients who have initially responded to these therapies may subsequently lose response and experience recurrence of UC symptoms. Recent systematic reviews and meta-analyses have reported that the estimated incidence rates of loss of response (LOR) to vedolizumab was 39.8 (per 100 person-years of follow-up) in patients with UC (Peyrin-Biroulet et al. 2019) and the loss of response to anti-TNF agents was approximately 25% in one year and in 33% in 3 years in patients with IBD (Guberna et al. 2021).

Although multiple approved therapies are available, there remains a need for novel therapies for patients who have had an inadequate response, intolerance, or loss of response to available therapies and would benefit from the availability of additional therapeutic options.

The currently approved systemic therapies for the treatment of moderately to severely active UC are summarized in Table 1 below.

Table 1. Summary of Systemic Therapies for the Treatment of Moderately to Severely Active Ulcerative Colitis

Product (s) Name	Relevant Indication	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Tumor Necrosis Factor (TNF) Blocker				
Infliximab (Remicade®) BLA-103772 Approval: 1998 Infliximab Biosimilars: Avsola® (Infliximab-AXXQ) BLA-761086 Inflectra® (Infliximab-DYYB) BLA-125544 Ixifi® (Infliximab-QBTX) BLA-761072 Renflexis® (Infliximab-ABDA) BLA-761054	Reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use	IV 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks	Study I: 69% and 62% of subjects taking infliximab 5 mg/kg and 10 mg/kg, respectively, achieved clinical response at week 8 (37% plc) 39% and 32% of subjects taking infliximab 5 mg/kg and 10 mg/kg, respectively, achieved clinical remission at week 8 (15% plc) 35% and 34% of subjects taking infliximab 5 mg/kg and 10 mg/kg, respectively, achieved clinical remission at week 54 (17% plc) 62% and 59% of subjects taking infliximab 5 mg/kg and 10 mg/kg, respectively, achieved mucosal healing at week 8 (34% plc) 45% and 47% of subjects taking infliximab 5 mg/kg and 10 mg/kg, respectively,	Boxed Warning Increased risk of serious infections. leading to hospitalization or death Perform test for latent TB; if positive, start treatment for TB prior to starting Infliximab. Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with tumor necrosis factor (TNF) blockers, including Infliximab. Postmarketing cases of fatal hepatosplenic T-cell lymphoma (HSTCL) have been reported in patients treated with TNF blockers including Infliximab. Warnings and precautions: Serious infections including TB, invasive fungal infections, hepatitis B reactivation, malignancies (including lymphoma, melanoma, and Merkel cell carcinoma), heart failure, demyelinating disorders, cytopenias, Lupus-like syndrome, hypersensitivity, Cardiovascular and Cerebrovascular reactions, Most common adverse reactions (>10%) infections (e.g., upper respiratory, sinusitis, pharyngitis), infusion-related reactions, headache, and abdominal pain.

Product (s) Name	Relevant Indication	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
			achieved mucosal healing at week 54 (18% plc)	
Adalimumab (Humira®) BLA-125057 Approval: 2002 Adalimumab Biosimilars: Abrilada® (Adalimumab-AFZB) BLA-761118 Amjevita® (Adalimumab-ATTO) BLA-761024 Cyltezo® (Adalimumab-ADBM) BLA-761058 Hadlima® (Adalimumab-BWWD) BLA 761059 Hulio® (Adalimumab-FKJP) BLA-761154 Hyrimoz® (Adalimumab-ADAZ)	Inducing and sustaining clinical remission in adult patients with moderately to severely active UC who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6 mercaptopurine (6- MP). Limitations of Use: The effectiveness of Humira has not been established in patients who have lost response to or were intolerant to TNF blocker.	SQ Initial dose (Day 1): 160 mg SQ Second dose two weeks later (Day 15): 80 mg SQ Two weeks later (Day 29): Begin a maintenance dose of 40 mg every other week.	Study I: 18.5% of subjects receiving adalimumab 160/80 mg achieved clinical remission at week 8 (9.2% plc) Study II: 16.5% of subjects receiving adalimumab 160/80 mg achieved clinical remission at week 8 (9.3% plc) 8.5% of subjects receiving adalimumab 160/80 mg achieved sustained clinical remission (clinical remission at both weeks 8 and 52. (4.1% plc)	Boxed Warning Same as infliximab Warnings and precautions: Serious infections including TB, invasive fungal infections, hepatitis B reactivation, malignancies, heart failure, demyelinating disorders, cytopenias/pancytopenia, Lupus-like syndrome, anaphylaxis, or hypersensitivity reactions. Most common adverse reactions (>10%): Infections (upper respiratory, sinusitis), injection site reactions, headache, and rash.

Product (s) Name	Relevant Indication	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
BLA-761071 Idacio (Adalimumab-AACF) BLA-761255 Yusimry (Adalimumab-AQVH) BLA-761216				
Golimumab (Simponi®) BLA-125289 Approval: 2009	Moderate to severe UC with an inadequate response or intolerant to prior treatment or requiring continuous steroid therapy: - inducing and maintaining clinical response - improving endoscopic appearance of the mucosa during induction - inducing clinical remission - achieving and sustaining clinical remission in induction responders	SQ Initial dose (week 0): 200 mg SQ Second dose (week 2): 100 mg SQ then 100 mg SQ every 4 weeks	Study I: 51% of subjects receiving golimumab 200/100 mg achieved clinical response at week 6 (30% plc) 18% of subjects achieved clinical remission at week 6 (6% plc) 42% of subjects achieved improvement in endoscopic appearance of the mucosa at week 6 (29% plc) Study II: 50% of subjects receiving golimumab 100 mg achieved clinical response through week 54 (31% plc)	Boxed Warning Same as infliximab Warnings and precautions: Serious infections, invasive fungal infections, hepatitis B reactivation, malignancies (lymphoma), congestive heart failure, demyelinating disorders, Lupus-like syndrome, and hypersensitivity, reaction. Most common adverse reactions (>5%): Upper respiratory tract infection, nasopharyngitis, and injection site reactions.

Product (s) Name	Relevant Indication	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
			28% of subjects achieved clinical remission at both week 30 and week 54 (16% plc)	
Integrin Receptor Antagonist (inhibits α4β7 integrin)				
Vedolizumab (Entyvio®) BLA-125476 Approval: 2014	In adult patients for the treatment of moderately to severely active UC	IV 300 mg infused IV over 30 minutes at 0, 2 and 6 weeks, then every 8 weeks thereafter	Study I: 47% of subjects achieved clinical response at week 6 (26% plc) 17% of subjects achieved clinical remission at week 6 (5% plc) Study II: 42% of subjects achieved clinical remission at week 52 (16% plc) 57% of subjects achieved clinical response at both weeks 6 and 52 (24% plc) 52% of subjects achieved improvement of endoscopic appearance of the mucosa at week 52 (20% plc)	Warnings and precautions: Infusion related hypersensitivity reactions, Infections, Progressive Multifocal Leukoencephalopathy (PML) Most common adverse reactions (incidence ≥3% and ≥1% higher than placebo): nasopharyngitis, headache, arthralgia, nausea, pyrexia, upper respiratory tract infection, fatigue, cough, bronchitis, influenza, back pain, rash, pruritus, sinusitis, oropharyngeal pain, and pain in extremities.

Product (s) Name	Relevant Indication	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Janus Kinase (JAK) Inhibitors				
Tofacitinib (Xeljanz®/ Xeljanz XR™) NDA 203214/ NDA 208246	Adult patients with moderately to severely active UC, who have had an inadequate response or who are intolerant to TNF blockers. Use in combination with biological therapies for UC or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended	Tablets/Extended-Release Tablets/Oral Solution Xeljanz: 10 mg twice daily for at least 8 weeks for a maximum of 16 weeks; then 5 or 10 mg twice daily Xeljanz XR: 22 mg once daily for at least 8 weeks for a maximum of 16 weeks, then 11 mg once daily	Study I: 18% of subjects taking 10 mg twice daily achieved clinical remission at week 8 (8% plc) 31% of subjects taking 10 mg twice daily achieved improvement of endoscopic appearance of the mucosa at week 8 (16% plc) Study II: 17% of subjects taking 10 mg twice daily achieved clinical response at week 8 (4% plc) 28% of subjects taking 10 mg twice daily achieved improvement of endoscopic appearance of the mucosa at week 8 (12% plc) Study III: 34% and 41% subjects taking 5 mg twice daily and 10 mg twice daily, respectively, achieved maintenance of clinical remission at week 52 (11% plc) 37% and 46% subjects taking	Boxed warning: Increased risk of serious bacterial, fungal, viral, and opportunistic infections leading to hospitalization or death, including tuberculosis (TB). Malignancies (lymphomas and lung cancers) Higher rate of all-cause mortality, including sudden cardiovascular death. Higher rate of MACE (defined as cardiovascular death, myocardial infarction, and stroke) Thrombosis (including pulmonary, deep venous and arterial). Warnings and precautions: Serious infections, gastrointestinal perforations, changes in lymphocytes, neutrophils, hemoglobin, liver enzymes and lipids. Most common adverse reactions (incidence ≥5% and ≥1% higher than placebo): nasopharyngitis, elevated cholesterol levels, headache, upper respiratory tract infection, increased blood creatine phosphokinase, rash, diarrhea, and herpes zoster.

Product (s) Name	Relevant Indication	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
			5 mg twice daily and 10 mg twice daily, Respectively, achieved improvement of endoscopic appearance at week 52 (13% plc)	
Upadacitinib (Rinvoq®) NDA-211675 Approval: 2021	Adult patients with moderately to severely active ulcerative colitis, who have had an inadequate response or intolerance to one or more TNF blockers LOU: Rinvoq is not recommended for use in combination with other JAK inhibitors, biological therapies for ulcerative colitis, or with other potent immunosuppressants such as azathioprine and cyclosporine	Extended-Release Tablets Induction: 45 mg once a day for 8 weeks Maintenance: 30 mg or 15 mg once daily (30 mg QD for patients with refractory, severe, or extensive disease)	Induction studies:	Boxed warning: Serious infections, higher rate of all-cause mortality, including sudden cardiovascular death, Malignancies (lymphoma and lung cancer) , higher rate of major adverse cardiovascular events (MACE), and thrombosis (pulmonary embolism, venous and arterial) Warnings and precautions: Serious infections, including localized infection, hypersensitivity, GI perforation, laboratory abnormalities in lymphocytes, neutrophils, hemoglobin, liver enzymes and lipids, embryo-fetal toxicity Adverse reactions (≥ 5%): upper respiratory tract infections, increased blood creatine phosphokinase, acne, neutropenia, elevated liver enzymes, and rash

			Study I: 26% of subjects achieved clinical remission at 8 weeks (5% plc) 73 % of subjects achieved clinical response at 8 weeks (27% plc) 36% of subjects achieved improvement of endoscopic appearance of the mucosa at week 8 (7% plc) Study II: 33 % of subjects achieved clinical remission at 8 weeks (4% plc) 74 % of subjects achieved clinical response at 8 weeks (25% plc) 44% of subjects achieved improvement of endoscopic appearance of the mucosa at week 8 (8% plc) Maintenance Study: Study III: 52%, and 42% of subjects treated with 30 mg and 15 mg, respectively, achieved maintenance of clinical remission at 52 weeks (12% plc)	

Product (s) Name	Relevant Indication	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
			62%, and 49% of subjects treated with 30 mg and 15 mg, respectively, achieved Improvement of endoscopic appearance of the mucosa at 52 weeks (14% plc)	
Human Interleukin (IL 12 and 23) Antagonist				
Ustekinumab (Stelara®) BLA-761044 Approval: 2009	Adult patients with moderately to severely active UC	SQ or IV A single IV infusion using weight-based dosing. Induction: Up to 55 kg: 260 mg (2 vials), greater than 55 kg to 85 kg: 390 mg (3 vials), greater than 85 kg 520 mg (4 vials) 8 weeks after the initial dose Maintenance: 90 mg SQ injection every 8 weeks	Study I: 19% of subjects achieved clinical remission at 8 weeks (7% plc) 58% of patients achieved clinical response at 8 weeks (31% plc) 25% of subjects achieved endoscopic improvement at 8 weeks (13% plc) 17% of subjects achieved histologic endoscopic mucosal improvement at 8 weeks (8% plc) Study II: 66% of subjects who achieved clinical remission 8 weeks after induction achieved maintenance of clinical	Warnings and precautions: Serious infections, tuberculosis, malignancies, hypersensitivity reactions, reversible posterior leukoencephalopathy syndrome (PRES), and noninfectious pneumonia Most common AEs: induction (≥3%): Nasopharyngitis; maintenance (≥3%): Nasopharyngitis, headache, abdominal pain, influenza, fever, diarrhea, sinusitis, fatigue, and nausea

Product (s) Name	Relevant Indication	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
			remission at 44 weeks (36% plc) 74% of subjects achieved maintenance of clinical response at 44 weeks (48% plc) 47% of subjects achieved endoscopic improvement at 44 weeks (27% plc)	
Sphingosine 1-Phosphate (S1P) Receptor Modulator				
Ozanimod (Zeposia®) NDA-209899 Approval: 2020	Adult patients with moderately to severely active ulcerative	Capsule Titration is required for treatment initiation Days 1-4: 0.23 mg once daily Days 5-7: 0.46 mg once daily Maintenance dosage Day 8 and thereafter: 0.92 mg once daily	Induction study:	Warnings And Precautions: Infections, bradyarrhythmia and atrioventricular conduction delays, liver injury, fetal risk, increased blood pressure, respiratory effects (may cause a decline in pulmonary function), macular edema Most common adverse reactions (incidence ≥4%): liver test increased, upper respiratory infection, and headache

Product (s) Name	Relevant Indication	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
			Study I: 18 % of subjects achieved clinical remission at 10 weeks (6% plc) 48 % of subjects achieved clinical response at 10 weeks (26% plc) 27% of subjects achieved endoscopic improvement at 10 weeks (12% plc) Maintenance Study: Study II: 37% of subjects achieved maintenance of clinical remission at 52 weeks (19% plc) 60 % of subjects achieved clinical response at 52 weeks (41% plc) 46% of subjects achieved endoscopic improvement at 52 weeks (26% plc)	

Source: Reviewer's table
Abbreviations: Subcutaneous (SQ); intravenous (IV); plc: placebo

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Mirikizumab is an original biologic that is not currently marketed in the US.

3.2. Summary of Presubmission/Submission Regulatory Activity

A summary of pertinent regulatory interactions between the Applicant and FDA are described in Table 2. Responses by FDA that are relevant to the review of this BLA are included in the table.

Table 2. Presubmission Correspondence History

Date	Activity	Outcome/Discussion
July 15, 2015	Initial IND submitted	Deemed safe to proceed on August 27, 2015.
November 15, 2017	Type C, Guidance meeting, Face to Face	Discussion focused on the Sponsor's clinical development program including patient exposure, dose selection for phase 2 induction and maintenance, secondary endpoints and immunogenicity sampling and evaluation.
November 17, 2017	Type C, Written Responses Only (WRO), Guidance	Feedback was provided on the Sponsor's nonclinical, clinical pharmacology development plans, safety monitoring and assessments, and the study data standardization plan.
May 24, 2018	Type B, End of Phase 2 meeting, Face to Face	Discussion focused on the proposed phase 3 development plan seeking feedback on the following areas: Proposal to support effectiveness with a single induction study *FDA noted that two adequate and well-controlled trials are generally required, and that adequacy of a single trial would depend upon the of the results.* Dose selection for the phase 3 induction and maintenance UC trials *FDA noted that a clear dose-/exposure-response relationship for efficacy was not demonstrated in the phase 2 trial, thus the selection of the 300 mg IV Q4W induction dosage is not well justified. FDA recommended an additional, higher dose cohort in the phase 3 induction study. The*

Date	Activity	Outcome/Discussion
		maintenance dosage selection of 300 mg SC Q4W appeared reasonable. Bridging data from the planned psoriasis program with respect to the phase 1/2 and phase 3 formulations and presentations to the to-be marketed formulations and presentations Safety monitoring and the estimated number of patient exposures for the durations specified to support a marketing application Proposed drug-drug interaction study
September 30, 2019	Type C, Guidance, teleconference that was cancelled following receipt and review of FDA's preliminary meeting comments	Discussion focused on the following areas: Clinical meaningfulness of bowel urgency as a symptom of UC *FDA agreed that bowel urgency is a relevant and clinically meaningful symptom of UC for patients.* The development and psychometric analysis plan for an Urgency Numeric Rating Scale (NRS) patient-reported outcome (PRO) as a measure of bowel urgency *FDA agreed that the Urgency NRS appeared acceptable.* (b) (4) [redacted] *FDA recommended the urgency NRS endpoint be analyzed as a continuous or ordinal variable with anchor-based analyses to support the clinical meaningfulness of any demonstrated change.*
February 20, 2020	FDA Advice Letter	FDA recommended a change to the definition of clinical remission, as FDA thinking had evolved. The Applicant incorporated the recommended endpoint as a multiplicity-controlled, secondary endpoint in its phase 3 development program as "alternate clinical remission."
July 20, 2020	Type C, Guidance, WRO	Feedback was provided on the Sponsor's plan to address the impact of a data integrity issue related to personal eCOA device for sites in Poland and Turkey

Date	Activity	Outcome/Discussion
November 13, 2020	Type C, Guidance, WRO	Feedback was provided on the proposed sensitivity analyses due to COVID-19 mitigations in the statistical analysis plan (SAP) for Study I6T-MC-AMAN, a phase 3 study of mirikizumab in patients with moderately to severely active ulcerative colitis.
August 3, 2021	Type C, Guidance, WRO	Feedback was provided on the key components of a future marketing application as well as the efficacy endpoint definition of histologic-endoscopic mucosal remission.
January 21, 2022	Type B, pre-BLA meeting	Preliminary comments focused on the adequacy of data from the following phase 3 induction and maintenance studies, I6T-MC-AMAN (AMAN) I6T-MC-AMBG (AMBG) I6T-MC-AMAP(AMAP) to support the submission and review of an original BLA to be submitted in Q2 of 2022 for mirikizumab to support the proposed indication statement, "for the treatment of adult patients with moderately to severely active ulcerative colitis (UC)." *FDA stated that because the induction study (AMAN) used a two-sided alpha level of 0.00125 to define statistical significance, the approach to submit results from a single induction study appeared reasonable.* *FDA recommended an analysis of the primary endpoint and multiplicity-controlled secondary endpoints with FDA's preferred definition of "moderate to severely active UC" defined as a modified Mayo Score of 5 to 9 with an endoscopic subscore of at least 2.* Following receipt of FDA's preliminary comments, the Sponsor elected to cancel the teleconference scheduled for January 26, 2022, as the preliminary comments addressed the Sponsor's questions, and no further feedback was needed.

4. Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Site inspections were conducted to assess the quality and integrity of the data submitted in this marketing application. Clinical investigators (CI), Nicholas Martinez, MD (Site 2822, San Antonio, Texas) and Juris Pokrotnieks, MD (Site 2423, Riga, Latvia) were selected for inspections

based on large subject enrollment, high treatment response, each CI having conducted both studies (AMAN and AMBG), and no recent inspection history. The non-US CI, Dr. Pokrotnieks in Latvia, was selected due to the large amount of data from sites outside the US in the application.

No significant good clinical practice (GCP) violations were observed. The two audited studies appear to have been conducted in compliance with GCP principles and regulations. The audited data for the two CIs (Site 2822, San Antonio, Texas and Site 2423, Riga, Latvia) appear acceptable in support of the BLA.

Refer to the Clinical Inspection Summary by Dr. John Lee on December 1, 2022, under BLA 761279 for full details of the inspections.

4.2. Product Quality

The Office of Pharmaceutical Quality (OPQ), CDER, has completed assessment of BLA 761279 for Omvoh (mirikizumab-mrkz) manufactured by Eli Lilly and Company. The data submitted in this application are not sufficient to support a conclusion that the manufacture of Omvoh (mirikizumab-mrkz) is well-controlled and will lead to a product that is pure and potent. From a CMC standpoint, OPQ is recommending a Complete Response letter be issued to Eli Lilly and Company to outline the deficiencies noted below and the information and data that will be required to support approval.

Facility Inspections

Following pre-license inspection of the ELI LILLY AND COMPANY, Indianapolis, Indiana (FEI 1819470), manufacturing facility listed in this application, FDA conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

See the OPQ Executive Summary Integrated Quality Assessment for more detailed assessment by Dr. Nailing Zhang that was placed in DARRTS on February 17, 2023, under BLA 761279.

4.3. Devices and Companion Diagnostic Issues

The Center for Devices and Radiological Health (CDRH) assessed the device constituent of the combination product, (b) (4) an autoinjector. The CDRH reviewed the Device Description, Labeling, Design Controls, Risk Analysis, and Design Verification to provide a recommendation of the approvability of the device constituent of the combination product. The device constituent of the combination product was found to be approvable for the proposed indication.

Refer to the CDRH review by Drs. Papatya Kaner, Courtney Evans, and Alan Stevens dated January 27, 2023, that was placed in DARRTS on February 15, 2023, under BLA 761279 for full details of the device review.

(b) (4)

Refer to DMEPA review by Matthew Barlow and Jason Flint dated December 19, 2022, and late-cycle meeting minutes dated February 14, 2023.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

No safety issues related to the approval of mirikizumab 300 mg administered via intravenous (IV) infusion every 4 weeks or 200 mg administered subcutaneously (SC) every 4 weeks for the treatment of adult patients with UC have been identified from the conducted nonclinical studies.

Mirikizumab had similar binding affinity to both human and cynomolgus monkey IL-23 (K_d = 21 pM and 55 pM, respectively). A surrogate mouse antibody (LSN2479016) neutralized mouse IL-23 in two murine models of inflammatory bowel disease, demonstrating efficacy. No adverse cardiovascular, central nervous system, or respiratory findings were observed in monkeys as part of the 4-week toxicology study administered via both IV (doses up to 100 mg/kg) and SC (doses up to 30 mg/kg) routes.

Two six-month toxicity studies were conducted in cynomolgus monkeys, one by IV (twice weekly) and the other by SC (once weekly) routes of administration. In the IV study, changes in hematology parameters were limited to mild to moderate decreases in red blood cell mass indices for one female monkey at the high dose of 300 mg/kg/dose on day 180, likely representing an idiosyncratic immune-mediated effect of mirikizumab. In the SC study, minimal to mild inflammatory reactions were observed at the SC injection sites. In some monkeys, antidrug antibody-related reduced exposures were observed which did not affect overall study interpretations.

No adverse effects on male or female reproductive organs were observed in sexually mature cynomolgus monkeys in the 6-month repeat dose SC study at doses up to 100 mg/kg/dose once weekly. An enhanced pre- and postnatal development study was conducted in cynomolgus monkeys administered mirikizumab by intravenous injection during organogenesis to parturition at a dose of 300 mg/kg twice weekly. No maternal toxicity was noted in this study. There were no treatment-related effects on morphological, functional, or immunological development in infant monkeys from birth through 6 months of age. However, incidences of embryo/fetal loss were higher in the treated groups compared to control (6.7% [1 of 15] in controls vs 26.7% [4 of 15] at 300 mg/kg) but were within the range of historical control data.

Conventional rodent carcinogenicity studies were not conducted for the evaluation of the carcinogenic potential of mirikizumab as rodents are not a pharmacologically relevant species.

The Applicant provided a weight-of-evidence analysis of available information to address the carcinogenic potential of mirikizumab. Concurrence has been received from the Executive Carcinogenicity Assessment Committee of CDER that a 2-year rodent carcinogenicity study is not needed.

5.2. Referenced NDAs, BLAs, DMFs

All the pivotal nonclinical studies have been reviewed under INDs 125444 (b) (4). Summary pharmacology/toxicology information is provided in this review.

5.3. Pharmacology

Mirikizumab is a humanized IgG4 monoclonal antibody that binds with high affinity and specificity to the p19 subunit of human IL-23 cytokine and inhibits its interaction with the IL-23 receptor. It has no observed cross-reactivity to other members of the IL-12 cytokine family. Neutralization of IL-23 using a surrogate mouse antibody, LSN2479016, demonstrated efficacy in two murine models of inflammatory bowel disease. Mirikizumab had similar binding affinity to both human and cynomolgus monkey IL-23 (K_d = 21 pM and 55 pM, respectively).

5.4. ADME/PK

Table 3. ADME/PK Study Findings

Type of Study	Major Findings
Absorption	
Pharmacokinetics of LY3074828 Formulated With and Without rHuPH20 in Cynomolgus Monkeys Following a Single Subcutaneous Administration (8340712)	• LY3074828 alone and with rHuPH20 (hyaluronidase enzyme) were detected through 336 hours and 504 hours, respectively. • Mean C_{max} increased from 16.5 µg/mL to 37.1 µg/mL and T_{max} shifted from 36 to 9.3 hours. The mean clearance decreased from 3.83 mL/hr/kg to 2.08 mL/hr/kg. Mean half-life was similar with and without rHuPH20 at 50.5 and 59.1 hours.
A Pharmacokinetic Study of the Second Generation IL-23 Antibody - LY3074828 (b) (4) Following a Single Intravenous or Subcutaneous Dose to Cynomolgus Monkey (8256194)	○ $T_{1/2}$ was 5 days and mean clearance was 0.79 mL/hr/kg following IV administration. • Rapidly absorbed after SC administration, T_{max} 12-24 hours; mean clearance 1.81 mL/hr/kg. $T_{1/2}$ was 3 days, bioavailability was 43%.

Type of Study	Major Findings
TK data from general toxicology studies	Monkey (4-week SC) T1/2: 25 – 48 hours Avg M+F C_{max}: 126 µg/mL (30 mg/kg NOAEL) Avg M+F AUC_{0-168}: 8055 µg*h/mL (30 mg/kg NOAEL) Accumulation: None observed Dose proportionality: Roughly dose proportional Monkey (4-week IV) T1/2: 40 – 48 hours Avg M+ F C_{max}: 2385 µg/mL (100 mg/kg NOAEL) Avg M+F AUC_{0-168}: 51,050 µg*h/mL (100 mg/kg NOAEL) Accumulation: None observed Dose proportionality: Not tested Monkey (6-month SC) T1/2: 31 hours Avg M+F C_{max}: 352 µg/mL (100 mg/kg NOAEL) Avg M+F AUC_{0-168}: 21,450 µg*h/mL (100 mg/kg NOAEL) Accumulation: Slight 0.243-1.71 accumulation ratio Dose proportionality: Roughly dose proportional at the beginning of dosing; suspected ADA at end of dosing Monkey (6-month IV) T1/2: 1 hour Avg M+F C_{max}: 2250 µg/mL (100 mg/kg NOAEL) Avg M+F AUC_{0-96}: 55000 µg*h/mL (100 mg/kg NOAEL) Accumulation: 0.947 – 1.5 accumulation ratio Dose proportionality: Increased with increasing dose

Type of Study	Major Findings
TK data from reproductive toxicology studies *An Assessment of the Effect of LY3074828 on Pre- and Postnatal Development When Administered by Intravenous Injection Twice Weekly to Pregnant Cynomolgus Monkeys (Report No. 20102344)* • *Maternal NOAEL: 300 mg/kg/dose* • *Developmental NOAEL: 300 mg/kg/dose*	Monkey F0 AUC_{0-96}: 127000 hr*µg/mL on GD70 (69x MRHD) F1 AUC: Serum Concentration – BD14 5.41 – 17.8 µg/mL (males) 2.16 – 12.3 µg/mL (females)

5.5. Toxicology

5.5.1. General Toxicology

Two six-month (IV and SC) toxicity studies in cynomolgus monkeys were conducted to support the chronic use of mirikizumab in patients. Injection site reactions were observed in the subcutaneously dosed groups. No adverse effects were observed in monkeys at doses up to 30 times the MRHD (300 mg Q4W IV), based on AUC comparison.

Study title/number: A Repeat Dose Toxicity and Toxicokinetic Study in Cynomolgus Monkeys Given LY3074828 by Intravenous or Subcutaneous Injection Once Weekly for 4 Weeks with an 8-week Recovery (Study No. 20029153)

- There was no mortality. The NOAEL for each route of administration was the highest dose tested, 30 mg/kg SC and 100 mg/kg IV.
- Minimal perivascular mononuclear cell, or mononuclear and eosinophil cell infiltrates were observed in the subcutis in one or more of the subcutaneous injection sites in animals at ≥ 1 mg/kg (males and females).

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 1, 30 (SC), 100 mg/kg (IV) once weekly

Route of administration: IV (100 mg/kg) and SC (0, 1, and 30 mg/kg)

Formulation/Vehicle: 10 mM sodium citrate, 150 mM NaCl, 0.02%, polysorbate 80, pH 6.0

Species/Strain: Cynomolgus monkeys

Number/Sex/Group: 3 animals/sex/group (main study), 2 animals/sex/group (recovery)

Age: 2.3 – 3.8 years

Satellite groups/ unique design: Recovery (2 animals/sex/group)

Deviation from study protocol affecting interpretation of results: No

Table 4. Observations and Results: Changes From Control

Parameters	Major findings
Mortality	No mortalities
Clinical Signs	2/3 females at 100 mg/kg had transient slight tremors postdose on day 29
Body Weights	No treatment related effects
Ophthalmoscopy	No treatment related effects
ECG	No treatment related effects
Hematology	No treatment related effects
Clinical Chemistry	No treatment related effects
Urinalysis	No treatment related effects
Gross Pathology	No treatment related effects
Organ Weights	No treatment related effects
Histopathology Adequate battery: Yes	Minimal perivascular mononuclear and eosinophil cell infiltrates were observed in the subcutis in one or more of the subcutaneous injection sites in animals at ≥ 1 mg/kg (males and females). Generally, these findings were seen mostly at the high dose (30 mg/kg, SC); however, the infiltrates were similar in severity (minimal) in both the low and high dose groups. There were no treatment related microscopic findings in animals treated IV at 100 mg/kg.
Anti-Drug Antibody (ADA) Analysis	ADA analysis results were not provided in the report
Immunophenotyping	No treatment related effects

Study title/ number: A Repeat-Dose Toxicity and Toxicokinetic Study in Cynomolgus Monkeys Given LY3074828 by Once Weekly Subcutaneous Injection for 6 Months (Study No. 20043324)

- No treatment-related adverse effects were observed
- Non-adverse injection site reactions, consisting of minimal to mild perivascular mononuclear and eosinophil cell infiltrates were observed at both doses. Changes were observed in control animals, were not clearly dose-dependent, and were not accompanied by any gross observations.
- The NOAEL was considered as 100 mg/kg.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 10, 100 mg/kg once weekly

Route of administration: Subcutaneous

Formulation/Vehicle: 10 mM sodium citrate buffer, 150 mM NaCl,0.02%, polysorbate 80, pH 6.0

Species/Strain: Cynomolgus monkeys

Number/Sex/Group: 4 animals/sex/group

Age: Males: 6.7 – 8.3 years, Females: 4.8 – 7.5 years

Satellite groups/ unique design: None

Deviation from study protocol affecting interpretation of results: No

Table 5. Observations and Results: Changes From Control

Parameters	Major findings
Mortality	There were no mortalities.
Clinical Signs	No treatment related effects
Body Weights	No treatment related effects
Ophthalmoscopy	No treatment related effects
ECG	No treatment related effects
Hematology	LD: transient moderate increase in monocytes (5.18x baseline) on Day 36 (in single female) HD: moderately increased eosinophil count (5.10x baseline) on Day 183 in single female that correlated with chronic pancreatitis (moderate eosinophilic infiltrate observed microscopically). Due to limited exposure to mirikizumab in that animal (undetectable blood levels after Day 85), relationship to the treatment was considered unlikely.
Clinical Chemistry	LD: Moderate decrease in albumin (0.58x) associated with a minimal increase in globulin (1.27x) and mild decrease in total protein (0.83x), and mild decreases in sodium and chloride (0.93x and 0.87x, respectively) with a concurrent increase in monocytes, likely indicating acute phase protein reaction in a single female. Based on the sporadic and transient nature of these findings in addition to the lack of a dose response, these were considered unlikely to be treatment related. LD: Triglycerides increased to ≥ 200 mg/dL in one male and one female HD: Triglycerides increased to ≥ 200 mg/dL in 2 males
Urinalysis	No treatment related effects

Gross Pathology	No treatment related effects
Organ Weights	No treatment related effects
Histopathology Adequate battery: Yes	LD and HD: Minor mixed cell infiltrates at the subcutaneous injection sites were observed. The changes consisted of minimal to mild perivascular mononuclear and eosinophil cell infiltrates. These changes were not clearly dose related, also observed in control animals, and were not accompanied by any gross observations and were not considered adverse. HD: Single female monkey had chronic pancreatitis characterized by fibrosis, proliferation of ductular elements, and increased eosinophils. Due to limited exposure in that animal (undetectable blood levels after Day 85), any relationship to the treatment was considered unlikely. Although rare, chronic pancreatitis is seen as a background lesion in Macaque monkeys (Sato J, et al., 2012, Histopathology of Incidental Findings in Cynomolgus Monkeys (Macaca fascicularis) Used in Toxicity Studies, J Toxicol Pathol, 25: 63-101; Tsuchitani M and Narama I,1988, Chronic Pancreatitis in Macaca Monkeys. Jpn J Vet Sci, 50: 439-444). Special stains to attempt identification of potential pathogenic organisms were negative.
Immunophenotyping	There were no significant treatment related changes in the lymphocyte subsets evaluated.
Natural-killer (NK) Cell Activity Assay	No treatment related effects
T-Cell Dependent Antibody Response (TDAR)	No treatment related effects

LD: low dose; MD: mid dose; HD: high dose.

Study title/number: A Repeat-Dose Toxicity, Immunotoxicity, and Toxicokinetic Study in Cynomolgus Monkeys Given LY3074828 by Twice Weekly Intravenous Injection for 6 Months (Study No. 20119229)

- The NOAEL was 100 mg/kg/dose
- Findings were limited to changes in hematology parameters which included mildly to moderately decreased red blood cell indices for one female monkey at 300 mg/kg/dose on day 180. The effects in this monkey most likely represent an idiosyncratic immune-mediated effect of mirikizumab

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 100 or 300 mg/kg/dose twice weekly

Route of administration: Intravenous bolus

Formulation/Vehicle: 10 mM sodium citrate, 150 mM sodium chloride, 0.03% polysorbate 80, pH 5.5

Species/Strain: Cynomolgus Monkey

Number/Sex/Group: 4 animals/sex/group

Age: 2.3 – 2.5 years old/immature

Satellite groups/ unique design: None

Deviation from study protocol affecting interpretation of results: No

Table 6. Observations and Results: Changes From Control

Parameters	Major Findings
Mortality	None
Clinical Signs	No treatment related effects
Body Weights	No treatment related effects
Ophthalmoscopy	No treatment related effects
ECG	No treatment related effects
Hematology	HD: In one female monkey -37% RBC count, -23% hemoglobin, -26% hematocrit, +264% reticulocytes, +17% mean corpuscular volume, +21% corpuscular hemoglobin, +66% red cell distribution width consistent with responsive erythropoiesis suggestive of immune-mediated hemolysis which correlated microscopically with minimal increased erythroid cellularity in the bone marrow, extramedullary hematopoiesis in the lymph node, and erythrophagocytosis/hemosiderin deposition in the spleen
Clinical Chemistry	HD: Mildly increased hemoglobin in the monkey found to have hemolysis HD: Reversible and minimally increased cholesterol (male and female) and glucose (male only).
Urinalysis	No treatment related effects
Gross Pathology	No treatment related effects
Organ Weights	Absolute and relative spleen weights increased in female with hemolysis correlating with mild congestion microscopically

Histopathology Adequate battery: Yes	Minimal increased cellularity of the erythroid lineage in the bone marrow, minimal extramedullary hematopoiesis in the inguinal lymph node, mild red pulp congestion with minimal erythrophagocytosis, minimal golden brown granular pigment within the macrophage cytoplasm, minimal golden brown to brown granular pigment in Kupffer cells of the liver with intracytoplasmic red blood cells
Immunogenicity	On day 85, 7 animals tested positive for ADA (N=4 at 100 mg/kg/dose; N=3 at 300 mg/kg/dose); on day 180, 5 animals tested positive for ADA (N=3 at 100 mg/kg/dose; N=2 at 300 mg/kg/dose)
Immunophenotyping	There were no treatment related changes in any of the lymphocyte subsets evaluated
Natural-killer (NK) Cell Activity Assay	No treatment related changes were observed in the NK cell cytolytic activity
T-Cell dependent Antibody Response (TDAR)	No treatment related differences in center point titer (CPT) values

LD: low dose; MD: mid dose; HD: high dose.
-: indicates reduction in parameters compared to control.

5.5.2. Genetic Toxicology

Not conducted, in line with ICH S6(R1).

5.5.3. Carcinogenicity

Conventional rodent carcinogenicity studies were not conducted for the evaluation of the carcinogenic potential of mirikizumab as rodents are not a pharmacologically relevant species. Concurrence has been received from the Executive Carcinogenicity Assessment Committee of CDER that a 2-year rodent carcinogenicity study is not needed. The Applicant provided a weight-of-evidence analysis of available information to address the carcinogenic potential of mirikizumab.

In general, an overview of the published literature supports that neutralization of IL-23 would not be expected to increase cancer risk, but rather IL-23 increases tumor incidence and promotes tumor growth and progression. Mirikizumab is highly selective against IL-23, with no evidence of binding to other cytokines or cell surface targets *in vitro* and no evidence of off-target toxicity observed in toxicity studies. No evidence of increased cellular proliferation or effects on immunosurveillance (circulating lymphocytes, natural killer cell function, primary immune response, lymphoid organ histopathology) have been observed in repeat dose toxicity studies in cynomolgus monkeys administered mirikizumab 100 mg/kg subcutaneously (once weekly) or 300 mg/kg/dose intravenously (twice weekly) for 26 weeks.

5.5.4. Reproductive and Developmental Toxicology

Prenatal and Postnatal Development

Study title/ number: An Assessment of the Effect of LY3074828 on Pre- and Postnatal

Development When Administered by Intravenous Injection Twice Weekly to

Pregnant Cynomolgus Monkeys (Report No. 20102344)

Key Study Findings

- Higher incidences of embryo/fetal loss in the 300 mg/kg treated groups compared to control (6.7% [1 of 15] in controls vs 26.7% [4 of 15] at 300 mg/kg) but within the range of historical control data.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes.

Methods

Dose and frequency of dosing: 0 and 300 mg/kg twice weekly.

Route of administration: Intravenous bolus.

Formulation/Vehicle: 10 mM Sodium citrate, 150 mM sodium chloride, 0.03% polysorbate 80, pH 5.5.

Species/Strain: Monkey/Cynomolgus.

Number/Sex/Group: 15 animals/female/group.

Satellite groups: None.

Study design: Only one dose level was used in the study.

Deviation from study protocol affecting interpretation of results: No.

Table 7. Observations and Results

Generation	Major Findings
F0 Dams	Incidences of embryo/fetal loss were higher in the treated groups compared to control (6.7% [1 of 15] at 0 mg/kg vs 26.7% [4 of 15] at 300 mg/kg) but were within the range of historical control data
F1 Generation	Infants were evaluated up to 6 months. There were no treatment-related effects on PPND endpoints. Mirikizumab exposure was detected in all infants for at least 28 days after birth.
F2 Generation	Not evaluated

5.5.5. Other Toxicology Studies

Excipients, Leachables, and Elemental Impurities Assessment

Mirikizumab is administered once every four weeks via intravenous infusion or subcutaneous injection. Mirikizumab for subcutaneous injection is an aqueous solution of 100 mg/mL. The maximum dose volume is 2 mL. Mirikizumab for intravenous injection is an aqueous solution of 20 mg/mL, the maximum dose volume is 15 mL. All identified leachables and elemental impurities were below the Safety Concern Threshold (SCT) or calculated permitted daily exposure (PDE). Thus, there are no safety concerns for leachables or elemental impurities. There are no novel excipients, or excipients of human or animal origin used in the manufacturing of mirikizumab drug product. Levels used in this drug product are similar to or lower than those in other FDA approved products.

Subcutaneous Product

The container closure system (CCS) for mirikizumab for subcutaneous injection consists of a (b) (4) glass syringe barrel with (b) (4) elastomeric plunger, (b) (4) Leachables testing using the drug formulation in the CCS was conducted on three batches of drug product at accelerated conditions for 6 months and long-term, refrigerated storage condition for 24-months.

The analytical evaluation threshold (AET) was calculated based on ICH M7(R1). Leachables of concern were identified at the threshold of toxicological concern (TTC) for chronic exposure to a genotoxic or carcinogenic compound of 1.5 µg/day, used as the SCT. This was used to derive the following AET:

SC AET (ug/mL) = SCT (1.5 ug/day) x (28 day /2 mL) = 21 ug/mL

The Sponsor's AET for the subcutaneous product is (b) (4) ug/mL, a lower and more conservative threshold.

Potential leachables were tested for based on an extractable study of the (b) (4) CCS. Headspace gas chromatography/mass spectroscopy (GC-MS), direct injection GC-MS, and high-performance liquid chromatography-photodiode-array detection-mass spectroscopy (HPLC-PDA-MS) screening methods were developed to ensure detection of any volatile (VOC), semi-volatile (SVOC), or non-volatile organic compounds (NVOCs). The reporting limits were set less than the AET (b) (4) µg/mL) at (b) (4) µg/mL for VOC, ≥ (b) (4) µg/mL for SVOC and NVOCs. Three lots of mirikizumab d ug product were stored in the horizontal orientation and tested for potential leachables up to 36 months (completed 24 months) at 2°-8°C and up to 6 months at 30°C/75% relative humidity (completed). No leachables were detected above the AET for the following batches (C961553 (b) (4); C965266 – (b) (4) C915405 – (b) (4) . The long-term refrigerated (2°C - 8°C) leachable study is ongoing. One NVOC leachable was reported at a concentration of (b) (4) µg/mL at the initial time point for a single product batch in the long-term refrigerated study. However, the concentration is well below the AET. The peak was not reported at later time points (up to 24 months).

Elemental Impurities

The alert level was set at (b) (4)% of the permitted element concentration for a 1200 mg (60 mL) dose. Samples were analyzed by inductively coupled plasma – mass spectrometry (ICP-MS) for elemental impurities at the initial and 24-month time points. Samples are planned to be analyzed at the 36-month time point.

The only element reported in the subcutaneous product leachables study was (b) (4). The maximum result was (b) (4) ug/mL. Potential exposure for a 2 mL dose is (b) (4) ug every 28 days.

A PDE of (b) (4) ug/day for intravenous exposures to (b) (4) was calculated from a 90-day repeat-dose rat NOAEL of (b) (4) mg/kg (b) (4) The margin of safety is 488x even at a daily exposure of the dose.

<u>Intravenous Product</u>

The CCS for mirikizumab for intravenous injection is a 20 mL, clear, (b) (4) glass tubing vial with a (b) (4) l elastomeric closure (stopper) and a two piece, (b) (4), flip-top seal. Leachables testing using the drug formulation in the CCS was conducted on two batches of drug product for 6 months, 24-months (completed) and 36 months (ongoing).

The AET was calculated based on ICH M7(R1). Leachables of concern were identified at the TTC for chronic exposure to a genotoxic or carcinogenic compound of 1.5 µg/day, used as the SCT. This was used to derive the following AET:

IV AET (ug/mL) = SCT (1.5 ug/day) x (28/15 mL) = 2.8 ug/mL

The Sponsor's AET for the intravenous product is (b) (4) ug/mL, a lower and more conservative threshold.

Potential leachables were tested for based on an extractable study of the CCS. Headspace GC-MS, direct injection GC-MS, and HPLC-PDA-MS screening methods were utilized to detect and characterize VOC, SVOC, and NVOC, respectively. The reporting limits were set conservatively less than the AET at [(b) (4)] ug/mL. Two lots of mirikizumab drug product and two different lots of vial components were stored in the inverted orientation at 2°-8°C and 30°C/75% relative humidity. Samples were analyzed up to 6 months at 30°C and up to 36 months for 2°-8°C.

Leachable study results for the 24-month time point were submitted. No VOCs were detected ≥ [(b) (4)] ug/mL for product batches C995781 and C995785. [(b) (4)] was detected at concentrations of [(b) (4)] ug/mL after 3 months of accelerated study condition (30°C/75% relative humidity), which exceeded the Sponsor's AET of [(b) (4)] ug/mL.

The acceptable daily intake (ADI) for [(b) (4)] established by the European Food Safety Authority is [(b) (4)] mg/kg/day. After applying a safety factor of 10 for IV dosing, the ADI is [(b) (4)] mg/kg/day. For an average human weighing 50 kg, IV PDE of [(b) (4)] is [(b) (4)] mg/kg/day x 50 kg = [(b) (4)] mg/day or [(b) (4)] ug/day. The margin of safety (MOS) is 98x with a daily exposure of the dose.

Elemental Impurities

No elemental leachables were reported for the product batches tested up to 24 month time point. The alert level was [(b) (4)]% of the permitted element concentration for a 1200 mg (60 mL) dose.

6. Clinical Pharmacology

6.1. Executive Summary

The Applicant submitted an original Biologics License Application (BLA) 761279 for mirikizumab (OMVOH®) for the treatment of adult patients with moderately-to-severely active ulcerative colitis (UC). Mirikizumab is a 144 kDa humanized immunoglobulin G4 (IgG4) monoclonal antibody directed against the p19 subunit of human interleukin (IL)-23. Binding to IL-23 inhibits its interaction with the IL-23 receptor, which affects the differentiation, expansion, and survival of T cell and innate immune cell subsets thought to mediate the pathology in UC. Currently, there are no approved biologic products for UC that specifically target IL-23 p19. Risankizumab, another monoclonal antibody directed against IL-23 p19, is approved for Crohn's disease (CD).

The proposed dosage regimen is 300 mg infused intravenously (IV) for at least 30 minutes at Week 0, Week 4, and Week 8 for induction treatment followed by 200 mg subcutaneous (SC) (given as two consecutive SC injections of 100 mg each) every 4 weeks (Q4W) for maintenance treatment.

Proposed dosage forms/presentations are: 300 mg/15 mL in a single-dose vial for IV infusion and 100 mg/mL in a single-dose prefilled pen (PFP) (i.e., autoinjector [AI]) (b) (4) for SC injection

The submission includes data from three phase 1 studies conducted in healthy subjects (AMAA, AMAD, and AMBD), one phase 2 study (AMAC) for induction and maintenance treatment in subjects with moderately to severely active UC, and one phase 3 induction study (AMAN) and a phase 3 maintenance study (AMBG) in subjects with moderately to severely active UC. A long-term extension study (AMAP) enrolling subjects with UC rolled over from the phase 2 and phase 3 trials, is also currently ongoing. No study report has been submitted for AMAP, although some data on immunogenicity was included using data up to the time of data cutoff (December 6, 2021). In addition, the results from a clinical study in subjects with psoriasis (AMAA) and a drug-drug interaction (DDI) study conducted in subjects with psoriasis (AMBP) were submitted. Of note, the Applicant has not pursued an indication for psoriasis.

The proposed dosage regimens were supported by phase 3 trials using the to-be-marketed formulation and presentations (PFS). The proposed PFP (AI) for SC injection was not used in the phase 3 trial but was adequately bridged to the PFS used in the phase 3 trial via a relative bioavailability study (AMBW) conducted in healthy subjects.

Key review issues and comments are summarized below in Table 8.

Table 8. Summary of Clinical Pharmacology Review

Review Issues	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The effectiveness of mirikizumab for the treatment of moderate to severe ulcerative colitis was established in two phase 3 trials: AMAN, which evaluated the proposed induction dosing regimen of 300 mg IV Q4W, and AMBG, which evaluated the proposed maintenance dosing regimen of 200 mg SC Q4W.
Recommended Dosage Regimens	**Induction dosage**: 300 mg IV infused for at least 30 minutes at Weeks 0, 4, and 8 **Maintenance dosage**: 200 mg SC (given as two consecutive 100 mg SC injections) starting after completion of induction treatment, then every 4 weeks thereafter
Dosage in patient subgroups (intrinsic and extrinsic factors)	Alternative dosage based on intrinsic or extrinsic factors is not recommended. No intrinsic or extrinsic patient factors are expected to result in mirikizumab exposure differences that would have a clinically significant impact on efficacy or safety.
Bridging between the to-be-marketed and	(b) (4) the to-be-marketed formulation and PFS presentation that were used in the phase 3 studies, the Applicant proposes a PFP (AI) presentation

Review Issues	Recommendations and Comments
clinical trial formulations	for SC maintenance dosing which was not used in phase 3. In a relative bioavailability study (AMBW), which compared the AI to the PFS used in phase 3, comparable exposure and immunogenicity incidence between the two presentations were observed. Overall, the data support the comparability of the (b) (4) PFS and AI presentations for SC administration of mirikizumab.
Immunogenicity	23% of subjects treated with mirikizumab developed anti-drug antibodies (ADAs). Of those who developed ADAs, 38% developed high titers (≥ 160 defined by the Applicant). Ten out of 33 subjects (30%) with higher treatment emergent (TE) ADA titers (≥ 160) had reduced serum mirikizumab trough concentrations, and 5 of these 10 did not achieve clinical response at the end of maintenance treatment, despite initially responding to induction treatment. Overall, the response rate for clinical remission and endoscopic improvement among TE ADA positive subjects was not adversely affected relative to TE ADA negative subjects. Neutralizing ADAs could not be analyzed due to the limitation of the assay. Refer to the OBP's review by Dr. Nailing Zhang that was placed in DARRTS on February 17, 2023, under BLA 761279.
Pharmacodynamics	In the phase 2 study AMAC, reductions in plasma IL-17A and IL-22 were observed during induction treatment (IV infusion with mirikizumab at weeks 0, 4, and 8) at 4 and 12 weeks after treatment initiation. In the phase 3 induction study (AMAN), reductions from baseline in mean C-reactive protein (CRP) and fecal calprotectin (markers of inflammation) were observed, following mirikizumab induction treatment at Week 12 (AMAN), but not following treatment with placebo. CRP and fecal calprotectin remained low among mirikizumab induction responders who were randomized to mirikizumab maintenance treatment in study AMBG. Both CRP and fecal calprotectin are general markers of inflammation that are not specific to UC. Their utility in predicting clinical response in UC is therefore unclear.
Pharmacokinetics	In healthy subjects, mirikizumab systemic exposure increased proportionally from 60 to 2400 mg following single IV infusion over at least 30 minutes and from 200 mg and 400 mg following single SC administration. The median T_{max} following a SC dose was 4 days, and the half-life following either IV or SC doses ranged from 10.2 to 10.8 days. The mean bioavailability of a 200 mg SC dose of mirikizumab was approximately 38% to 39% in healthy subjects. The PK of mirikizumab was similar between healthy subjects and subjects with UC based on a comparison of PK parameter estimates in healthy subjects pooled across phase 1 studies with phase 3 population PK estimates in subjects with UC
Exposure-Response	In AMAN, higher mirikizumab average concentration was associated with higher rates of clinical remission, clinical response, endoscopic remission, and endoscopic response. With maintenance treatment of 200 mg SC Q4W (Study AMBG), efficacy plateaued at higher exposures.
Disease-Drug Interactions	No drug-drug interaction studies were conducted in subjects with UC. Results from clinical drug-drug interaction study (AMBP) in subjects with moderate-to-severe psoriasis indicates that mirikizumab, 250 mg SC Q4W, did not result in changes in the exposure of midazolam (CYP3A substrate), warfarin (CYP2C9 substrate), dextromethorphan (CYP2D6 substrate), omeprazole (CYP2C19 substrate), or caffeine (CYP1A2 substrate).

Review Issues	Recommendations and Comments
	However, given possible differences in inflammatory burden across disease states, it is not clear that data generated in subjects with moderate-to-severe psoriasis are fully applicable to patients with UC. As such, the label will clarify that the study was not done in subjects with UC at the recommended dosage.

6.1.1. Recommendation

The Office of Clinical Pharmacology reviewed this submission and found it acceptable for approval.

6.1.2. Post-marketing requirement/Post-marketing commitment

None.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

6.2.1.1. *Mechanism of Action and Pharmacodynamics*

Mirikizumab is a humanized IgG4 monoclonal antibody that binds to the p19 subunit of IL-23, a naturally occurring proinflammatory cytokine. Binding to IL-23 inhibits its interaction with the IL-23 receptor, which affects the differentiation, expansion, and survival of T cell and innate immune cell subsets thought to mediate the pathology in UC.

Subjects randomized to receive mirikizumab showed significant reductions from baseline in mean C-reactive protein (CRP) and fecal calprotectin (markers of inflammation) at Week 12 of induction treatment (AMAN). CRP and fecal calprotectin remained low among mirikizumab induction responders who were randomized to mirikizumab maintenance treatment (AMBG). Because CRP and fecal calprotectin are general markers of inflammation that are not specific to UC, the relationship between these observed PD changes and the mechanisms through which mirikizumab exerts its clinical effects in UC is not known.

6.2.1.2. *Clinical Pharmacokinetics of Mirikizumab*

In healthy subjects, following single dose IV administration infused over at least 30 minutes, mirikizumab systemic exposure increased proportionally from 60 to 2400 mg in healthy subjects. Following single SC administration, mirikizumab systemic exposure increased proportionally from 200 mg and 400 mg in healthy subjects. The median T_{max} following a SC dose was 4 days, and the half-life following either IV or SC doses ranged from 10.2 to 10.8 days. The geometric mean bioavailability of a 200 mg SC dose of mirikizumab was approximately 38% to 39% in healthy subjects. Mirikizumab PK parameters in healthy subjects are summarized in Table 9.

Table 9. Mirikizumab PK Parameters Following Single Dose of Mirikizumab Administered Intravenously or Subcutaneously in Healthy Subjects

	300 mg IV[a] Geometric mean (CV%) (n=10)	200 mg SC[b] Geometric mean (CV%) (n=120)
C_{max} (µg/mL)	145 (6%)	14.3 (44 %)
AUC_{inf} (µg·day/mL)	936 (12%)	246 (44%)
T_{max} (day)[c]	0.03 (0.03 - 0.25)	4.0 (1.8 - 10.2)
$T_{1/2}$ (day)[d]	9.53 (7.73 - 11.7)	10.9 (4.6 - 20.5)
CL or CL/F (L/day)	0.321 (12%)	0.813 (44%)

[a]Study AMBD in healthy Chinese Subjects; [b]Study AMBW in healthy subjects following SC administration with prefilled syringe; [c]Median (min-max); [d]Geometric mean (min-max)
AUC_{inf} = Area under the concentration-versus-time curve from time of administration to infinity following a single dose; CL = total body clearance of mirikizumab; CL/F = apparent total body clearance of mirikizumab calculated after extravascular administration; C_{max} = maximum concentration; CV = geometric coefficient of variation; F = absolute bioavailability; IV = intravenous; SC = subcutaneous; $T_{1/2}$ = half-life associated with the terminal rate constant in non-compartmental analysis; T_{max} = time of maximum observed mirikizumab concentration after start of IV infusion or after SC injection.
Source: Table 2.7.2.4 in Summary of Clinical Pharmacology and Table 2.7.1.7 in Summary of Biopharmaceutic Studies

The PK of mirikizumab was found to be similar between healthy subjects and subjects with UC based on a comparison of PK parameter estimates in healthy subjects pooled across phase 1 studies with phase 3 population PK estimates in subjects with UC .

In subjects with UC, pharmacokinetics were characterized using population PK (popPK) analysis. Mirikizumab concentrations did not significantly accumulate over time when administered as 300 mg IV Q4W or 200 mg SC Q4W and the clearance (CL) was independent of dose. The geometric mean absolute bioavailability following SC dosing was estimated to be 44% (geometric CV% = 34%).

In subjects with UC, geometric mean (CV%) clearance was 0.0229 L/hours (34%) and the geometric mean (CV%) half-life was 9.3 days (40%). The geometric mean (CV%) total volume of distribution was 4.83 L (21%). Following SC dosing of mirikizumab in subjects with UC, median T_{max} was 5 days (range = 3.08 to 6.75 days) post dose. Mirikizumab exposure in subjects with UC at steady state are summarized in Table 10.

Table 10. Mirikizumab Steady State Exposure in Subjects With UC

	Geometric mean (CV%)	
Dosage Regimen	**Induction Treatment 300 mg IV Q4W**	**Maintenance Treatment 200 mg SC Q4W**
$C_{max,ss}$ (µg/mL)	99.7 (22.7%)	10.1 (52.1%)
$AUC_{tau,ss}$ (µg·day/mL)	538 (34.4%)	160 (57.6%)
$C_{trough,ss}$ (µg/mL)	2.75 (101%)	1.70 (83.3%)

$AUC_{tau,ss}$ = Area under the concentration-versus-time curve over one dosing interval at steady state; $C_{max,ss}$ = maximum concentration at steady state; $C_{trough,ss}$ = concentration at the end of the dosing interval at steady state; CV = geometric coefficient of variation; IV = intravenous; Q4W = every 4 weeks; SC = subcutaneous; UC = ulcerative colitis.
Source: Applicant's Summary of Clinical Pharmacology Section 2.7.2.1.1.1 and Applicant's Population PK report

6.2.1.3. *Immunogenicity*

Out of 378 evaluable subjects treated with mirikizumab 300 mg IV Q4W induction followed by 200 mg SC Q4W maintenance over 52 weeks in phase 3 studies AMAN and AMBG, 88 (23%) developed treatment-emergent (TE) anti-drug antibodies (ADAs) to mirikizumab. Population PK

analysis did not identify any differences in PK according to TE ADA status (positive versus negative).

Overall, the efficacy was not lower in subjects who are TE ADA positive compared to those who are TE ADA negative: clinical remission (58% vs. 48%) and endoscopic improvement (66% versus 57%) at Week 40 in phase 3 (AMBG).

Of note, out of 32 subjects with higher TE ADA titers (≥160), 10 (31%) had reduced serum trough mirikizumab concentrations that correlated with increasing TE ADA titers, and 5 of these 10 did not achieve clinical response at the end of maintenance treatment (study AMBG). The proportion of subjects with ADA titers ≥160 that achieved clinical outcomes tended to be lower as compared with subjects with lower titers. Following maintenance treatment with 200 mg SC Q4W in Study AMBG, 38% of subjects with ADA ≥160 versus 51% of subjects with ADA <160 achieved clinical remission at Week 40. See Section 6.3.1.4 for details.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The recommended dosing regimens are as follows:

- **Induction dosing**: 300 mg IV infused for at least 30 minutes at Weeks 0, 4, and 8
- **Maintenance dosing**: 200 mg SC (given as two consecutive 100 mg SC injections (b) (4) starting at Week 12 after completion of induction dosing, then every 4 weeks thereafter. SC injection can be administered in abdomen, upper arm, or thigh.

The recommended induction and maintenance dosage was supported by clinical efficacy and safety data as well as population PK and exposure-response analyses in subjects with UC from phase 3 studies AMAN and AMBG.

The phase 3 induction dosage was selected based on the dose cohort with highest observed efficacy at Week 12 of induction treatment in phase 2 study AMAC (see Section 6.3.2.2). The phase 3 maintenance dosage was selected based on maintenance treatment in study AMAC, where subjects who received 200 mg SC Q4W appeared to have more consistent symptomatic scores within a dosing interval compared to subjects who received 200 mg SC Q12W in the open-label period (see Section 16.3.1.2).

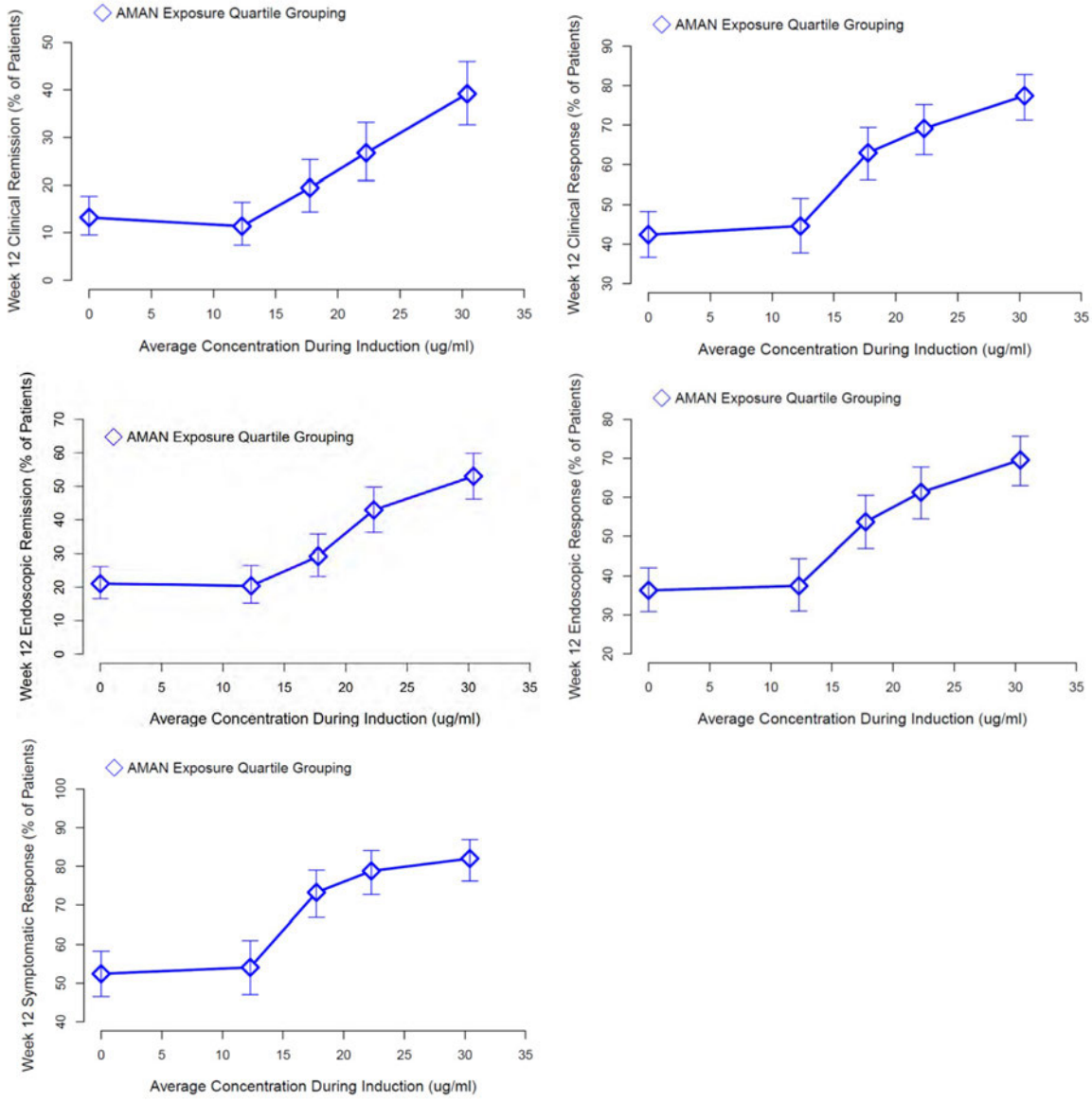
Exposure-Response Relationships for Efficacy

In the phase 3 induction study (AMAN), the proportion of subjects achieving clinical remission at Week 12 following treatment with 300 mg IV Q4W mirikizumab was 23.5% relative to 13.9% following placebo treatment. The proportion of subjects achieving clinical response at Week 12 after mirikizumab treatment and placebo treatment was 64.7% and 43.4%, respectively. The proportion of subjects achieving endoscopic remission at Week 12 after mirikizumab treatment and placebo treatment was 34.5% and 21.0%, respectively. Refer to Section 8.1.2 for additional details.

As shown in Figure 1, higher mirikizumab average concentration (C_{avg}) was associated with higher rates of clinical remission, clinical response, endoscopic remission, endoscopic response, and symptomatic response at Week 12. Subjects in the lowest induction exposure quartile had no significant difference in clinical efficacy compared to placebo across all efficacy endpoints for induction.

The proposed 300 mg IV Q4W induction dosage is acceptable in terms of efficacy from a clinical pharmacology perspective. Additional details regarding E-R analyses of induction treatment can be found in Section 6.3.2.2.

Figure 1. Percent of Subjects Achieving Efficacy Endpoints at Week 12 of Induction Treatment Versus Mirikizumab C_{avg} Quartile in Phase 3 Study AMAN



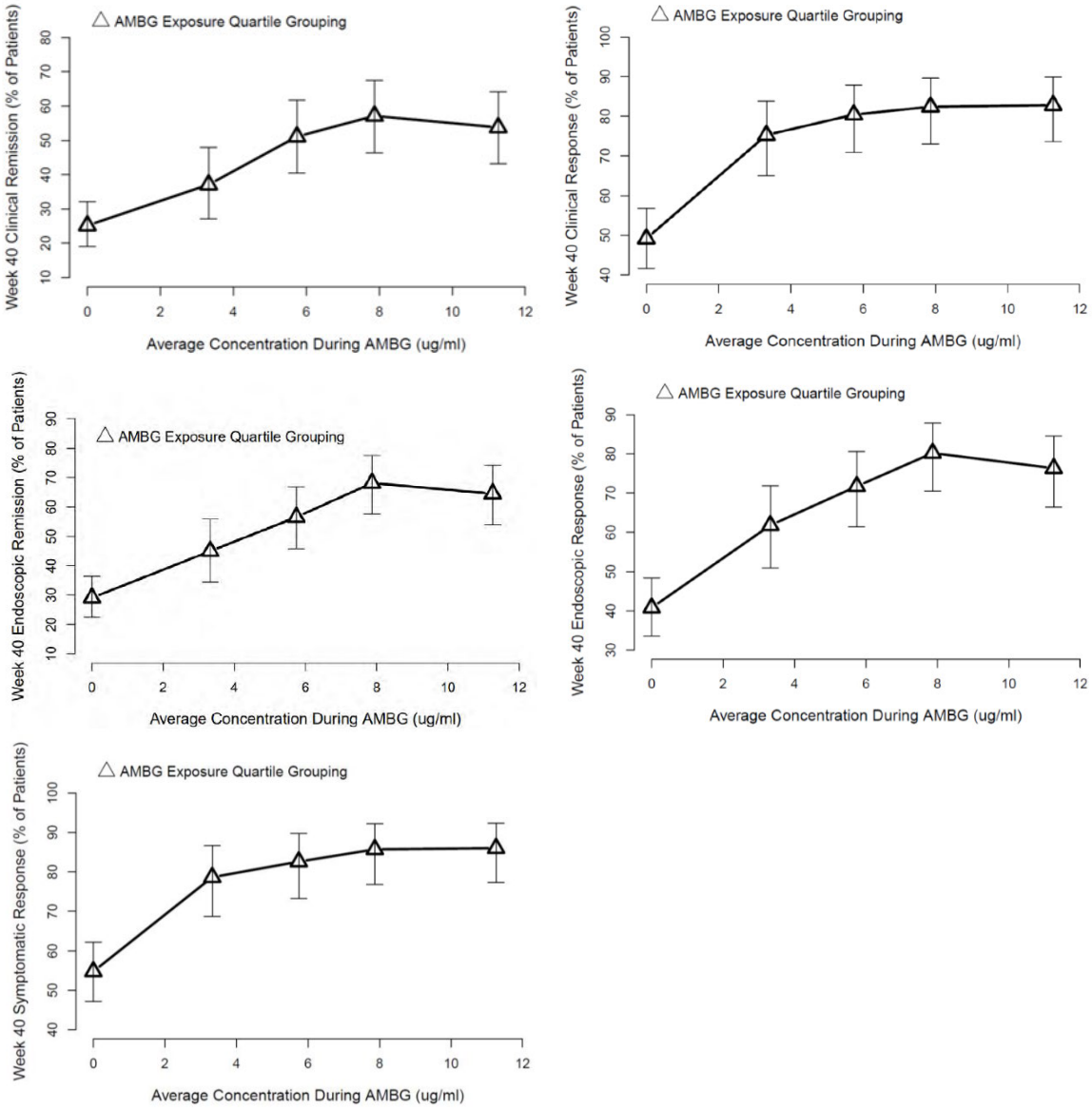
C_{avg} = average mirikizumab concentration during induction treatment; N = number of subjects; Q = quartile.
Note: The AMAN data points represent the rates of clinical efficacy endpoints in the placebo group (N = 295) and the subjects that received 300 mg mirikizumab subdivided into C_{avg} quartiles (N = 211, 216, 217, 217 for Q1 to Q4, respectively). The points are plotted along the x-axis at the median C_{avg} for each quartile. Error bars represent 95% confidence intervals.
Source: Figures 4.1 to 4.4 in Applicant's Response (dated 25May2022) to 18May2022 Information Request; Figure 3 in Applicant's Response (dated 25July2022) to 18July2022 Information Request

In the phase 3 maintenance study (AMBG) in subjects who achieved clinical response following mirikizumab 300 mg IV Q4W induction treatment, the proportion of subjects achieving clinical remission at Week 40 was 50.4% in subjects who received mirikizumab 200 mg SC Q4W maintenance treatment relative to 26.0% in subjects who received placebo maintenance treatment. The proportion of subjects achieving endoscopic remission at Week 40 following

mirikizumab maintenance treatment and placebo treatment was 57.9% and 29.6%, respectively. Refer to Section 8.1.4 for additional details.

Figure 2 displays the exposure-response associations for efficacy endpoints in Study AMBG according to maintenance C_{avg} quartile. Higher mirikizumab exposure was associated with higher rates of clinical remission, endoscopic remission, and endoscopic response at Week 40 of maintenance treatment. The rates of clinical remission, clinical response, endoscopic remission, endoscopic response, and symptomatic response were higher in all maintenance exposure quartiles compared to placebo. The E-R analysis of efficacy in Study AMBG supports the proposed maintenance dosage of mirikizumab. Additional details regarding E-R analyses of maintenance treatment can be found in Section 6.3.2.2.

Figure 2. Percent of Subjects Achieving Efficacy Endpoints at Week 40 of Maintenance Treatment Versus Mirikizumab C_{avg} Quartile in Phase 3 Study AMBG



C_{avg} = average maintenance mirikizumab concentration during 1 dosing interval; Q = quartile.
Note: The data points from left to right represent the rates of clinical efficacy endpoints in the placebo group (N = 179) and the subjects that received 200 mg mir kizumab SC subdivided into C_{avg} quartiles (N = 89, 92, 91, 93 for Q1 to Q4, respectively). The points are plotted along the x-axis at the median C_{avg} for each quartile. Error bars represent 95% confidence intervals.
Source: Figures 4.6 to 4.9 in Applicant's Response (dated 25May2022) to 18May2022 Information Request; Figure 4 in Applicant's Response (dated 25July2022) to 18July2022 Information Request

Exposure-Response Relationship for Safety

Based on data from the phase 3 induction study AMAN and maintenance study AMBG, no clear exposure-response associations were observed between exposure and incidence of TEAE leading to dose modifications, infusion site reactions, injection site reactions, infections, serious infections, opportunistic infections, or hypersensitivity reactions. See Section 16.3.5 for details.

Bridging To-Be-Marketed AI Presentation to PFS Presentation Used in the Clinical Trial

The Applicant is proposing to market an AI device, (b) (4) for SC administration. The AI was not used in phase 3 maintenance study AMBG. Pivotal evidence to support use of the AI was derived from the relative bioavailability study AMBW bridging the PFS and AI presentations.

Based on a linear fixed-effects model that adjusted for injection site (arm, abdomen, or thigh) and weight stratification (<70 kg, 70 to 80 kg, >80 kg), mirikizumab exposure following administration of a single 200 mg dose via PFS (2 injections x 1 mL) was similar to that after administration via AI (2 injections x 1 mL). The geometric mean ratios (90% CI) for AUC_{last}, $AUC_{0\text{-}inf}$, and C_{max} were 1.05 (0.97, 1.14), 1.06 (0.98, 1.15), and 1.06 (0.98, 1.14), respectively. The review team has analyzed the mirikizumab concentration data provided by the Applicant for study AMBW and confirmed the Applicant's conclusion of BE between the PFS and AI presentations.

An inspection of the analytical and clinical sites for study AMBW was requested to the Office of Study Integrity and Surveillance (OSIS). Inspection of the analytical site was declined based on a Remote Regulatory Assessment for the site in (b) (4), which falls within the surveillance interval. At that time, OSIS concluded that data from the reviewed study were reliable. Refer to the Bioequivalence Establishment Inspection Report review by Dr. James Lumalcuri dated August 2, 2022.

OSIS also concluded that data from all clinical sites were reliable. Additional clinical review of laboratory results and safety data was recommended for several subjects enrolled in study AMBW as clinical laboratory reports of some visits were not documented as reviewed by the clinical investigator. Refer to the Bioequivalence Establishment Inspection Report review by Dr. Gajendiran Mahadevan dated March 15, 2023. Clinical review of adverse events and laboratory data did not identify any safety concerns.

Comparison of SC Administration 2 x 1 mL versus 1 x 2 mL

The Applicant's proposal for maintenance dosing specifies administration of mirikizumab as "two consecutive subcutaneous injections of 100 mg each" (i.e., 2 x 1 mL). In the phase 3 maintenance study (AMBG), mirikizumab was administered as two injections, consistent with the Applicant's proposal. Prior to the phase 3 trial, the Applicant evaluated the effects of SC injection volume on PK by administering mirikizumab as two injections (2 x 1 mL) versus as a single injection (1 x 2 mL) using an extemporaneously prepared 125 mg/mL formulation (Study AMAL). Notably, exposure following administration of mirikizumab as two SC injections (2 x 1 mL) was 25 to 27% lower relative to that after administration as a single SC injection (1 x 2 mL).

Therapeutic Individualization

Alternative dosing regimens based on intrinsic or extrinsic patient factors are not necessary based on currently available data.

Population PK analysis identified a statistically significant associations between mirikizumab clearance (CL) and baseline serum albumin, but no clinically relevant differences in exposure were identified across serum albumin concentrations (range 2 to 5.8 g/dL).

Higher body weight and higher BMI were associated with lower mirikizumab exposure during induction and maintenance treatment. However, the proposed induction dosage of 300 mg IV Q4W and maintenance dosage of 200 mg SC Q4W have demonstrated efficacy across all body weights (range 34 to 151.5 kg) and BMI values (range 13.8 to 53.5). Therefore, current evidence does not indicate a strong need for alternative dosage according to body weight or BMI.

Refer to Section 6.3.2.3 for the comprehensive analysis of exposure differences due to intrinsic and extrinsic patient factors.

Drug Interactions

A clinical DDI study in subjects with moderately to severely active UC was not conducted. However, the Applicant submitted results from a clinical DDI study conducted in subjects with moderate-to-severe psoriasis (AMBP). Study AMBP evaluated the impact of mirikizumab treatment, administered as 250 mg SC Q4W, on the PK of a cocktail of CYP substrates, including caffeine (CYP1A2), warfarin (CYP2C9), omeprazole (CYP2C19), dextromethorphan (CYP2D6), and midazolam (CYP3A4). Of note, the dosage evaluated in study AMBP is greater than the dosage regimen proposed for maintenance treatment of 200 mg SC Q4W but lower than 300 mg IV for induction treatment.

In study AMBP, there was no clinically relevant effect of mirikizumab on drugs metabolized by CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 in patients with moderate-to-severe psoriasis. As this study was conducted in a different patient population from UC and the study did not evaluate the recommended induction dosage, there remains a gap of information to fully inform labeling. Therefore, the labeling will indicate the lack of data in subjects with UC.

Nevertheless, no specific management strategy for DDIs is recommended for labeling based on the following: 1) no evidence of DDI based on results from study AMBP, 2) reversal of CYP suppression by mirikizumab treatment, if any, is expected to lead to a decrease in CYP substrate exposure, and 3) despite concerns for drugs with a narrow therapeutic index, monitoring of AEs or efficacy for such drugs is generally done regardless.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

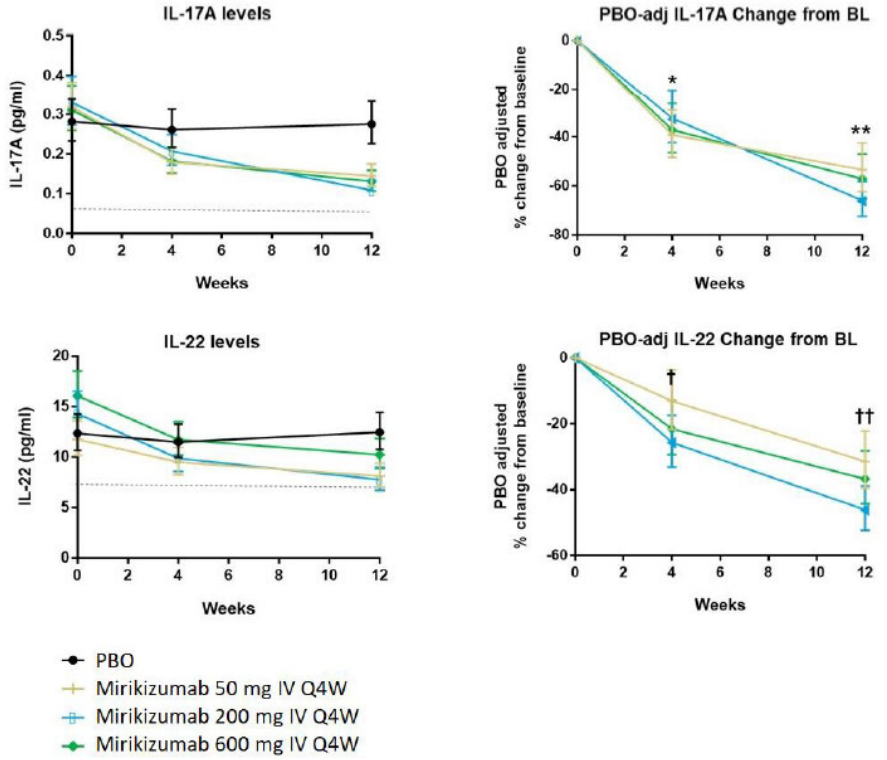
6.3.1.1. *Pharmacology and Pharmacodynamics*

Mirikizumab is a humanized IgG4 monoclonal antibody that binds to the p19 subunit of IL-23, a naturally occurring proinflammatory cytokine. IL-23 is comprised of two components: the p40

subunit, which is shared with IL-12, and the p19 subunit only found in IL-23. As mirikizumab targets the p19 subunit, only IL-23 is affected. This is the same mechanism of action as risankizumab, which has been approved for CD. Mirikizumab does not exhibit any cross-reactivity with IL-12, in contrast to other antibodies that target the p40 subunit (e.g., ustekinumab). Binding to IL-23 inhibits its interaction with the IL-23 receptor, which affects the differentiation, expansion, and survival of T cell and innate immune cell subsets thought to mediate the pathology in UC.

The PD effect of mirikizumab was evaluated in phase 2 (AMAC) and phase 3 (AMAN, AMBG) and supports its mechanism of action targeting IL-23. In phase 2 induction study AMAC, statistically significant reductions in plasma IL-17A and IL-22, downstream components of the IL-23 signaling pathway, were observed at 4 and 12 weeks during induction treatment with mirikizumab (Figure 3). Reductions were observed in all cohorts that received mirikizumab at Week 4 relative to placebo and continued to decrease over 12 weeks.

Figure 3. Changes in IL-17A and IL-22 Concentrations After Administration of 50, 200, and 600 mg IV Q4W Induction Doses in Subjects With UC in Phase 2 Study AMAC (Average Doses of 100, 250, and 600 mg From Exposure-Based Dose Adjustment)



Note: * 50 mg mirikizumab p=0.002; 200 mg mirikizumab p=0.015; 600 mg mirikizumab p=0.004; ** All miri groups p<0.001; † 50 mg mirikizumab p=0.178; 200 mg mirikizumab p=0.005; 600 mg mirikizumab p=0.020; †† 50 mg mirikizumab p=0.003; 200 mg mirikizumab p<0.001; 600 mg mirikizumab p<0.001.
Horizontal dashed line indicates IL-17A and IL-22 concentrations in healthy subjects.
Abbreviations: adj = adjusted; BL = baseline; IL = interleukin; IV = intravenous; PBO = placebo; Q4W = every 4 weeks; UC = ulcerative colitis.
(Source: Figure 2.7.2.12, Summary of Clinical Pharmacology, page 51, BLA 761279 SDN 1, submitted Mar. 30, 2022)

During induction treatment in phase 3 (AMAN), subjects randomized to receive mirikizumab showed significant reductions from baseline in mean high-sensitivity C-reactive protein (hsCRP) and fecal calprotectin (markers of inflammation) at Week 12 of induction treatment (AMAN) (Table 11). Among subjects who were considered mirikizumab induction responders after induction dosing in AMAN and continued to receive 200 mg SC Q4W maintenance treatment in AMBG, mean hsCRP and fecal calprotectin remained low (Table 88).

Table 11. Changes in Mean and Median High-Sensitivity C-Reactive Protein and Fecal Calprotectin From Baseline to Week 12 in Phase 3 Study AMAN After Induction Dosing With Placebo or Mirikizumab in Subjects With UC.

	High-Sensitivity C-Reactive Protein		Fecal Calprotectin	
	Placebo IV Q4W (n = 294)	Mirikizumab 300 mg IV Q4W (n = 868)	Placebo IV Q4W (n = 294)	Mirikizumab 300 mg IV Q4W (n = 868)
Baseline				
N	279	837	243	722
LS mean (SE), mg/L	9.44 (0.91)	9.25 (0.53)	2970 (304)	3121 (176)
Median, mg/L	4.25	4.04	1465	1556
Week 12				
N	279	837	243	722
LS mean (SE), mg/L	8.42 (0.57)	4.68 (0.35)	2386 (207)	1222 (130)
Median, mg/L	3.13	1.70	1040	398

Note that sample sizes remained the same at Baseline and Week 12 as a modified baseline observation carried forward approach was used to handle missing data.
IV = intravenous; LS = least squares; Q4W = every 4 weeks; SE = standard error; UC = ulcerative colitis.
(Source: Reviewer-generated table adapted from Tables 2.7.2.11 and 2.7.2.13, Summary of Clinical Pharmacology, pages 52 and 54, BLA 761279 SDN 1, submitted Mar. 30, 2022)

The observed PD changes support the purported mechanism of action of mirikizumab, including blocking binding of IL-23 with subsequent reductions in inflammatory markers. Because CRP and fecal calprotectin are general markers of inflammation that are not specific to UC, the relationship between these PD effects and the mechanisms through which mirikizumab exerts its clinical effects in UC is not known.

6.3.1.2. *Pharmacokinetics in Healthy Subjects*

The single dose pharmacokinetics of mirikizumab in healthy subjects was evaluated across three clinical studies: Study AMAA (Dose: 120 mg SC), Study AMAD in healthy Japanese and Caucasian subjects (Dose: 60, 200, 600, 1200, or 2400 mg IV; or 200 mg SC); Study AMBD in healthy Chinese subjects (Dose: 300, 600, or 1200 mg IV; or 200 or 400 mg SC). For additional details on study design and PK analysis, refer to Section 16.3.1.1.

The T_{max} following a SC dose occurred after approximately 3 days, and the geometric mean half-life following IV and SC doses were between 10.2 to 10.8 days. The geometric mean bioavailability of a 200 mg SC dose of mirikizumab was approximately 38% to 39% in healthy subjects. PK parameters in healthy subjects were found to be consistent across all three clinical studies, with no significant differences observed between Caucasian, Chinese, and Japanese

subjects (Table 12). Representative mirikizumab concentration versus time curves derived from study AMAD are shown in Figure 4.

Table 12. Summary of Mirikizumab PK Parameters in Healthy Subjects

	Study AMAA/AMAD (Caucasian)				Study AMBD (Chinese)				Study AMAD (Japanese)			
	IV		SC		IV		SC		IV		SC	
	N	Geometric Mean (%CV)	N	Geometric Mean (%CV)	N	Geometric Mean (%CV)	N	Geometric Mean (%CV)	N	Geometric Mean (%CV)	N	Geometric Mean (%CV)
t_{max}[a] (hr)	15	1.62 (0.50-2.10)	8	73.28 (22.97-120.02)	30	1.27 (0.75-6.00)	20	71.5 (71.27-168.93)	17	1.50 (0.50-6.00)	3	72.00 (72.00-168.00)
CL or CL/F[b] (L/day)	15	0.388 (24)	8	1.02 (36)	30	0.325 (18)	20	0.849 (39)	17	0.358 (21)	3	0.922 (47)
V or V/F[b] (L)	15	5.90 (17)	8	15.5 (22)	30	4.95 (17)	20	12.9 (33)	17	5.55 (28)	3	13.6 (38)
$t_{1/2}$[c] (Day)	15	10.5 (7.90-13.0)	8	10.5 (8.08-14.1)	30	10.6 (7.73-15.9)	20	10.5 (8.44-12.00)	17	10.8 (7.62-15.4)	3	10.2 (9.56-11.2)
F(%)		NA	8	37.9		NA	20	38.2		NA	3	38.8
C_{max}[d] (µg/mL)		NA	3	12.2 (16)	10	145 (6)	10	14.9 (28)		NA	3	11.3 (62)
AUC(0-∞)[d] (µg·day/mL)		NA	3	204 (5)	10	936 (12)	10	263 (29)		NA	3	217 (47)

Abbreviations: AUC(0-∞) = area under the concentration versus time curve from zero to infinity; CL = total body clearance of drug calculated after intravenous administration; CL/F = apparent total body clearance of drug calculated after subcutaneous administration; C_{max} = maximum observed drug concentration; CV = coefficient of variation; F= bioavailability; IV = intravenous; N = number of subjects; NA = not available; SC = subcutaneous; $t_{1/2}$ = half-life associated with the terminal rate constant; t_{max} = time of maximum observed drug concentration; V = volume of distribution during the terminal phase after intravenous administration; V/F = apparent volume of distribution during the terminal phase after subcutaneous administration.

Note:

[a] Median (minimum-maximum).

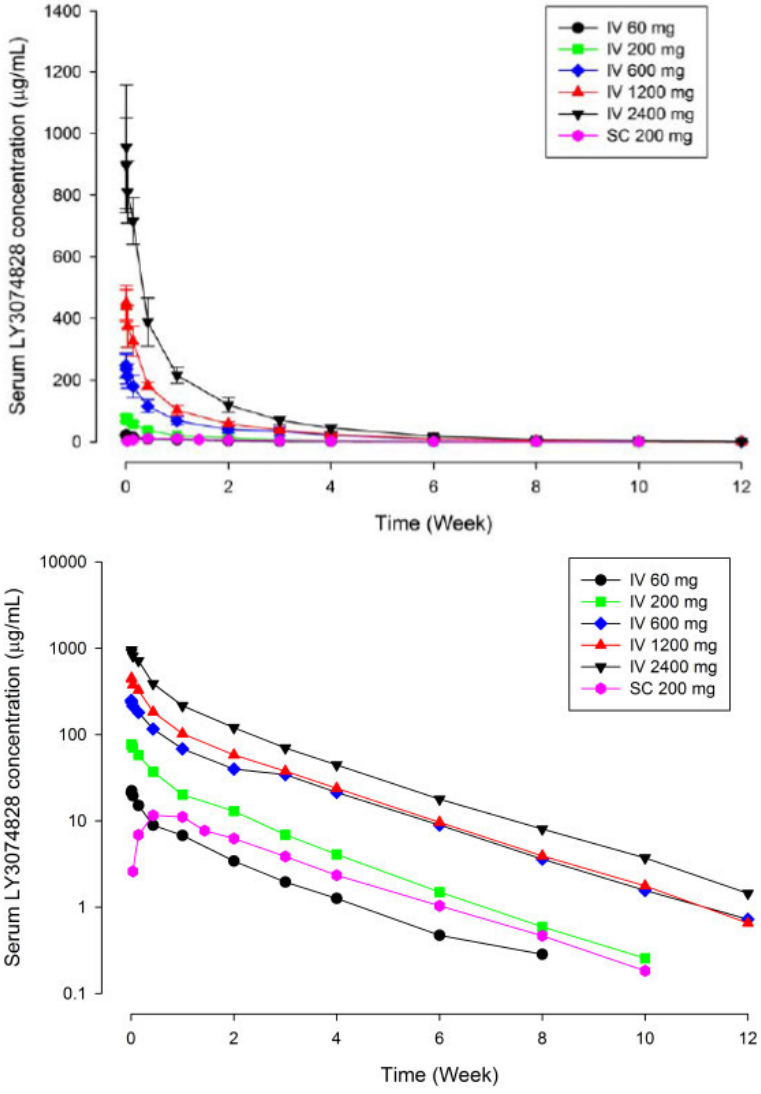
[b] CL and V for IV dosing and CL/F and V/F for SC dosing.

[c] Geometric mean (minimum-maximum).

[d] Only C_{max} and AUC values from subjects who received 300 mg IV or 200 mg SC are summarized.

(Source: Table 2.7.2.8, Summary of Clinical Pharmacology, page 38, BLA 761279 SDN 1, submitted Mar. 30, 2022)

Figure 4. Mirikizumab Mean ± SD Serum Concentration vs. Time Profiles (Upper: Linear Scale, Lower: Logarithmic Scale) After Single-Dose Administration to Healthy Caucasian and Japanese Subjects in Study AMAD.



Abbreviations: IV = intravenous; SC = subcutaneous; SD = standard deviation.

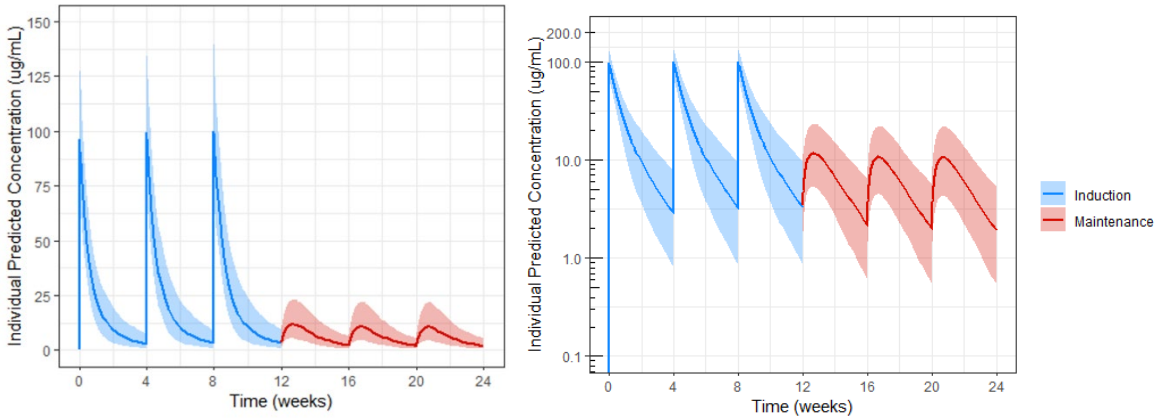
(Source: Figure 2.7.2.2, Summary of Clinical Pharmacology, page 22, BLA 761279 SDN 1, submitted Mar. 30, 2022)

6.3.1.3. *Pharmacokinetics in Subjects with UC*

The PK in subjects with UC was determined using population PK analysis. The population PK model utilized PK data during induction treatment and maintenance treatment from phase 3 studies AMAN and AMBG as input. A 2-compartment model with first-order absorption for subcutaneous administration was found to best describe the PK of mirikizumab in subjects with UC. Refer to Section 16.3.3 for details regarding the population PK model and population PK analysis.

The model-predicted concentration versus time profile for the recommended induction treatment dosage of 300 mg IV Q4W at Week 0, Week 4, and Week 8, followed by the recommended maintenance dosage of 200 mg SC Q4W is shown in Figure 5.

Figure 5. Median Mirikizumab Concentration Versus Time Following Administration of the Proposed Induction and Maintenance Dosage in Subjects With UC, Linear (Left) and Semi-Log (Right).



Individual mirikizumab concentrations over time were predicted using the final popPK model and data from 954 unique subjects with popPK data in Study AMAN and Study AMBG (954 subjects received 300 mg IV Q4W induction treatment in Study AMAN and 389 subjects who responded to mirikizumab induction received 200 mg SC Q4W maintenance treatment in Study AMBG).
Solid line = median concentration. Shaded region = 5th to 95th percentile.
IV = intravenous; popPK = population pharmacokinetic; Q4W = every 4 weeks; SC = subcutaneous; UC = ulcerative colitis.
Source: Reviewer's analysis

Table 13 summarizes exposure in subjects with UC following the first induction and maintenance doses, and Table 10 summarizes steady state exposure during induction and maintenance treatment following the proposed dosage.

Table 13. Predicted Geometric Mean (CV%) Mirikizumab Exposure in Subjects With UC.

	First Induction Dose of 300 mg IV (n=954)	First Maintenance Dose of 200 mg SC (n=389)
C_{max} (µg/mL)	96.2 (21.9)	11.4 (49.3)
C_{avg} (µg/mL)	18.5 (30.6)	6.6 (56.6)
AUC_{tau} (µg·day/mL)	517.5 (30.6)	184.3 (56.6)
C_{trough} (µg/mL)	2.6 (80.4)	2 (85.8)

Individual mirikizumab concentrations over time were predicted using the final popPK model and data from 954 unique subjects with popPK data in Study AMAN and Study AMBG (954 subjects received 300 mg IV Q4W induction treatment in Study AMAN and 389 subjects who responded to mirikizumab induction treatment continued to receive 200 mg SC Q4W maintenance treatment in Study AMBG).
AUC_{tau} = area under the concentration versus time curve over one dosing interval; C_{avg} = average mirikizumab concentration; C_{max} = maximum mirikizumab concentration; C_{trough} = mirikizumab concentration at the end of one dosing interval; CV = coefficient of variation; IV = intravenous; PopPK = population pharmacokinetic; Q4W = every 4 weeks; SC = subcutaneous; UC = ulcerative colitis.
Source: Reviewer's analysis

6.3.1.4. *Immunogenicity*

The evaluation of immunogenicity was based on data pooled from phase 3 studies AMAN and AMBG, in which the proposed to-be-marketed formulation/presentation of mirikizumab was used. The primary assessment was based on subjects that were randomized to receive the proposed dosing regimen for treatment of UC. Subjects included in this analysis were

randomized to mirikizumab 300 mg IV Q4W in study AMAN, responded to induction therapy at Week 12, and were then re-randomized to receive mirikizumab 200 mg SC Q4W in study AMBG.

Out of 378 evaluable subjects treated with mirikizumab 300 mg IV Q4W induction followed by 200 mg SC Q4W maintenance over 52 weeks, 88 (23%) developed treatment-emergent (TE) anti-drug antibodies (ADAs) to mirikizumab. Among TE ADA positive subjects, approximately 30% (26/88) developed ADAs within the first 3 months of mirikizumab treatment (i.e., during induction treatment), while approximately 58% (51/88) developed ADAs within 6 months after first exposure to mirikizumab. Out of 88 TE ADA positive subjects, 33 (38%) had titers ≥160. The highest titer of 327,680 was observed in a single subject.

Overall, higher TE ADA titers that were associated with reductions in mirikizumab PK and reduced clinical response were observed in approximately 2% (7/356) of ADA evaluable subjects treated with mirikizumab induction (300 mg IV Q4W) followed by mirikizumab maintenance (200 mg SC Q4W) in phase 3 studies AMAN and AMBG.

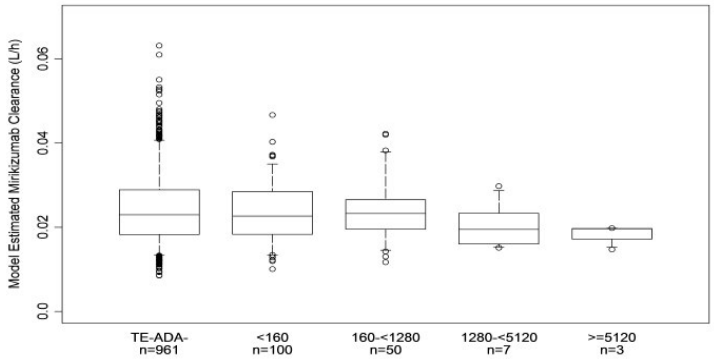
The definitive conclusion on the effects of high TE ADA on PK and efficacy is limited due to the low numbers of subjects with higher TE ADA titers ≥160.

The Office of Biotechnology Products (OBP) has determined that the screening and confirmatory immunogenicity assays are adequate. However, it was determined that the format of the neutralizing antibody (NAb) assay was likely to result in overestimation of the incidence of NAbs. There is thus concern that test samples were not accurately evaluated for NAbs, which may lead to underestimation of the impact of NAbs on efficacy, safety, and PK. Refer to the OBP review by Dr. Nailing Zhang that was placed in DARRTS on February 17, 2023, under BLA 761279 for additional details.

Impact of Immunogenicity on PK

Across the phase 3 studies AMAN and AMBG, TE ADA positive subjects generally had mirikizumab exposures similar to that in subjects who were negative for TE ADAs. Population PK analysis determined that neither TE ADA status nor TE ADA titer had a statistically significant impact on individual predicted clearance (Figure 6).

Figure 6. Mirikizumab Individual Predicted Clearance Versus TE ADA Titer Categories in Phase 3 Studies AMAN and AMBG.



Abbreviations: n = number of subjects; PK = pharmacokinetics; TE-ADA = treatment-emergent anti-drug antibody.
Note: Subjects were categorized by the maximum observed TE-ADA in the population PK analysis dataset. The horizontal line in each box represents the median; the top and bottom sides of the box represent the 75th and 25th percentiles; the whiskers extend to the 95th and 5th percentiles; and circles represent data points outside of 5th or 95th percentile.
(Source: Figure ISI.8.2, Integrated Summary of Immunogenicity, page 67, BLA 761279 SDN 1, submitted Mar. 30, 2022)

On the other hand, out of 32 subjects with TE ADA titers ≥160, 10 (31%) were identified as having "reduced mirikizumab serum trough concentrations"[5], including 4 subjects with undetectable trough concentrations.

All 10 subjects with reduced mirikizumab exposures in the presence of TE ADA achieved clinical response (n = 7) or clinical remission (n = 3) after induction treatment at Week 12 in Study AMAN. Out of these 10 subjects, reduced clinical response[6] at Week 40 was observed in 7 (70%) subjects, including 5 subjects who did not achieve clinical response after maintenance treatment. One subject classified as having reduced clinical response received rescue induction therapy and was transitioned to open-label mirikizumab 300 mg IV Q4W. This subject was discontinued from the study due to lack of efficacy after receiving three doses of rescue induction therapy. Although loss of efficacy in 7 subjects was associated with reduced mirikizumab exposure in the presence of TE ADA, it is noteworthy that two subjects still achieved either clinical remission or clinical response at Week 52 despite having mirikizumab trough concentrations below the limit of quantitation. For additional details refer to Section 16.3.1.3 and Figure 34.

[5] Based on the Applicant's definition, to be classified as having reduced exposures due to TE ADAs, changes in mirikizumab concentrations needed to occur after the emergence of TE ADAs, and concentrations were required to drop below a cutoff of 0.511 µg/mL during maintenance treatment. This cutoff is the 5th percentile of trough concentrations associated with ADA negative samples among subjects randomized to receive mirikizumab 200 mg SC Q4W in study AMBG.

[6] Subjects were classified as having reduced clinical response if they achieved either clinical remission or clinical response at the end of study AMAN (Week 12), but no longer met that same endpoint at the end of study AMBG (either at Week 52, or at the second of two Loss of Response visits).

Impact of Immunogenicity on Efficacy

The impacts of both TE ADA presence and titer on clinical outcomes were assessed at Week 40 of maintenance study AMBG (52 weeks of treatment including the induction study AMAN), including clinical remission, endoscopic improvement, and clinical response. Refer to Section 8.1 for the definitions of clinical endpoints.

The proportion of TE ADA positive subjects (n = 87) that achieved outcomes of clinical remission and endoscopic improvement was not lower relative to TE ADA negative subjects (n = 269; 58% versus 48%, respectively for clinical remission; and 66% versus 57%, respectively for endoscopic improvement) (Table 90). A similar proportion of subjects achieved clinical response at Week 40 regardless of TE ADA status (83% versus 80%). Among ADA titer groups, a lower proportion of TE ADA positive subjects with titers ≥160 (n = 32) achieved clinical remission (38% versus 51%), endoscopic improvement (50% versus 60%), and clinical response (72% versus 81%). However, the analysis in TE ADA positive subjects with titers ≥160 is limited by the small sample size (n=32).

Overall, TE ADA status (positive versus negative) was not associated with lower efficacy at Week 52 following the proposed induction and maintenance dosage. TE ADA titers ≥160 may be associated with lower efficacy at Week 52, but the presence and magnitude of this effect is uncertain due to the limited number of subjects with titers ≥160.

Impact of Immunogenicity on Safety

The impact of immunogenicity on safety in phase 3 was also evaluated among subjects randomized to receive the proposed treatment regimen for UC (300 mg IV Q4W in study AMAN followed by 200 mg SC Q4W in study AMBG). Overall, the frequency of hypersensitivity reactions, infusion site reactions, and injection site reactions did not significantly differ between TE ADA positive and TE ADA negative subjects (Table 14).

Table 14. Numbers and Proportions of Subjects With Hypersensitivity, Infusion Site Reactions, or Injection Site Reactions by TE ADA Status Among Subjects Randomized to Receive Mirikizumab 300 mg IV Q4W in Study AMAN Followed by 200 mg SC Q4W in Study AMBG.

Adverse Event Category	TE ADA Positive, n(%) (N=88)	TE ADA Negative, n(%) (N=290)
Hypersensitivity SMQ (Narrow Terms)	5 (5.7%)	32 (11.0%)
Hypersensitivity SMQ (All Narrow and Broad Terms)	14 (15.9%)	44 (15.2%)
≥ 1 TEAE in Infusion Site Reactions	0 (0.0%)	1 (0.3%)
≥ 1 TEAE in Injection Site Reactions	9 (10.2%)	24 (8.3%)

IV = intravenous; Q4W = every 4 weeks; SC = subcutaneous; SMQ = standardized MedDRA queries; TE ADA = treatment-emergent anti-drug antibody; TEAE = treatment-emergent adverse event.
(Source: Reviewer-generated table adapted from Tables APP.2.10, APP.2.11, and APP.2.12, Integrated Summary of Immunogenicity Appendix, pages 28-40, BLA 761279 SDN 1, submitted Mar. 30, 2022)

6.3.2. Clinical Pharmacology Questions

6.3.2.1. *Does the clinical pharmacology program provide supportive evidence of effectiveness?*

The effectiveness of the product is primarily supported by the statistically significant treatment effects for rate of clinical remission following the induction and maintenance dosing regimens in phase 3 trials. In addition, the Phase 2 and Phase 3 E-R analyses indicated improved efficacy with higher exposures following both induction and maintenance treatment, which provides supportive evidence of effectiveness. Refer to Section 16.3.4 for detailed E-R efficacy analyses.

The clinical pharmacology program provides evidence of effectiveness for a new prefilled pen (autoinjector) presentation that was not evaluated in the phase 3 clinical trials. Based on the comparable systemic exposure, which met bioequivalence criteria, to the trial presentation (prefilled syringe) and comparable AE profiles, the efficacy and safety of the proposed autoinjector, a device-drug combination, was established.

Refer to Section 8.1 for evaluation and definition of clinical endpoints.

6.3.2.2. *Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?*

Yes, from a clinical pharmacology perspective, the proposed induction and maintenance dosing regimens are appropriate for the general patient population. For the treatment of moderately to severely active UC, the Applicant has proposed the following mirikizumab dosing regimens:

- **Induction dosing**: 300 mg IV infused over at least 30 minutes at Weeks 0, 4, and 8
- **Maintenance dosing**: 200 mg SC (given as two consecutive 100 mg SC injections) starting after completion of induction dosing, then every 4 weeks thereafter

The proposed induction and maintenance dosing regimens are supported by efficacy data from phase 3 studies AMAN and AMBG as well as exposure-response analyses in studies AMAC, AMAN, and AMBG.

Dose-/Exposure-Response Relationship for Efficacy

Induction Dosing

Phase 2 Study AMAC

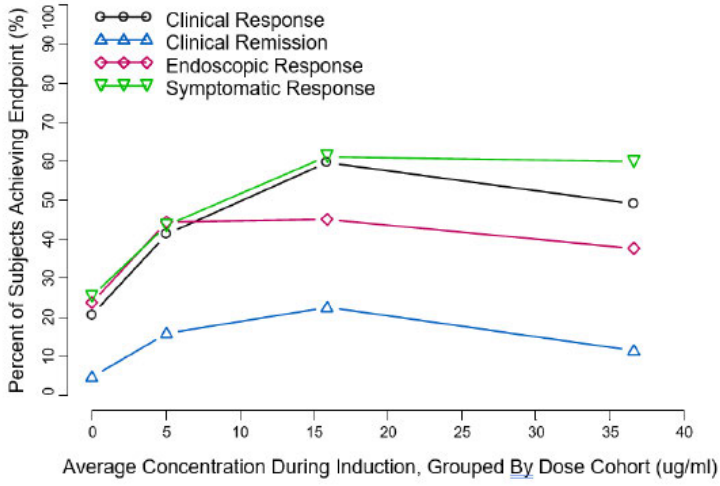
In Study AMAC, subjects with moderate to severe UC were randomized to receive IV placebo or mirikizumab IV Q4W induction at starting doses of 50, 200, or 600 mg IV. Subjects in the 50 and 200 mg cohorts had their doses increased at Weeks 4 and 8 if mirikizumab C_{trough} was lower than the prespecified thresholds of 0.5 and 2 µg/mL for the 50 and 200 mg cohorts, respectively. During the treatment, 73% of patients in the 50 mg starting dose cohort and 44%

in the 200 mg starting dose cohort increased the dose to make the average induction dose at Week 8 140 mg and 290 mg, respectively (Table 82).

Figure 7 shows the percentage of subjects achieving efficacy endpoints at Week 12 of Study AMAC in each cohort. A higher proportion of subjects in the 200 mg starting dose cohort achieved clinical efficacy endpoints at Week 12 compared to placebo, the 50 mg starting dose cohort, or the 600 mg cohort. The observed efficacy appeared similar or worse in the 600 mg cohort compared to the 200 mg starting dose cohort, even though the 600 mg cohort had higher median C_{avg} during induction treatment.

An induction dosage of 300 mg IV Q4W was selected to closely match the average Week 8 dose in the cohort with the highest rates of efficacy (i.e., 290 mg at Week 8 in the 200 mg starting dose cohort following exposure-based dose adjustment).

Figure 7. Percent of Subjects Achieving Efficacy Endpoints at Week 12 of Induction Treatment Versus Median Mirikizumab C_{avg} According to Cohort in Phase 2 Study AMAC.



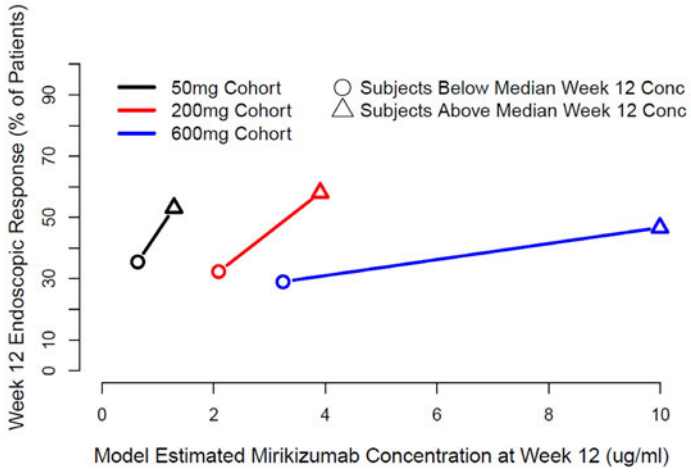
Abbreviation: PK = pharmacokinetics.
Note: Concentration points are at the median of the PK model-estimated average concentration in the placebo, 50-, 200-, and 600-mg cohorts from left to right.

Subjects in the 50 mg starting dose and 200 mg starting dose cohorts received exposure-based mirikizumab dose adjustment at Week 4 and Week 8 up to a maximum of 600 mg per dose.
C_{avg} = average mirikizumab concentration during induction treatment (i.e., Week 0 to Week 12).
(Source: Figure 2.7.2.13, Summary of Clinical Pharmacology, page 57, BLA 761279 SDN 1, submitted Mar. 30, 2022)

Although the association between exposure and efficacy appeared to plateau at higher exposures in Study AMAC, multiple factors may be confounding the exposure-response analyses. The exposure-based dose adjustment in the 50 mg and 200 mg starting dose cohorts may have impacted outcomes across cohorts independent of mirikizumab exposure. Within each cohort, subjects who received exposure-based dose adjustment did not have significantly different clinical remission rate, clinical response rate, or mean Mayo symptomatic score (comprised of the sum of the Stool Frequency and Rectal Bleeding Mayo subscores) compared to subjects without dose adjustment. However, subjects with higher exposure appeared to have better efficacy within cohorts, suggesting the dose adjustment may have not sufficiently

increased the systemic exposure or other factors may have contributed to the treatment response, as illustrated by the rate of endoscopic response in Figure 8.

Figure 8. Relationship Between Mirikizumab Week 12 Concentration and Week 12 Endoscopic Response in Subjects with High Versus Low Concentrations Within Randomized Study Cohorts in Study AMAC.



Subjects in the 50 mg starting dose and 200 mg starting dose cohorts received exposure-based mirikizumab dose adjustment at Week 4 and Week 8 up to a maximum of 600 mg per dose. The average dose at Week 8 was 140 mg IV in the 50 mg starting dose cohort and 290 mg IV in the 200 mg starting dose cohort.
Conc = mirikizumab concentration.
Source: Figure 10.2 in Applicant's PopPK Report

Subjects in the 600 mg induction cohort had numerically higher baseline high-sensitivity C-reactive protein (hsCRP) concentration (median of 6.6 mg/L) compared to the placebo, 50 mg, and 200 mg cohorts (medians of 4.9, 4.9, and 3.7 mg/L, respectively) while other demographics and baseline characteristics did not appear to differ significantly between cohorts. The higher baseline hsCRP levels in the 600 mg cohort may indicate more severe disease at baseline and may have confounded the apparent plateau of the exposure-response relationship.

The Study AMAC E-R analysis suggested efficacy rates plateaued above the C_{avg} for an induction dose of 250 mg IV Q4W. The Study AMAC E-R efficacy analysis supported the induction dose of 250 mg or greater IV Q4W for phase 3 trial.

Phase 3 Induction Study AMAN

Study AMAN evaluated an induction dosage of mirikizumab 300 mg IV Q4W in subjects with moderately to severely active UC. Relative to subjects in higher exposure quartiles, subjects in the lower exposure quartiles tended to have more severe disease and higher levels of inflammatory markers including C-reactive protein and fecal calprotectin. Subjects in lower exposure quartiles were also more likely to have received prior treatment with biologics. Refer to Section 16.3.4.3 for details regarding distribution of baseline characteristics across C_{avg} values.

In Study AMAN higher mirikizumab C_{avg} was associated with higher rates of clinical remission, clinical response, endoscopic remission, endoscopic response, and symptomatic response at

Week 12. Figure 1 and Table 15 summarize the rates of efficacy at Week 12 in Study AMAN according to induction C_{avg} quartile.

Table 15. Percent of Subjects Achieving Efficacy Endpoints at Week 12 Following Mirikizumab 300 mg IV Q4W Induction Treatment by Exposure Quartile in Phase 3 Study AMAN.

		Mirikizumab C_{avg} Quartile During Induction			
	Placebo	1st Quartile	2nd Quartile	3rd Quartile	4th Quartile
Number of subjects	295	211	216	217	217
Median mirikizumab C_{avg} (ug/mL)	--	12.3	17.8	22.3	30.4
Clinical remission rate (%)	13.2	11.4	19.4	26.7	39.2
Clinical response rate (%)	42.4	44.5	63	69.1	77.4
Endoscopic remission rate (%)	21.0	20.4	29.2	42.9	53.0
Endoscopic response rate (%)	36.3	37.4	53.7	61.3	69.6
Symptomatic response rate (%)	52.4	54	73.3	78.8	82

C_{avg} = average mirikizumab concentration.
Source: Table 4.1 in Applicant's Response (dated 25May2022) to 18May2022 Information Request; Table 1 in Applicant's Response (dated 25July2022) to 18July2022 Information Request

In Study AMAN, the response rate for various endpoints in subjects in the lowest exposure quartile was similar to the rates in subjects who received placebo. This could be related to worse disease at baseline in the lowest exposure quartile, as subjects in the lowest exposure quartile appeared to have higher mean C-reactive protein at baseline (mean [SD] values of 16 [21] for subjects in the lowest exposure quartile vs. 9.6 [14], 6.6 [9.5], and 5.0 [8.1] mg/L for subjects in the 2nd, 3rd, and 4th exposure quartiles, respectively) and a higher percentage of subjects with prior biologic or tofacitinib experience compared to higher exposure quartiles (see Section 16.3.4.3) which may have negatively impacted efficacy.

Similarly, induction responders tended to have numerically higher serum mirikizumab C_{trough} and C_{avg} during induction relative to induction non-responders (Table 16). Nevertheless the ranges of individual exposure still overlapped between responders and non-responders. The data should be interpreted with caution given the observed variability and potential for confounding factors such as baseline disease characteristics.

Table 16. Summary of Mirikizumab Estimated Exposure Following 300 mg IV Q4W Induction Treatment by Clinical Response Status in Study AMAN

	$C_{avg\ week\ 0\text{-}12}$(µg/mL)		C_{trough} at Week 12 (µg/mL)	
Concentration	Responders (n=548)	Non-responders (n=313)	Responders (n=548)	Non-responders (n=313)
Median (5th – 95th percentile)	21.4 (11.3 - 36.7)	17.8 (7.8 - 31.1)	3.8 (0.9 - 10.7)	2.3 (0.1 - 7.8)
Min – Max	7.8 - 53.5	3.7 - 46.6	0 - 23.7	0 - 15.9

C_{avg} = average mirikizumab concentration during induction treatment (Week 0 to Week 12); C_{trough} = mirikizumab concentration at the end of one dosing interval; IV = intravenous; Q4W = every 4 weeks.
Source: Reviewer's analysis of Applicant's Study AMAN efficacy dataset ('admayo.xpt') and Applicant's exposure-response dataset

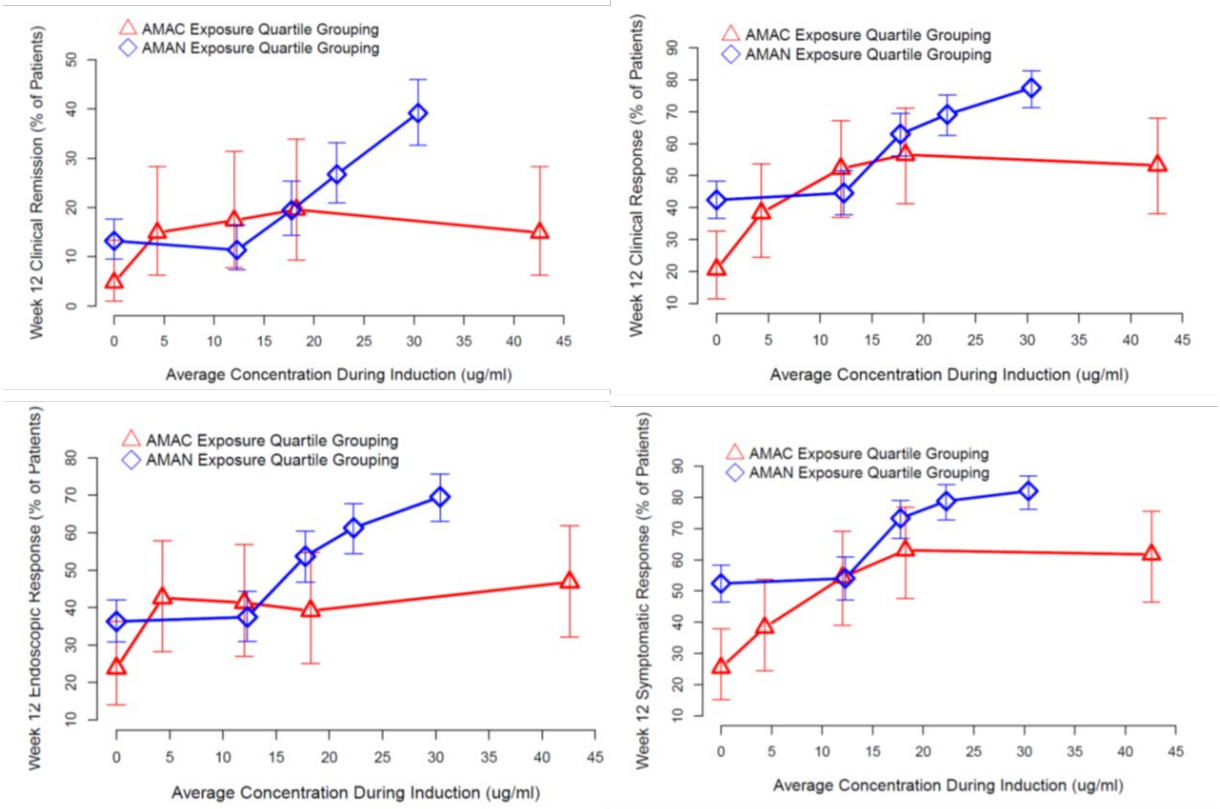
Overall, induction treatment with 300 mg IV Q4W mirikizumab resulted in acceptable exposure for efficacy and is appropriate for the general patient population. E-R analyses for induction

efficacy in phase 2 and phase 3 studies indicate higher rates of primary and secondary clinical efficacy were associated with higher mirikizumab exposure, providing supportive evidence of effectiveness for the proposed mirikizumab induction dosing of 300 mg IV at Weeks 0, 4, and 8. The inconsistent exposure-response relationship between phase 2 AMAC and phase 3 AMAN indicates some uncertainty of both analyses. It is unknown if higher induction dosage would further improve the efficacy while higher rates of achieving efficacy endpoints with greater mirikizumab exposure with no plateau was observed in Study AMAN.

Comparison of E-R Analyses for Induction Dosing in AMAC and AMAN

In Study AMAN, efficacy rates at Week 12 increased with higher mirikizumab C_{avg} during induction treatment. Although the exposure ranges overlapped in studies AMAC and AMAN, the E-R analysis for AMAN did not show the same plateau of efficacy at higher exposures that was observed with AMAC (Figure 9). This discrepancy in E-R trends at higher exposures may be related to differences in subject characteristics across exposure quartiles according to cohort, study, or both. As discussed previously in this section, Study AMAC used exposure-based dose adjustment in the 50 mg starting dose and 200 mg starting dose cohorts while subjects in the 600 mg cohort did not receive exposure-based dose adjustment. Additionally, subjects in the 600 mg cohort had higher median C-reactive protein levels at baseline which may have reflected worse baseline disease compared to the two other mirikizumab cohorts (Table 83). Conversely, in Study AMAN, only one dose level was tested, and higher baseline C-reactive protein was potentially associated with lower mirikizumab exposure (see Section 16.3.4.3 for details).

Figure 9. Percent of Subjects Achieving Efficacy Endpoints at Week 12 of Induction Treatment Versus Mirikizumab C_{avg} Quartile in Phase 2 Study AMAC and Study Phase 3 AMAN.



Study AMAC (red) data points represent rates of clinical efficacy endpoints in subjects who received placebo induction (N = 63) and subjects who received any dose IV Q4W mirikizumab induction subdivided into C_{avg} quartiles (N = 47, 46, 46 and 47 for Q1-Q4, respectively).
Study AMAN (blue) data points represent the rates of clinical efficacy endpoints in subjects who received placebo induction (N = 295) and subjects who received 300 mg IV Q4W mirikizumab induction subdivided into C_{avg} quartiles (N = 211, 216, 217, 217 for Q1-Q4, respectively).
The points for both AMAC and AMAN are plotted along the x-axis at the median C_{avg} for each quartile. Error bars represent 95% confidence intervals.
C_{avg} = average mirikizumab concentration during induction treatment; IV = intravenous; N = number of subjects; Q = quartile; Q4W = every 4 weeks.
Source: Figures 4.5 and 4.10 in Applicant's Response (dated 25May2022) to 18May2022 Information Request

Maintenance Dosing

Phase 2 Study AMAC

The maintenance dosage selected for phase 3 was based on maintenance treatment cohorts in the phase 2 study AMAC. In study AMAC, subjects who achieved clinical response at Week 12 after induction treatment were re-randomized to receive mirikizumab 200 mg SC at a frequency of Q4W or Q12W for maintenance treatment. Subjects who received the Q4W maintenance regimen had 2.9-fold higher C_{avg} compared to those who received the Q12W maintenance regimen (geometric mean [CV%] = 5.5 ug/mL [41%] versus 1.9 ug/mL [42%]). Under the Q12W

regimen, most trough concentrations fell below the limit of quantitation (BLQ) due to the longer dosing interval (Figure 28).

In subjects receiving the Q12W maintenance regimen, the symptomatic score, comprised of the sum of the Stool Frequency and Rectal Bleeding Mayo subscores, tended to increase (i.e., worsen) at the end of each dosing interval (Figure 29), consistent with the observed mirikizumab concentration-time profiles.

Overall, the results from study AMAC suggest that the average symptomatic scores were lower with the Q4W regimen compared to the Q12W regimen. The 200 mg SC Q4W regimen was therefore selected for evaluation in phase 3. No E-R analysis of maintenance treatment data was performed for Study AMAC.

***Phase 3 Maintenance Study AM*BG**

Study AMBG evaluated a maintenance dosing regimen of mirikizumab 200 mg SC Q4W in subjects with moderately to severely active UC who responded to 12 weeks of mirikizumab induction treatment in study AMAN. Subjects were included in the study AMBG E-R efficacy analysis if they had achieved clinical response with mirikizumab 300 mg IV Q4W induction treatment and then received 200 mg SC Q4W maintenance treatment (n=365) or if they had achieved clinical response with placebo IV Q4W induction treatment and then received placebo SC Q4W maintenance treatment (n=179).

Notably, compared to subjects in higher C_{avg} quartiles, subjects in lower C_{avg} quartiles tended to have higher levels of inflammatory markers including C-reactive protein and fecal calprotectin, were more likely to have received prior treatment with biologics or tofacitinib, and were less likely to have achieved clinical remission at Week 12 of induction treatment. Relevant baseline characteristics for each maintenance C_{avg} quartile are described in Section 16.3.4.3.

Figure 2 and Table 17 show the rates of efficacy at Week 40 of maintenance treatment (i.e., Week 52 of mirikizumab treatment) according to each maintenance C_{avg} quartile in Study AMBG. Higher maintenance C_{avg} was associated with higher rates of clinical remission, endoscopic remission, and endoscopic response at Week 40 of maintenance treatment. All maintenance exposure quartiles appeared to have higher efficacy relative to subjects receiving placebo for maintenance treatment. However, efficacy appeared to plateau at higher maintenance exposures. Overall, the proposed dosage results in exposure associated with clinical efficacy for maintenance treatment and is appropriate for general population.

Table 17. Percent of Subjects Achieving Efficacy Endpoints at Week 40 After Mirikizumab 200 mg SC Q4W Maintenance Treatment by Exposure Quartile in Phase 3 Study AMBG

	Placebo	Mirikizumab C_{avg} Quartile During Maintenance			
		1st Quartile	2nd Quartile	3rd Quartile	4th Quartile
Number of subjects	179	89	92	91	93
Median mirikizumab C_{avg} (ug/mL)	--	3.32	5.74	7.87	11.3
Clinical remission rate (%)	25.1	37.1	51.1	57.1	53.8
Clinical response rate (%)	49.2	75.3	80.4	82.4	82.8
Endoscopic remission rate (%)	29.1	44.9	56.5	68.1	64.5
Endoscopic response rate (%)	40.8	61.8	71.7	80.2	76.3
Symptomatic response rate (%)	54.7	78.7	82.6	85.7	86.0

C_{avg} = average mirikizumab concentration during 1 maintenance dosing interval.
Source: Table 4.2 in Applicant's Response (dated 25May2022) to 18May2022 Information Request; Table 2 in Applicant's Response (dated 25July2022) to 18July2022 Information Request

Exposure-Response Relationship for Safety

Exposure-response relationships for safety were investigated in phase 3 induction study AMAN and maintenance study AMBG. No clear exposure-response associations were observed between average mirikizumab concentration quartile during induction treatment or maintenance treatment and incidence of TEAEs leading to dose modifications, infusion site reactions, injection site reactions, infections, serious infections, opportunistic infections, and hypersensitivity reactions. See Section 16.3.5 for the detailed E-R safety analysis.

Bridging of To-Be-Marketed PFS and AI Presentations

(b) (4) The Applicant is (b) (4) proposing to market an AI device for SC administration. The AI was not used in AMBG but was only used in a subset of Japanese subjects in ongoing study AMAP. No PK data from study AMAP was provided to support comparability of the AI with the PFS. Pivotal evidence to support use of the AI was therefore derived from the relative bioavailability study AMBW bridging the PFS and AI presentations.

Study AMBW was an open-label, randomized, parallel-design, single-dose study to evaluate the PK of mirikizumab after SC administration of 200 mg doses administered via PFS (2 x 1 mL) or AI (2 x 1 mL) in healthy subjects (n = 240).

PK analysis was conducted using a linear fixed-effects model that adjusted for injection site (upper arm, abdomen, or thigh) and weight stratification (<70 kg, 70 to 80 kg, >80 kg). Mirikizumab exposure following administration of a single 200 mg dose via PFS (2 x 1 mL) was similar to that after administration via AI (2 x 1 mL) (Table 18). The geometric mean ratios (90% CI) for AUC_{last}, $AUC_{0\text{-}inf}$, and C_{max} were 1.05 (0.97, 1.14), 1.06 (0.98, 1.15), and 1.06 (0.98, 1.14), respectively. No notable difference in mirikizumab T_{max} was identified between the PFS and AI.

The review team's independent analysis similarly concluded BE between the PFS and AI presentations for AUC_{last}, $AUC_{0\text{-}inf}$, and C_{max}.

Table 18. Summary of Mirikizumab PK Parameter Estimates Following a Single SC 200 mg Dose Administered via PFS or AI in Study AMBW.

	Geometric mean (Geometric CV%) [n]	
Parameter	PFS (Reference) (N=120)	AI (Test) (N=120)
AUC(0-tlast) (ug.day/mL)	244 (44%) [116]	257 (39%) [119]
AUC(0-∞) (ug.day/mL)	246 (44%) [120]	262 (39%) [120]
%AUC(tlast-∞) (%)	1.43 (78%) [120]	1.44 (61%) [120]
Cmax (ug/mL)	14.3 (44%) [120]	15.2 (40%) [120]
tmax (day)#	4.00 (1.81-10.23) [120]	4.00 (1.83-7.05) [120]
t½ (day)*	10.9 (4.59-20.5) [120]	11.1 (6.09-21.3) [120]
CL/F (L/day)	0.813 (44%) [120]	0.764 (39%) [120]
Vz/F (L)	12.8 (37%) [120]	12.2 (35%) [120]
Vss/F (L)	13.6 (39%) [120]	12.9 (36%) [120]

Abbreviations: %AUC(tlast-∞) = percentage of AUC(0-∞) extrapolated; AI = 200 mg Mirikizumab 2 x 1-mL (100 mg/mL) autoinjector (Test); AUC(0-∞) = area under the concentration versus time curve from time zero to infinity; AUC(0-tlast) = area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration; CL/F = apparent total body clearance of drug calculated after extra-vascular administration; Cmax = maximum observed drug concentration; CV = coefficient of variation; N = number of participants; n = number of observations; PFS = prefilled syringe; t½ = half-life associated with the terminal rate constant in non-compartmental analysis; tmax = time of maximum observed drug concentration; Vss/F = apparent volume of distribution at steady state after extra-vascular administration; Vz/F = apparent volume of distribution during the terminal phase after extra-vascular administration

Median (minimum-maximum)

* Geometric mean (minimum-maximum)

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Note the exclusion of 5 subjects from the overall summary of $AUC_{0\text{-tlast}}$ due to missing one or more samples at the end of the sampling schedule.
(Source: Table AMBW.5.6, Clinical Study Report for Study AMBW, page 45, BLA 761279 SDN 1, submitted Mar. 30, 2022)

Differences in immunogenicity between the two presentations were also evaluated in study AMBW using the same ADA assay as that used for analysis of phase 3 studies AMAN and AMBG. Refer to the OBP review by Dr. Nailing Zhang that was placed in DARRTS on February 17, 2023, under BLA 761279 for additional details on the assay. All 240 subjects enrolled in the study were evaluable for TE ADAs. The TE ADA incidence was comparable regardless of the delivery device used for administration (14.2% vs. 13.3% for PFS vs. AI, respectively).

Overall, the data support the comparability of the proposed PFS and AI presentations for SC administration of mirikizumab.

Impact of Injection Site on PK

The proposed labeling for mirikizumab indicates that sites for SC injection of the drug product include the abdomen, thigh, and back of the upper arm.

An exploratory endpoint of study AMBW was to evaluate the impact of injection site location on the PK. Table 19 and Table 20 below show statistical analysis of PK parameters AUC_{last}, AUC_{inf}, and C_{max} across injection sites for the PFS and AI presentations, respectively.

Table 19. Statistical Analysis of PK Parameters Across Injections Following a Single SC Dose of 200 mg Mirikizumab Administered via PFS in Study AMBW.

Delivery device: PFS (Reference)

Parameter	Injection Location	n	Geometric least squares mean	Ratio of geometric least squares mean (Arm or Thigh versus Abdomen)	90% CI for the ratio (Lower, Upper)
AUC(0-tlast) (ug.day/mL)	Abdomen	39	244		
	Arm	38	215	0.883	(0.759, 1.03)
	Thigh	39	279	1.15	(0.986, 1.33)
AUC(0-∞) (ug.day/mL)	Abdomen	40	248		
	Arm	41	213	0.860	(0.743, 0.997)
	Thigh	39	284	1.15	(0.987, 1.33)
Cmax (ug/mL)	Abdomen	40	15.0		
	Arm	41	12.4	0.825	(0.711, 0.957)
	Thigh	39	16.1	1.08	(0.925, 1.25)

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

(Source: Table AMBW.8.5, Clinical Study Report for Study AMBW, page 97, BLA 761279 SDN 1, submitted Mar. 30, 2022)

Table 20. Statistical Analysis of PK Parameters Across Injections Following a Single SC Dose of 200 mg Mirikizumab Administered via AI in Study AMBW.

Delivery device: AI (Test)

Parameter	Injection Location	n	Geometric least squares mean	Ratio of geometric least squares mean (Arm or Thigh versus Abdomen)	90% CI for the ratio (Lower, Upper)
AUC(0-tlast) (ug.day/mL)	Abdomen	39	243		
	Arm	39	235	0.966	(0.850, 1.10)
	Thigh	41	297	1.22	(1.08, 1.39)
AUC(0-∞) (ug.day/mL)	Abdomen	40	248		
	Arm	39	240	0.968	(0.853, 1.10)
	Thigh	41	303	1.22	(1.08, 1.39)
Cmax (ug/mL)	Abdomen	40	14.7		
	Arm	39	13.4	0.908	(0.798, 1.03)
	Thigh	41	17.7	1.20	(1.06, 1.37)

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

(Source: Table AMBW.8.5, Clinical Study Report for Study AMBW, page 99, BLA 761279 SDN 1, submitted Mar. 30, 2022)

Following administration with the PFS, geometric mean C_{max} and AUC were 12 to 17% lower after injection in the upper arm relative to the abdomen, while geometric mean AUC was 15% higher with no significant change in geometric mean C_{max} after injection in the thigh relative to the abdomen. Following administration with the AI, geometric mean C_{max} was approximately 9% lower with no significant change in AUC after injection in the arm relative to the abdomen, while geometric mean C_{max} and AUC were 20 to 22% higher after injection in the thigh relative to the abdomen.

While evaluation of the impact of injection site on PK in study AMBW was considered an exploratory endpoint, results reveal little difference in mirikizumab exposure across injection sites. Changes in exposure up to 22% across injection sites and presentations are smaller relative to the variability (CV%) observed for steady state C_{max} and AUC_{tau} at the recommended SC dosing regimen (52 to 58%), as determined via population PK analysis.

Population PK modeling was also used to assess possible impact of injection site (abdomen versus arm versus thigh) on SC bioavailability. Analysis determined that injection site was not a

statistically significant factor impacting the PK of mirikizumab. See Section 16.3.3.6 for additional details.

Following assessment of clinical and popPK data, the data from relative bioavailability study AMBW and the phase 3 population PK analysis support the conclusion that mirikizumab PK does not significantly differ following SC injection in the abdomen, arm, or thigh.

6.3.2.3. *Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?*

No alternative dosing regimens based on intrinsic patient factors are recommended. Refer to Section 16.3.3.6 for detailed analysis regarding associations between subject covariates, PK parameters and exposure, and clinical outcomes.

The population PK analysis evaluated potential impacts from intrinsic and extrinsic subject factors on mirikizumab PK and exposure in induction Study AMAN and maintenance Study AMBG. The following statistically significant associations were identified:

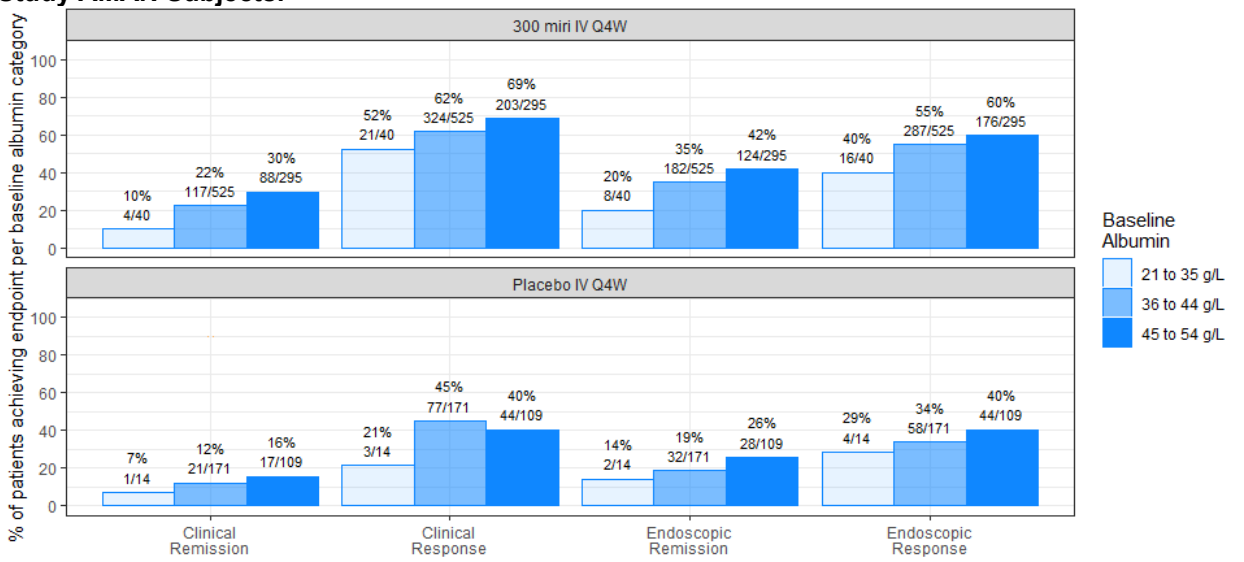
- Lower serum albumin was associated with higher clearance (CL).
- Higher baseline body weight was associated with higher CL and volume of distribution (V_d).
- Higher baseline BMI was associated with lower SC bioavailability.

Albumin Concentration

Serum albumin is a marker of disease state severity, and patients with high protein turnover can have faster clearance of both albumin and monoclonal antibodies such as mirikizumab. In Phase 3 subjects with UC (n=954), AUC_{tau} following a 300 mg IV induction dose is expected to be 19% lower in subjects with a baseline albumin concentration of 35 g/L or lower (n = 45) compared to subjects with a baseline albumin concentration of 45 g/L or higher (n = 337) (geometric mean [CV%] 447 µg·day/mL [26%] versus 553 µg·day/mL [30%]). There is also a large degree of overlap in mirikizumab exposure across the range of serum albumin (20 to 58 g/L).

In order to assess whether the lower exposure with lower albumin may impact clinical outcomes, efficacy was compared across subgroups of low, average, and high albumin concentrations. As displayed in Figure 10, subjects with baseline albumin of 35 g/L or lower had numerically lower efficacy rates at Week 12 following 300 mg IV Q4W compared to subjects with baseline albumin of >35 to <45 g/L or ≥45 g/L. However, similar trends were also observed following placebo IV Q4W. Because this trend is observed in the placebo cohort, subject factors including disease severity and catabolism profile are likely confounding the association between albumin, exposure, and efficacy.

Figure 10. Study AMAN Efficacy Endpoints at Week 12 Stratified by Baseline Albumin Category for Study AMAN Subjects.



% and n/N displayed on top of each column.
IV = intravenous; Q4W = every 4 weeks.
Source: Reviewer's Analysis of the Applicant's Exposure-Response Dataset

Body Weight and BMI

Although body weight and BMI have statistically significant associations with CL, V_d, and bioavailability, no alternative dosage regimens are recommended according to body weight or BMI.

In the phase 3 studies AMAN and AMBG, baseline body weight ranged from 34 to 152 kg and BMI ranged from 13.8 to 53.5 kg/m^2. Higher body weight is associated with greater mirikizumab CL and higher V_d. Higher BMI is associated with reductions in SC bioavailability which is likely due to other subject factors that are associated with BMI but more difficult to quantify, such as composition or distribution of adipose tissue.

Compared to subjects weighing 60 to 90 kg, AUC_{tau} is expected to be 17% higher in subjects weighing 60 kg or less and 15% lower in subjects weighing over 90 kg following the first 300 mg IV induction dose. Exposure differences between weight categories are larger during maintenance compared to induction because IV induction doses are not impacted by the effect of BMI on SC bioavailability. Following maintenance treatment with 200 mg SC Q4W, subjects weighing 60 kg or less are expected to have 37% higher maintenance AUC_{tau} compared to subjects who weighed 60 kg to 90 kg. Subjects weighing over 90 kg had 27% lower maintenance AUC_{tau} compared to subjects who weighed 60 kg to 90 kg. Predicted exposure according to weight category is summarized in Table 21.

Table 21. Summary of Individual Predicted Mirikizumab Exposure in Subjects With UC by Weight Category.

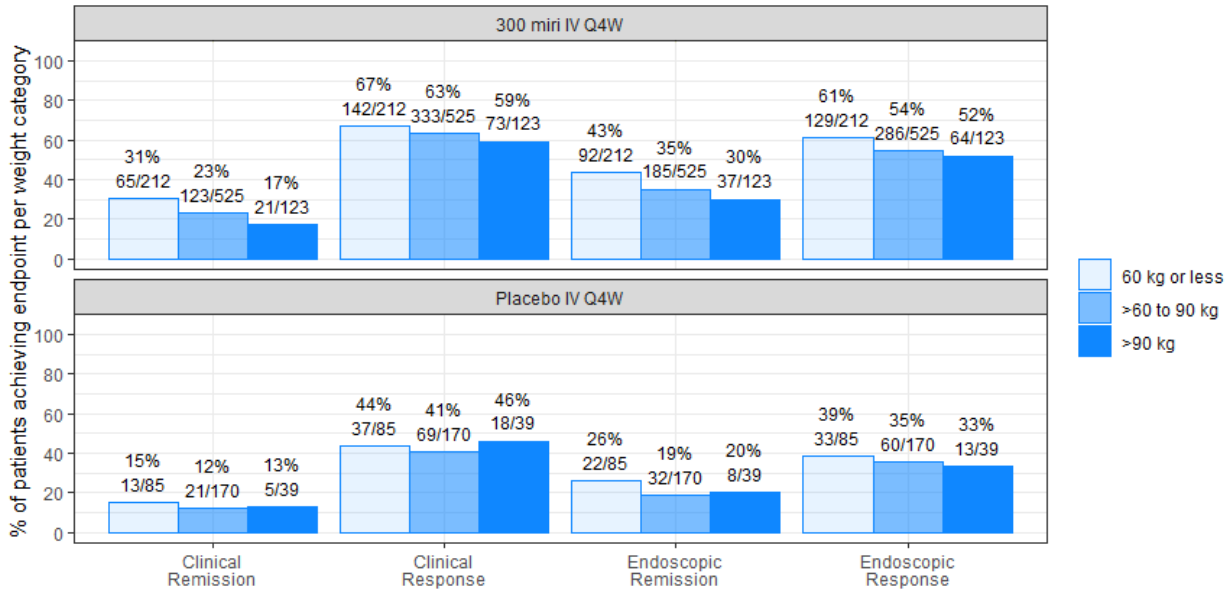
		60 kg or less	>60 to 90 kg	>90 kg
First Induction Dose of 300 mg IV (Week 0 to Week 4)	Number of subjects	230	588	136
	Median BMI	19.7	24.6	33.3
	C_{max} (ug/mL)[a]	113.1 (19.6)	93.8 (18.8)	81.3 (19.9)
	C_{avg} (ug/mL)[a]	21.3 (28.3)	18.2 (29.7)	15.5 (25.8)
	AUC_{tau} (ug·day/mL)[a]	597.6 (28.3)	509.8 (29.7)	433.2 (25.8)
	C_{trough} (ug/mL)[a]	3 (80.7)	2.6 (82)	2.2 (68.5)
First Maintenance Dose of 200 mg SC (Week 12 to Week 16)	Number of subjects	100	238	51
	Median BMI	19.7	24.5	33.3
	C_{max} (ug/mL)[a]	15 (39.1)	11 (47.8)	8 (39.4)
	C_{avg} (ug/mL)[a]	8.7 (46.4)	6.3 (56.4)	4.6 (44.4)
	AUC_{tau} (ug·day/mL)[a]	242.2 (46.4)	177.2 (56.4)	129.8 (44.4)
	C_{trough} (ug/mL)[a]	2.7 (72.6)	1.9 (90)	1.5 (63.9)

[a] Geometric mean (coefficient of variation)
In Study AMAN, 954 subjects with UC received 300 mg IV infused over 30 minutes Q4W mirikizumab induction treatment. In Study AMBG, 389 subjects who had previously achieved response with 300 mg IV Q4W mirikizumab induction treatment received 200 mg SC Q4W mirikizumab maintenance treatment.
AUC_{tau} = area under the concentration versus time curve over one dosing interval; C_{avg} = average mirikizumab concentration during one dosing interval; C_{max} = maximum mirikizumab concentration; C_{trough} = mirikizumab concentration at the end of one dosing interval; IV = intravenous; popPK = population pharmacokinetic; Q4W = every 4 weeks; SC = subcutaneous; UC = ulcerative colitis.
Source: Reviewer's analysis

Impact of Exposure/Dose on Induction Efficacy

When rates of efficacy were compared across body weight categories (Figure 11), higher body weight was associated with numerically lower rates of efficacy at Week 12 following 300 mg IV Q4W induction treatment. This trend was also supported by univariate logistic regression (see Section 16.3.3.6 for analysis). Similarly, the magnitude of risk difference in Week 12 clinical remission and endoscopic remission between mirikizumab and placebo induction treatment was smaller with higher BMI subgroups (see Section 16.3.3.6 for analysis).

Figure 11. Observed Rates of Efficacy Endpoints at Week 12 Across Weight Categories in Study AMAN.



% and n/N displayed on top of each column.
IV = intravenous; Q4W = every 4 weeks.
Source: Reviewer analysis of Applicant's Study AMAN E-R efficacy dataset

Subjects with higher body weight tended to have longer durations of disease at baseline and were more likely to have prior experience with biologics or tofacitinib, as shown in Table 22. As a result, baseline disease characteristics may also contribute to the difference in efficacy observed across body weight.

To evaluate the impact of exposure independent of potential confounding variables, the reviewer conducted multivariate E-R analysis for the primary induction efficacy endpoint of clinical remission at Week 12. The multivariate E-R analysis found that probability of clinical remission was associated with induction C_{avg}, prior use of biologics or tofacitinib (yes versus no), baseline modified Mayo score, baseline endoscopic findings subscore, baseline rectal bleeding subscore. After controlling for differences between baseline disease state, the difference in exposure between <90 kg subjects and ≥90 kg subjects was smaller than it appeared in the univariate analysis. Refer to Section 16.3.4.4 for the detailed multivariate E-R analysis of induction efficacy.

Table 22. Summary of Subject Disease Characteristics in Study AMAN Exposure-Response Dataset Across Weight Quartiles.

		300 mirikizumab IV Q4W				Placebo IV Q4W			
	Statistic	34 to <60.1 kg	60.1 to <70.1 kg	70.1 to >83 kg	83 to ≤152 kg	34 to <60.1 kg	60.1 to <70.1 kg	70.1 to >83 kg	83 to ≤152 kg
Number of Subjects	n	212	210	212	227	85	72	77	61
Baseline Body Weight (kg)	Mean	52.5	65.3	76.1	95.1	52.6	65.4	76.3	95.8
	SD	5.7	2.9	3.6	11.6	5.8	3.1	3.6	10.9
	Median	53.2	65.2	75.5	91.2	53.2	65.2	76	93.4
	Min - Max	34 - 60	60.1 - 70	70.1 - 82.9	83 - 151.5	33.8 - 60	60.1 - 70	70.3 - 82.9	83.1 - 124
Duration of UC from Diagnosis (years)	Mean	6.8	6.9	6.4	8.4	5.1	6.4	7.9	8.8
	SD	6.8	6.6	6.4	7.1	5.4	5.8	7.6	8.5
	Median	4.3	4.8	4.3	6.4	3	4.7	5.1	6.7
	Min - Max	0.3 - 35.7	0.4 - 44.3	0.3 - 40	0.2 - 39.7	0.2 - 28.7	0.4 - 21.7	0.2 - 33.9	0.4 - 47.6
Prior Use of Biologic or Tofacitinib	n (%)	81 (38%)	82 (39%)	88 (42%)	123 (54%)	22 (26%)	31 (43%)	40 (52%)	31 (51%)

IV = intravenous; Q4W = every 4 weeks; SD = standard deviation; UC = ulcerative colitis.
Source: Reviewer analysis of Applicant's Study AMAN exposure-response efficacy dataset

Following the proposed induction dose of 300 mg IV Q4W, the subgroup analysis and multivariate E-R analysis suggest that subjects weighing ≥90 kg may be less likely to achieve efficacy compared to subjects weighing <90 kg due to lower mirikizumab C_{avg} and potentially more severe disease at baseline. However, mirikizumab 300 mg IV Q4W was more effective than placebo across all weights and BMI values. The numerically lower observed rates of efficacy due to lower exposure in subjects weighing ≥90 kg may not be statistically and/or clinically significant. The current evidence does not support the need for alternative induction dosage according to body weight or BMI values, although the analysis is limited by the lack of dosages other than 300 mg IV Q4W in the phase 3 induction study.

Impact of Exposure/Dose on Maintenance Efficacy

In maintenance Study AMBG, there were no clear trends in clinical remission, clinical response, endoscopic remission, or endoscopic response at Week 40 according to body weight or BMI. Additionally, no clear trends for maintenance treatment were identified in the risk difference in Week 40 clinical remission and endoscopic remission between BMI subgroups. Therefore, there is no need for alternative maintenance dosage according to body weight or BMI. See Section 16.3.4.5 for analysis.

Impact of Exposure/Dose on Safety

In regard to safety, there were not any clear trends between body weight and incidence of TEAEs leading to dose modifications, infusion site reactions, injection site reactions, infections, opportunistic infections, serious infections, or hypersensitivity reactions (see Section 16.3.5 for

analysis). The exposure differences due to weight and BMI are not expected to result in any clinically relevant differences in safety following the proposed induction and maintenance dosages.

Overall, no dose adjustments according to body weight or BMI are recommended.

Renal Impairment and Hepatic Impairment

No dedicated studies have been conducted in subjects with renal impairment or hepatic impairment to evaluate the impact of renal or hepatic impairment on mirikizumab PK. As mirikizumab is a monoclonal antibody the expected elimination pathway is via proteolytic degradation. Based on the phase 3 population PK analysis, neither baseline creatinine clearance (range of 36.2 to 277.1 mL/min) nor baseline bilirubin (range of 1.5 to 29 µmol/L) were associated with statistically significant impacts on mirikizumab PK.

6.3.2.4. *Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?*

Mirikizumab is a monoclonal antibody that is expected to be metabolized via proteolytic degradation to peptides and amino acids. It is not likely that mirikizumab would have any direct effect on drug-metabolizing enzymes. However, mirikizumab may affect the PK of other drugs as a result of improvement in inflammation. Inflammatory stimuli may lead to down-regulation of cytochrome P450 (CYP) enzymes, resulting in increased exposure of substrates of these drug metabolizing enzymes relative to exposure in individuals without inflammatory conditions. As a result of reducing inflammatory burden, CYP levels may be normalized, leading to decreased exposure of CYP substrates.

The Applicant provided data from a clinical drug-drug interaction study AMBP, which was conducted in subjects with moderate-to-severe psoriasis. Of note, the Applicant is not seeking an indication for subjects with psoriasis.

Study AMBP was a two-period, fixed-sequence, open-label study aimed at evaluating the impact of mirikizumab treatment, administered as 250 mg SC Q4W, on the PK of a cocktail of CYP substrates, including caffeine (CYP1A2), warfarin (CYP2C9), omeprazole (CYP2C19), dextromethorphan (CYP2D6), and midazolam (CYP3A4). Of note, the dosage evaluated in study AMBP, i.e., 250 mg is greater than the dosage proposed for maintenance treatment of UC (200 mg SC Q4W). (b) (4)

In Period 1 of the study, the PK of CYP450 substrates in the cocktail was assessed after administration on Day 1. In Period 2 of the study, the same cocktail of CYP substrates was administered on Day 116 for PK assessment following 5 doses of SC administration of 250 mg mirikizumab Q4W on Days 1, 29, 57, 85, and 113. A total of 29 subjects were enrolled in the study. All subjects completed Period 1, while 26 subjects completed Period 2.

PK of CYP substrates was not affected by 250 mg SC mirikizumab. The geometric mean ratios and 90% CIs for C_{max}, AUC_{inf}, and AUC_{0-t} for probe substrates were mostly contained within the no-effect boundaries of 0.8 to 1.25 (Table 23). Overall, the data suggests low potential for clinically relevant drug interactions with drugs metabolized by all the CYPs evaluated (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) in subjects with moderate-to-severe psoriasis.

Table 23. Statistical Analysis of Plasma Cmax, AUCinf, and AUC0-t After Oral Administration of a Cocktail of CYP Substrates in the Absence of Mirikizumab (Period 1) and After SC Administration of 250 mg Mirikizumab Q4W (Period 2).

Probe Substrate	C_{max} (Period 2/Period 1)		AUC_{inf} (Period 2/Period 1)		AUC_{0-t} (Period 2/Period 1)	
	GMR	90% CI	GMR	90% CI	GMR	90% CI
Caffeine	0.965	[0.872, 1.07]	1.04	[0.967, 1.12]	1.04	[0.964, 1.11]
Warfarin	0.937	[0.893, 0.983]	0.958	[0.916, 1.00]	0.976	[0.934, 1.02]
Omeprazole	1.03	[0.844, 1.26]	1.06	[0.958, 1.18]	1.05	[0.874, 1.26]
Dextromethorphan	1.03	[0.872, 1.22]	0.971	[0.817, 1.15]	0.981	[0.820, 1.17]
Midazolam	1.09	[1.01, 1.18]	1.15	[1.06, 1.25]	1.14	[1.05, 1.23]

AUC_{inf} = area under the concentration-versus-time curve from time of administration to infinity following a single dose; AUC_{0-t} = area under the concentration-versus-time curve from time of administration to the time of last quantifiable concentration; CI = confidence interval; C_{max} = maximum concentration; CYP = cytochrome P450; GMR = geometric mean ratio; Q4W = every 4 weeks; SC = subcutaneous.
(Source: Reviewer-generated table adapted from Tables AMBP.7.3, AMBP.7.5, AMBP.7.7, AMBP.7.9, AMBP.7.11, Clinical Study Report for Study AMBP, pages 30, 34, 38, 42, 47, BLA 761279 SDN 1, submitted Mar. 30, 2022)

While the study results do not suggest clinically relevant drug-drug interactions by mirikizumab, inflammatory burden, which can impact CYP expression, may differ across disease states. We note that the mean hsCRP level was higher in subjects with UC than in subjects with psoriasis enrolled in the DDI study based on a cross-study comparison (Table 24). Nevertheless, hsCRP is a general marker of inflammation and the relationship between hsCRP levels and CYP expression is not clear.

Table 24. Mean (SD) and Median (IQR) hsCRP Concentrations and Number of Subjects With hsCRP <10 mg/L at Baseline in Subjects With Moderate-to-Severe Psoriasis (Study AMBP) and Subjects With Moderate-to-Severe UC (Studies AMAC and AMAN).

	Baseline hsCRP (mg/L)		Subjects with hsCRP <10 mg/L n(%)
	Mean (SD)	Median (IQR)	
AMBP (Psoriasis) (n = 29)	4.8 (4.5)	3.2 (1.9, 6.5)	27 (93%)
AMAC (UC) (n = 239)	10.7 (17.3)	4.7 (1.5, 12.8)	166 (69%)
AMAN (UC) (n = 1218)	9.7 (15.4)	4.3 (1.6, 9.9)	920 (76%)

Note that the number of subjects represented includes all enrolled subjects with non-missing baseline hsCRP measurements.
Abbreviations: hsCRP = high-sensitivity C-reactive protein; IQR = interquartile range; SD = standard deviation; UC = ulcerative colitis
(Source: Reviewer-generated table using data adapted from clinical laboratory datasets [adlb] for studies AMBP, AMAC, and AMAN)

As the study was done in a different patient population from UC and did not study the recommended induction dosage for UC, there remains a gap in information to fully inform the labeling. As such, the labeling will state the lack of data in subjects with UC.

Nevertheless, there is no specific management strategy to recommend for labeling based on the following: 1) no evidence of DDI potential in the in vivo DDI study, 2) the potential reversal of CYP suppression under inflammation by mirikizumab treatment, if any, is not expected to lead to a significant increase in systemic exposure to CYP substrates, but rather a decrease in systemic exposure, and 3) although there is a concern for drugs with narrow therapeutic index, monitoring of AEs or efficacy for such drugs is generally done regardless.

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Trials

Table 25. Clinical Trials Submitted in Support of Efficacy and Safety Determinations for Mirikizumab

Trial Identifier	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary Endpoints	No. of Subjects Planned; Actual Randomized	No. of Centers and Countries
I6T-MC-AMAN	Adult subjects with moderately to severely active ulcerative colitis	R, DB, PC, MC, phase 3	Mirikizumab 300 mg IV Q4W (n=959) Placebo IV infusion Q4W (n=322) Duration: 12 weeks	Primary: Proportion of subjects with clinical remission at Week 12	Planned: 1160 Actual: 1281	Centers: 383 Countries: 35
I6T-MC-AMBG	Adult subjects with moderately to severely active ulcerative colitis	RW, DB, PC, MC, phase 3	Mirikizumab induction responders (n=581): Mirikizumab 200 mg SC Q4W (n=389) Placebo SC Q4W (n=192) Placebo induction responders (n=135): placebo SC Q4W Duration: 40 weeks	Primary: The proportion of subjects with clinical remission at Week 40	Planned: 1044 Actual: 1177	Centers: 367 Countries: 34
I6T-MC-AMAC	Adult subjects with moderately to severely active ulcerative colitis	R, DB, PC, MC, Dose-ranging phase 2	Induction period: Mirikizumab 600 mg IV Q4W (n=61) Mirikizumab 200 mg IV Q4W EB (n=62) Mirikizumab 50 mg IV Q4W EB (n=63) Placebo IV Q4W (n=63) Maintenance period: mirikizumab 200 mg SC Q4W (n=47), mirikizumab 200 mg SC Q12W (n=46), PLB SC Q4W (n=13) Duration: 104 weeks (12-week induction; 92-week maintenance)	Primary: The proportion of subjects with clinical remission at Week 12	Planned: 240 Actual: 249	Centers: 85 Countries: 14

Trial Identifier	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary Endpoints	No. of Subjects Planned; Actual Randomized	No. of Centers and Countries
I6T-MC-AMAP	Adult subjects with moderately to severely active ulcerative colitis who participated AMBG and AMAC	OLE, phase 3 Single arm	Mirikizumab 200 mg SC Q4W Number treated: 904 Duration: Maximum 3 years	Primary: The proportion of subjects in clinical remission at Week 52	Planned: N/A Actual: 904	Centers: Ongoing Countries: Ongoing

Source: CDS and Clinical Study Report
Abbreviations: R, randomized; DB, double blind; PC, placebo-controlled; MC, multi center; RW, randomized withdrawal; PG, parallel group; OLE: Open label extension; ES, endoscopic subscore; IV, intravenous; n, number of subjects in specified population or group; mMS, modified Mayo score; PLB, placebo; Q4W, once every 4 weeks; Q12W, once every 12 weeks; R, randomized; RB, rectal bleeding; SC, subcutaneous; SF, stool frequency

7.2. Review Strategy

The phase 3 trials which are the focus of the primary determination of efficacy and safety include a single 12-week induction trial (AMAN) and a single 40-week randomized withdrawal maintenance trial (AMBG).

Efficacy:

No pooling of data across trials was conducted for efficacy assessment. During the review, several issues were identified which resulted in the primary efficacy analyses being conducted in a redefined population ("FDA preferred analysis population") as explained below.

Transcription Error:

The intent to treat (ITT) population included all randomized subjects and subjects were analyzed according to the treatment to which they were assigned. However, during AMAN, an important protocol deviation was reported because of a transcription error that occurred in the electronic clinical outcome assessment (eCOA) devices in Turkey and Poland that impacted 117 subjects. A decision was made to exclude subjects from Turkey and Poland from the primary efficacy analysis prior to study unblinding. The impacted population was excluded from the ITT population and defined as the modified ITT (mITT) population, which included 1162 subjects with baseline mMS of 4 to 9. The mITT population was used by the Applicant as the primary analysis population.

Disease Severity Criteria:

The AMAN protocol defined moderately to severely active UC as a mMS of 4 to 9. Prior to completion of the Applicant's phase 3 program, the Division communicated to the Applicant that the Division's recommended definition of moderately to severely active UC includes subjects with a mMS of 5 to 9 and an ES at least 2. The Division raised concerns that a mMS of 4 may result in the enrollment of subjects with mild symptoms (e.g., a subject with a SFS of 1, RBS of 1, and ES of 2), in whom achieving the definition of remission (which may include a SFS of 1) may not represent a clinically meaningful improvement.

The Applicant performed the requested additional analyses using the Division's recommended definition of moderately to severely active UC and the results of analyses in this population are the focus of this multidisciplinary review. Therefore, the primary efficacy population used in this review is "FDA's preferred analysis population" defined as the mITT population (excluding subjects impacted by transcription error from Turkey and Poland) and who had a baseline mMS of at least 5 and an ES of at least 2.

Table 26: Efficacy Populations Studies AMAN and AMBG

Population	Definition	Number of Subjects AMAN	Number of Subjects AMBG
Intent to treat (ITT)	All randomized subjects	N=1281	N=581
Modified ITT	All randomized subjects excluding subjects impacted by the eCOA transcription error	N=1162	N=544
FDA Preferred Analysis Population	Subset of mITT population where all subjects had baseline mMS of ≥5 and an ES ≥2	N=1062	N=506

Additional issues impacting efficacy assessment- Definition of Clinical Remission:

The protocol defines clinical remission as a stool frequency subscore (SFS) of 0 or 1 with at least a 1-point decrease from baseline, and rectal bleeding subscore (RBS) of 0, and endoscopic subscore (ES) of 0 or 1 (excluding friability). During development, the Division recommended to the Applicant a definition of clinical remission that differs from the Applicant's primary endpoint (consistent with the Division's current advice to sponsors). The Applicant added a multiplicity-controlled secondary endpoint to AMAN and AMBG of "alternate clinical remission" defined as a SFS of 0 or 1, RBS of 0; and an ES of 0 or 1 (excluding friability). The team recommends using this definition for assessment of the primary efficacy endpoint and for labeling, because its definition corresponds to the Agency's currently recommended definition of clinical remission (April 2022).

Safety:

Induction:

Safety was assessed in the safety population, consisting of all subjects randomized who received at least one dose of study treatment. One subject from the mirikizumab treatment arm and one subject from the placebo treatment arm were randomized but did not receive any study treatment. Therefore, the safety population for AMAN consisted of 1279 subjects (n=958 mirikizumab, n=321 placebo).

Maintenance:

The primary safety analysis was performed in the population of subjects who responded to 12 weeks of induction treatment with mirikizumab and were re-randomized into AMBG and received at least one dose of study treatment. The safety population for AMBG consisted of 581 subjects (n=389 mirikizumab, n=192 placebo).

Subjects who responded to placebo during AMAN were continued on blinded placebo in AMBG but were analyzed separately (n=135).

Additional Safety Data:

Additional uncontrolled safety data were derived from the following:

- Open-label Extended Induction Period (OLEI): Subjects who were not induction responders to mirikizumab or placebo during AMAN (n=461) who were enrolled in an open-label extended induction arm of study AMBG and received mirikizumab 300 mg IV Q4W for 12 weeks.
- Open-label Maintenance Period (OLM): Subjects who completed the open-label extended induction period and experienced clinical response had the opportunity to continue on open-label mirikizumab 200 mg SC Q4W for 28 weeks.
- Loss of Response Rescue Period (LORR): Mirikizumab induction responders enrolled in AMBG who experienced loss of response during maintenance (n=59) and received open-label rescue therapy with mirikizumab 300 mg IV Q4W for 12 weeks.
- Subjects who enrolled in study AMAP (open-label extension study), which enrolled subjects from both the phase 2 study AMAC and AMBG, and provided longer term exposure to open-label SC mirikizumab for up to 3 years. This study is ongoing; data are presented as of the data cutoff date December 06, 2021.

Given the open-label design of the OLEI, OLM, and LORR, results were not considered to provide substantial evidence of effectiveness and safety. However, safety data were reviewed to assess for rare events as part of the Safety in Non-randomized Study Cohorts 8.2.6.3. Similarly, given the open-label design of AMAP, safety data were reviewed for rare events and delayed-onset safety events as part of the Safety in Integrated Summary of Safety 8.2.6.4.

8. Statistical and Clinical Evaluation

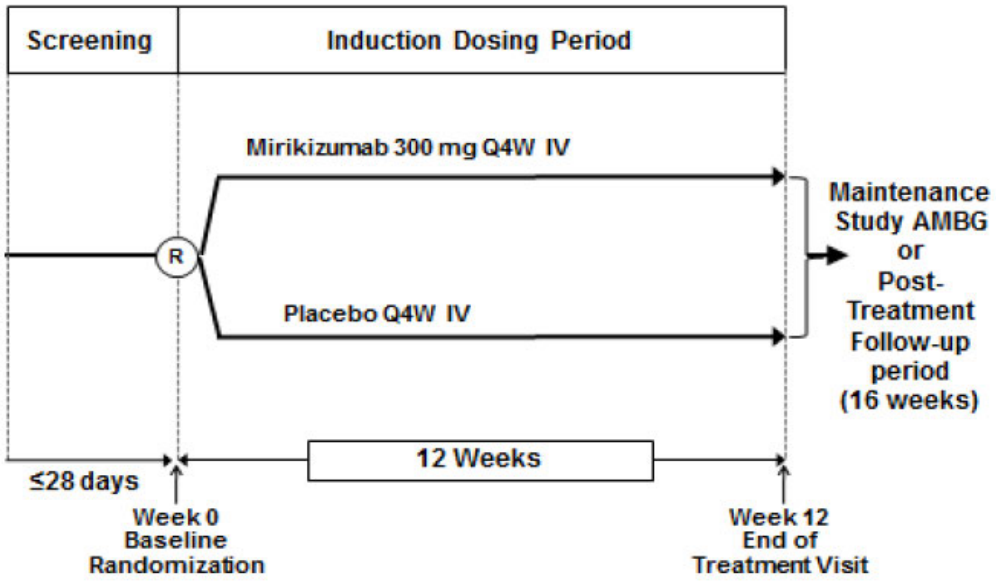
8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. I6T-MC-AMAN

Trial Design

AMAN was a multicenter, randomized, double-blind, parallel-arm, placebo-controlled trial designed to evaluate the safety and efficacy of mirikizumab, compared with placebo, over a 12-week induction period. The trial population included subjects with a modified Mayo score (mMS) of 4 to 9 who had an inadequate response, loss of response, or failed to tolerate any of the following: corticosteroids, immunomodulators (6-mercaptopurine, azathioprine), biologic therapy (TNF blocker, vedolizumab), or tofacitinib. A total of 1281 subjects from 35 countries were randomized with a 3:1 ratio to receive blinded mirikizumab 300 mg IV or placebo Q4W at Weeks 0, 4, and 8. Randomization was stratified by prior biologic or JAKi failure status (yes/no), baseline corticosteroid use (yes/no), baseline disease activity (mMS: [4-6] or [7-9]), and region (North America/Europe/Other). The overall trial design for AMAN is shown in Figure 12.

Figure 12. Trial Design for AMAN



Source: Applicant's BLA 761279 submission, Module 2.7.3 Summary of Clinical Efficacy, Figure 2.7.3.2.

Eligibility Criteria

Subjects were eligible for AMAN if they had an established diagnosis of UC at least 3 months prior to baseline with endoscopic and histologic evidence of UC extending proximal to the rectum. Subjects were also required to have moderately to severely active UC, defined as a mMS of 4 to 9 with an ES at least 2, with endoscopy performed within 10 days before baseline. Subjects were categorized as 1) "conventional-failed", defined as subjects with an inadequate response, loss of response, or intolerance to at least one of the following medications: corticosteroids or immunomodulators (azathioprine, 6-mercaptupurine, methotrexate) and who had not failed or demonstrated intolerance to a biologic (anti-TNF or anti-integrin antibodies) or to tofacitinib; or 2) "biologic-failed"**,** defined as subjects with an inadequate response, loss of response, or intolerance to at least one biologic therapy (anti-TNF antibodies or anti-integrin antibodies) or to tofacitinib. Stable doses of oral 5-aminosalicylates and oral corticosteroids (prednisone less than or equal to 20 mg/day or equivalent, or budesonide extended release tables 9 mg/day) were allowed if the dose had been stable for at least 2 weeks before the screening endoscopy. Stable doses of immunomodulators (azathioprine, 6-mercaptopurine, and methotrexate) were allowed if the dose had been stable for at least 8 weeks before the screening endoscopy. Subjects were excluded if they had previous bowel resection or intestinal or intra-abdominal surgery; history of adenoma, dysplasia, or gastrointestinal cancer; had ever received anti-IL-12p40 or anti-IL-23p19 antibodies; or had failed 3 or more biologic therapies for UC.

Study Endpoints

The primary efficacy endpoint was the proportion of subjects in clinical remission at Week 12. Clinical remission was evaluated using the modified Mayo Score (mMS) and was defined as stool frequency subscore (SFS) of 0, or SFS of 1 with at least a 1-point decrease from baseline, rectal bleeding subscore (RBS) of 0, and endoscopic subscore (ES) of 0 or 1 (excluding friability). The multiplicity-controlled secondary endpoints and their definitions are shown in Table 27.

Table 27. Multiplicity-Controlled Secondary Efficacy Endpoints for Study AMAN

Secondary Endpoint	Definition
Alternate Clinical Remission[1] at Week 12	SFS = 0 or 1, and RBS = 0, and ES = 0 or 1 (excluding friability)
Clinical Response at Week 12	Decrease ≥2 points and ≥30% from baseline and a decrease in RBS ≥1 from baseline or an absolute RBS ≤1
Endoscopic Remission[2] at Week 12	ES = 0 or 1 (excluding friability)
Symptomatic Remission at Week 4	SFS = 0 or 1 with a ≥1-point decrease from baseline, and RBS = 0
Symptomatic Remission at Week 12	
Clinical Response at Week 12 among biologic-failed population	
Histologic-Endoscopic Mucosal Improvement at Week 12	Geboes scoring system with neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue, PLUS ES = 0 or 1 (excluding friability)
Change from baseline in the Urgency NRS score at Week 12	

Source: Reviewer's table.
[1] The Applicant's "alternate clinical remission" definition is consistent with FDA's preferred definition of clinical remission.
[2] This endpoint is called "endoscopic improvement" in labeling
Abbreviations: SFS, stool frequency subscore; RBS, rectal bleeding subscore; ES, endoscopic subscore; NRS, Numeric Rating Scale.

Statistical Analysis Plan

Populations

The Applicant's primary efficacy analysis population was the modified Intent-to-Treat (mITT) population defined as all randomized subjects who received any amount of study treatment excluding subjects impacted by an eCOA transcription error that occurred at sites in Poland and Turkey (see Section 7.2). The Division's analyses (in addition to confirming the Applicant's analyses) focus on efficacy in the "FDA preferred analysis population" as previously described; see section 7.2 for details. The safety population included all randomized subjects who received any amount of study treatment, which is used for safety-related analysis.

Sample Size

The study was powered based on assumed clinical remission rates at Week 12 for mirikizumab versus placebo of 23% versus 7.8%. A sample size of 1160 subjects was expected to provide >90% power to demonstrate that mirikizumab is superior to placebo in achieving the primary

efficacy endpoint, as assessed using a chi-square test with a 2-sided significance level of 0.00125.

Calculation of SFS and RBS

The primary efficacy endpoint is based on the mMS which contains three components: SFS, RBS, and ES. For the SFS and RBS, the most recent 3 non-missing days of the 7-day period were averaged and rounded to the nearest integer to calculate the weekly score for each subject. Subjects with less than 3 measurements in the 7-day period were considered missing.

Analyses of Efficacy Endpoints

For assessments of the primary efficacy endpoint and other binary multiplicity-controlled efficacy endpoints, the estimated difference in proportions between arms and the corresponding 99.875% confidence interval were computed based on the stratified risk difference using the Cochran-Mantel-Haenszel (CMH) weights. The analyses adjusted for the following randomization stratification factors: previous biologic or JAKi therapy failure status (yes/no), baseline corticosteroid use (yes/no), baseline disease activity (mMS: <7 or ≥7)), and region (North America/Europe/Other).

For assessments of continuous multiplicity-controlled efficacy endpoints with multiple postbaseline time points, the estimated least squares (LS) means, and the corresponding 95% confidence interval were computed using mixed-effects model for repeated measures (MMRM) analysis. The MMRM included the following effects and covariates: treatment group, previous biologic of JAKi therapy failure status (yes/no), corticosteroid use (yes/no), disease activity (mMS: <7 or ≥7) at baseline), region (North America/Europe/Other), baseline value, visit, and the interactions of treatment-by-visit and baseline by- visit as fixed factors. The covariance structure to model the within-subject errors was unstructured.

Estimands and Intercurrent Events

The estimand corresponding to the primary efficacy endpoint evaluated the difference in the proportion of subjects in clinical remission at Week 12 for mirikizumab 300 mg IV versus placebo in the mITT population. For the intercurrent events of premature treatment discontinuation and use of rescue medication, subjects were considered non-responders. Other binary multiplicity-controlled efficacy endpoints used the same estimand as the primary endpoint.

For the continuous variables, data from planned visits prior to treatment discontinuation was used in the mixed-effects model for repeated measures (MMRM) analysis regardless of whether the subject took prohibited concomitant rescue medication or otherwise violated the protocol during the treatment period.

Handling of Missing Data

For analyses of the primary efficacy endpoint and other binary multiplicity-controlled efficacy endpoints, missing data were imputed using non-responder imputation (NRI). For continuous variables, the primary analysis was MMRM with the missing at random (MAR) assumption for handling missing data. For missing baseline data, the Applicant's pre-specified analyses used a subject's first available post-baseline value to impute the missing baseline value. The review team requested that the Applicant re-analyze the continuous endpoints using multiple imputation to impute the missing baseline values based on a linear model with stratification factors as predictors.

As sensitivity analyses for the primary endpoint and all multiplicity-controlled binary secondary endpoints except the endpoint of Histologic-Endoscopic improvement, a modified non-responder imputation (mNRI) approach was used to handle missing data. For subjects impacted by the eCOA transcription error, subjects who discontinued treatment due to SARS-CoV-2 (COVID-19)-related reasons, lost to follow-up, or a protocol deviation were imputed based on multiple imputation. The modified mayo subscores for all scheduled visits were imputed under the multivariate normal assumption. Indicator variables for treatment and for all stratification factors were included in the model. Subjects who discontinued from the study treatment period for other reasons such as an adverse event (AE) or lack of efficacy were categorized as non-responders.

Multiplicity Adjustment

A graphical multiple testing approach was specified to control the overall type I error rate at 2-sided alpha of 0.00125, for all primary and major secondary endpoints. The Applicant only conducted a single phase 3 induction study. However, achieving statistical significance at the pre-specified 2-sided alpha level of 0.00125 for this single induction study would provide the same statistical evidence against the null hypothesis as achieving statistical significance on two independent induction studies that are each tested at a 2-sided alpha level of 0.05. Refer to Figure 52 in Section 16.7.1 or the final proposed graphical testing procedure. This testing procedure controls the family-wise error rate across all endpoints, and any hypothesis with a multiple testing adjusted p-value of less than 0.00125 was considered statistically significant.

Protocol Amendments

Study I6T-MC-AMAN Protocol Amendments

The original study protocol (dated March 13, 2018) had 1 amendment and 2 addendums.

On September 12, 2019, "alternate clinical remission" defined as a SFS of 0 or 1, RBS of 0, and ES of 0 or 1 (excluding friability) was added as an objective and secondary endpoint in response to advice from the Division to use this definition for clinical remission that differed from the Applicant's definition of clinical remission. This endpoint was designated as a "major secondary endpoint" (i.e., multiplicity-controlled) in the SAP.

On March 6, 2019, a protocol addendum (13) allowed a site "to only enroll subjects who have failed both conventional and biological treatments, if the Ethics Committee, Institutional Review Board, or Regulatory Body for that site has required that enrollment be limited to these subjects, and the sponsor has determined that limiting enrollment to these subjects at that site will not significantly impact the prespecified ratio of biologic-failed versus conventional-failed subjects."

On August 21, 2020, a protocol addendum (15) was submitted with additional options for mitigation of the disruption and to enable the safe conduct of the clinical trial during the COVID-19 public health emergency. The changes included the following, which are aligned with the guidance for industry *FDA Guidance on Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health* Emergency (July 2020).

- Increasing visit windows
- Local laboratory option
- Telemedicine and alternative site visits
- Concomitant medications – The Applicant allowed tapering of stable doses of steroids based on guidance from gastrointestinal societies out of concern for increased risk of severe COVID.
- Missing endoscopy – The Applicant allowed subjects who missed the Week 12 or End of Treatment endoscopy to enroll in AMBG if subjects had "Clinical Benefit"[7] at the end of AMAN.

None of the changes had a major impact on the overall study design, efficacy assessments, or negatively impacted collection of safety data.

8.1.2. Study Results (AMAN)

Compliance with Good Clinical Practices

The study was performed in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki, and the International Conference on Harmonization guidelines for Good Clinical Practice, all applicable laws, rules, and regulations.

[7] Clinical benefit was defined as a decrease of at least 1-point in RBS from baseline, or a RBS of 0 or 1, and 1) for subjects with baseline mMS of less than or equal to 6, achieve a decrease from baseline of at least 2 points in the "symptomatic score" (i.e., SFS + RBS); 2) for subjects with baseline mMS of greater than 6, achieve a decrease from baseline of at least 3 points in the symptomatic score.

Data Quality and Integrity

The data were of sufficient quality to permit a substantive review.

Financial Disclosure

A single investigator [redacted] had reportable financial interests. [redacted] participated as a [redacted] of the study subjects treated. Given the trial size and total number of investigators, the potential impact of this financial interest was not expected to influence the trial outcome. A detailed summary of financial disclosures is included in the Appendix Section 16.2.

Subject Disposition

Study populations and subject disposition for AMAN are shown in Table 28 and Table 29, respectively. Additional details regarding population definitions are discussed in Section 7.2. All randomized subjects who received any amount of study treatment (n=1281) were included in the ITT population. One subject who was randomized to mirikizumab and one subject who was randomized to placebo did not receive study treatment; therefore, they were not included in the safety population (n=1279). The mITT population included 1162 subjects with baseline mMS of 4 to 9 and the FDA preferred analysis population included 1062 subjects with baseline mMS of 5 to 9.

Overall, few subjects had a premature discontinuation from study treatment during AMAN, 36 (11.2%) and 38 (4%) subjects in the placebo and mirikizumab treatment arm, respectively. The most frequently reported reasons for discontinuation from study treatment were adverse events (AEs), withdrawal by subject, and lack of efficacy and reported more frequently by subjects in placebo arm than mirikizumab treatment arm.

Table 28. Study Population, AMAN, 12 Week Induction Period

Study Population	Mirikizumab 300 mg IV Q4W n	Placebo n
Subjects randomized	959	322
ITT population	959	322
Safety population	958	321
mITT population	868	294
FDA preferred analysis population	795	267

Source: ds.xpt and adsl.xpt; Software: R
Abbreviations: mITT, modified intent-to-treat; n, number of subjects in specified population or group; Q4W, once every 4 weeks

Table 29. Subject Disposition, Safety Population, AMAN, 12 Week Induction Period

Subject Disposition	Mirikizumab 300 mg IV Q4W N=958 n	Placebo N=321 n	Risk Difference (%) (95% CI)
Discontinued study treatment (mITT)	38 (4.0)	36 (11.2)	-7.2 (-10.9,-3.6)*
Adverse event	15 (1.6)	23 (7.2)	-5.6 (-8.5, -2.7)*
Lack of efficacy	5 (0.5)	5 (1.6)	-1.0 (-2.5, 0.4)
Lost to follow-up	3 (0.3)	0	0.3 (-0.0, 0.7)
Other[1]	5 (0.5)	0	0.5 (0.1, 1.0)
Protocol deviation	4 (0.4)	1 (0.3)	0.1 (-0.6, 0.8)
Site terminated by sponsor	1 (0.1)	0	0.1 (-0.1, 0.3)
Withdrawal by subject	5 (0.5)	7 (2.2)	-1.7 (-3.3, 0.0)

Source: ds.xpt and adsl.xpt; Software: R
Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
[1] Other include Insufficient diary data (3), protocol non-compliance (1), no endoscopy (1).
Abbreviations: CI, confidence interval; IV, intravenous; mITT, modified intent-to-treat; N, number of subjects in treatment arm; n, number of subjects in specified population or group; NA, not applicable; Q4W, once every 4 weeks

Protocol Violations/Deviations

In mITT population of AMAN, important protocol deviations were reported in 90 (30.6%) subjects in the placebo group and 262 (30.2%) subjects in the mirikizumab treatment group.

The most frequently reported protocol deviations were related to inclusion criteria (e.g., no inadequate response to, loss of response to, or intolerance to at least 1 of the medications described in the protocol); laboratory and imaging criteria (e.g., hematology/chemistry laboratories were not obtained, incorrect biopsy collection); not maintaining stable dose of permitted oral corticosteroids or immunomodulators, and randomization error (e.g., incorrect stratification of subjects). The important protocol violations were reported at similar rates between placebo and mirikizumab treatment arm.

Demographic Characteristics

Demographic characteristics for AMAN are presented in Table 30. Overall, the baseline demographic characteristics were similar between treatment arms and representative of the population anticipated in UC. The mean age was 42.5 years with a range from 18 to 79 years, and the majority (92.4%) of subjects were younger than 65 years of age. Most subjects were White (74.3%), male (60.4%), and not Hispanic or Latino (75.0%). Approximately 41% of the subjects were from Europe, 15% from North America, 22% from Asia and 20% from the rest of the world. The treatment arms were balanced with respect to most demographic characteristics; however, there were slightly more males in the mirikizumab treatment arm compared to placebo. Results of subgroup analyses for the demographic subgroups were generally similar to results from the primary analysis of the FDA preferred analysis population (See Section 16.7.5). Overall, the minor differences in sex between treatment arms in AMAN did not impact the results of the analyses.

Table 30. Baseline Demographic Characteristics, AMAN, 12 Week Induction Period (Safety Population)

Characteristic	Mirikizumab 300 mg IV Q4W N=958	Placebo N=321	Total N=1279
Sex, n (%)			
Female	367 (38.3)	140 (43.6)	507 (39.6)
Male	591 (61.7)	181 (56.4)	772 (60.4)
Age, years			
Mean (SD)	42.8 (13.8)	41.3 (13.7)	42.46 (13.8)
Median (min, max)	41 (18, 79)	39 (18, 75)	41 (18, 79)
Age group, years, n (%)			
<65	881 (92.0)	301 (93.8)	1182 (92.4)
≥65	77 (8.0)	20 (6.2)	97 (7.6)
Age group ≥75, years, n (%)			
≥75	11 (1.1)	1 (0.3)	12 (0.9)
Weight, kg			
Mean (SD)	72.7 (17.2)	70.9 (16.8)	72.2 (17.1)
Median	70.55	69.75	70.55
(min, max)	(34.0, 151.5)	(33.8, 124)	(33.8, 151.5)
Weight group, kg (%)			
<80	654 (68.2)	236 (73.3)	890 (69.6)
≥80	304 (31.7)	86 (26.7)	389 (30.4)
Race, n (%)			
White	704 (73.5)	246 (77.6)	950 (74.3)
Asian	223 (23.3)	68 (21.2)	291 (22.8)
American Indian or Alaska Native	10 (1.0)	2 (0.6)	12 (0.9)
Black or African American	10 (1.0)	2 (0.6)	12 (0.9)
Multiple	1 (0.1)	2 (0.6)	3 (0.2)
Native Hawaiian or Other Pacific Islander	1 (0.1)	0	1 (0.2)
Missing	9 (0.9)	1 (0.3)	10 (0.8)
Ethnicity, n (%)			
Not Hispanic or Latino	711 (74.2)	248 (77.3)	959 (75.0)
Hispanic or Latino	32 (3.3)	12 (3.7)	44 (3.4)
Not reported	215 (22)	61 (19)	276 (22)
Region of participation, n (%)			
Eastern Europe	230 (24.0)	76 (23.7)	306 (23.9)
Asia	211 (22.0)	63 (19.6)	274(21.4)
Rest of the World	190 (19.8)	74 (23.1)	264 (20.6)
Western Europe	171 (17.8)	56 (17.4)	227 (17.7)
North America	138 (14.4)	47 (14.6)	185 (14.5)
Central America/South America	18 (1.9)	5 (1.6)	23 (1.8)

Source: adsl.xpt; Software: R
Abbreviations: IV, intravenous; N, number of subjects in treatment group; n, number of subjects with given characteristic; Q4W, once every 4 weeks; SD, standard deviation
Eastern Europe: Czech Republic, Hungary, Latvia, Lithuania, Poland, Romania, Slovakia
Asia: China, India, Japan, South Korea, Malaysia, Taiwan
Rest of the world: Australia, Israel, Russian Federation, Serbia, Turkey, Ukraine; Western Europe: Austria, Belgium, Denmark, France, Germany, Ireland, Italy, Netherlands, Spain, Switzerland, United Kingdom
North America: Canada, United States of America
Central/South America: Argentina, Mexico.

There were no notable differences in baseline demographic characteristics between the safety population and the FDA preferred analysis population. Refer to Table 121 of Section 16.7.2 of the Appendix.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Other baseline characteristics including baseline mMS, prior biologic or tofacitinib failure, and baseline corticosteroid use for AMAN are presented in Table 31. The majority of subjects had not failed a prior biologic or tofacitinib (60.2%) and did not have baseline corticosteroid use (59.8%). The treatment arms were balanced with respect to the baseline factors. Of note, the 113 missing values of baseline mMS were due to the eCOA transcription error.

Table 31. Other Baseline Characteristics, AMAN, 12 Week Induction Period (Safety Population)

Characteristic	Mirikizumab 300 mg IV Q4W N=958	Placebo N=321	Total N=1279
Prior biologic or tofacitinib failure, n (%)			
Failed	382 (39.9)	127 (39.6)	509 (39.8)
Not failed	576 (60.1)	194 (60.4)	770 (60.2)
Baseline modified Mayo score category, n (%)			
Mild [1-4]	73 (7.6)	26 (8.1)	99 (7.7)
Moderate [5-6]	334 (34.9)	113 (35.2)	447 (34.9)
Severe [7-9]	465 (48.5)	155 (48.3)	620 (48.5)
Missing[1]	86 (9.0)	27 (8.4)	113 (8.8)
Baseline modified Mayo score[2]			
Mean (SD)	6.5 (1.3)	6.5 (1.3)	6.5 (1.3)
Median (min, max)	7 (3[3], 9)	7 (4, 9)	7 (3, 9)
Baseline corticosteroid use, n (%)			
Yes	404 (42.2)	129 (40.2)	533 (41.7)
No	554 (57.8)	192 (59.8)	746 (59.8)

Source: adsl.xpt; Software: R
1: All missing values of baseline modified Mayo score were due to eCOA transcription error.
2: Missing values of baseline modified Mayo score were removed
3: One subject with an mMS of 3 at baseline was enrolled; however, the subject was not included in the efficacy analysis population.
Abbreviations: N, number of subjects in treatment group; n, number of subjects with given characteristic; Q4W, once every 4 weeks; IV, intravenous; SD, standard deviation

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The SAP defined treatment compliance (%) as 100 x N1/N2 where N1 is the total number of study drug infusions and N2 is the total number of infusions planned per protocol. “Overall compliance” with therapy was defined as missing no doses before discontinuing study treatment.

For AMAN, 290 subjects (98.6%) in the placebo group and 851 subjects (98.0%) in the mirikizumab treatment group were compliant with treatment. Compliance was similar across treatment arms.

Efficacy Results – Primary Endpoint

The Applicant’s pre-specified primary analysis was performed with the mITT population, which included subjects with baseline mMS 4 to 9 with an ES of at least 2. At the January 22, 2022, pre-BLA meeting, the Agency expressed concern that a mMS less than 5 may not reflect moderately active disease. Therefore, the Agency recommended additional analyses that

excluded subjects with a baseline mMS less than 5. In the mid-cycle communication with the Applicant on September 13, 2022, the Agency continued to recommend that moderately to severely active UC be defined as an mMS of 5 to 9 with an ES of at least 2, and considered this population to be the most appropriate primary analysis population. Unless otherwise specified, all efficacy results in this review are based on the FDA preferred analysis population (i.e., the mITT population excluding subjects with a baseline mMS < 5).

Efficacy results for the primary analysis of clinical remission in the FDA preferred analysis population are presented in Table 32 below. The mirikizumab 300 mg IV Q4W treatment group had a statistically significantly higher proportion of subjects with clinical remission (23.5%) at Week 12 in comparison with those treated with placebo (13.9%), p-value = 0.00057.

As described above in Section 7.2, the results based on the "alternate clinical remission" definition that aligns with the Agency's currently recommended definition will be included in labeling. Results for "alternate clinical remission" are shown in Table 32. The treatment difference versus placebo was 9.7% (95% CI: 4.5%, 14.8%), and this difference was statistically significant (p=0.00082).

The efficacy results for clinical remission at Week 12 and "alternate clinical remission" at Week 12 are consistent in terms of treatment difference, 95% confidence interval, and statistical significance. Efficacy results based on the mITT population (shown in Section 16.7.1) were similar to the FDA preferred analysis population.

Table 32. Clinical Remission at Week 12, FDA Preferred Analysis Population, AMAN

Parameter	Mirikizumab 300 mg IV Q4W (N=795)	Placebo (N=267)
Clinical Remission at Week 12, n (%)	187 (23.5)	37 (13.9)
Treatment Difference[1], (95% CI)	9.9 (4.8, 15.0)	
P-value[2]	0.00057[3]	
Alternate Clinical Remission at Week 12, n (%)	191 (24.0)	39 (14.6)
Treatment Difference[1], (95% CI)	9.7 (4.5, 14.8)	
P-value[2]	0.00082[3]	
Missing data, n (%)	33 (4.2)	35 (13.1)

Source: Reviewer analysis using Applicant submitted data admayo.xpt; based on Clinical Summary of Efficacy Appendix (Table APP.2.7.3.6.58, P 616)
[1] The common risk difference is the difference in proportions adjusted for the stratification factors: prior biologic or tofacitin b failure (yes/no), baseline corticosteroid use (yes/no), baseline disease activity (mMS: <7 or ≥7), and region (North America/Europe/Other), where the confidence intervals are calculated using Mantel-Haenszel-Sato method.
[2] Cochran-Mantel-Haenszel (CMH) test adjusted by prior biologic or tofacitinib failure (yes/no), baseline corticosteroid use (yes/no), baseline disease activity (mMS: <7 or ≥7), and region (North America/Europe/Other).
[3] The endpoint was tested at an alpha level of 0.00125. P-value < 0.001.
Abbreviations: N, number of subjects in treatment group; Q4W, once every 4 weeks; IV, intravenous; CI, confidence interval.

The percentage of subjects with missing data for the primary endpoint was 4.2% in the mirikizumab 300 mg arm, and 13.1% in the placebo arm. Most of the missing data were due to dropout, with a higher dropout rate in the placebo group. A non-responder imputation approach was used to handle missing data regardless of the reason for dropout. As UC is a chronic condition and mirikizumab is intended to provide chronic treatment, subjects who discontinued study treatment would not experience a long-term benefit from study treatment

without continued treatment. Therefore, non-responder imputation was considered appropriate for handling missing data due to dropout. The placebo group had higher rates of dropout due to adverse events (most commonly due to UC exacerbation), withdrawal by subject, and lack of efficacy (which accounted for the majority of dropout in the placebo group) compared to the mirikizumab group.

As for the sensitivity analysis, using multiple imputation to impute missing data due to COVID-19, lost to follow-up, or a protocol deviation, did not impact the statistical significance of mirikizumab 300 mg over placebo in terms of endpoints of clinical remission and "alternate clinical remission."

Efficacy Results – Secondary and other relevant endpoints

Efficacy results for the major secondary endpoints (b) (4) are presented in Table 33, assessed within the FDA preferred analysis population. All of the secondary endpoints showed statistically significant results for the mirikizumab 300 mg IV Q4W arm compared to placebo in the Applicant's analysis of the mITT population (Section 16.7.3), and all but one of the secondary endpoints (symptomatic remission at Week 4) were significant for the analysis of the FDA preferred analysis population. Symptomatic remission at Week 4 was not statistically significant when analyzed for the FDA preferred analysis population (p-value = 0.00202 > 0.00125).

Table 33. Results for Secondary Efficacy Endpoints, FDA Preferred Analysis Population, Study AMAN

Endpoints	Parameter	Mirikizumab 300 mg IV Q4W (N=795)	Placebo (N=267)	Treatment Difference[1] versus Placebo (95% CI)	P-value[2]
Clinical Response at Week 12	%	64.7	43.4	21.6 (14.8, 28.3)	<0.00001[3]
Endoscopic Remission[4] at Week 12	%	34.5	21	13.8 (8.1, 19.6)	0.00002[3]
Symptomatic Remission at Week 12	%	45.4	28.5	16.9 (10.6, 23.3)	<0.00001[3]
Clinical Response in the Biologic-Failed Population at Week 12	(N) %	(331) 55.9	(107) 30.8	25.7 (15.4, 36.0)	<0.00001[3]
Histologic-Endoscopic Mucosal Improvement at Week 12	%	25.2	14.2	11.3 (6.3, 16.4)	0.00009[3]
Symptomatic Remission at Week 4	%	20.5	12.4	8.5 (3.6, 13.4)	0.00202[3]
Change from Baseline in Urgency NRS Score	(N_{obs}) LSMEAN (SE)	(755) -2.67 (0.088)	(229) -1.72 (0.150)	-0.95 (-1.28, -0.62)	<0.00001[3]

Source: Reviewer analysis using Applicant submitted data admayo.xpt and addd4.xpt; based on Clinical Summary of Efficacy Appendix (Table APP.2.7.3.6.60 – Table APP.2.7.3.6.65, P 620 – P 630) and Applicant's response to information request submitted on 09/23/2022.

[1] For binary endpoints, the common risk difference is the difference in proportions adjusted for the stratification factors: prior biologic or tofacitinib failure (yes/no), baseline corticosteroid use (yes/no), baseline disease activity (mMS: <7 or ≥7), and region (North America/Europe/Other), where the confidence intervals are calculated using Mantel-Haenszel-Sato method; for continuous endpoint, The treatment difference, 95% CI, and p-value were calculated using a mixed model with repeated measures including treatment, baseline value, visit, interaction of baseline value-by-visit, interaction of treatment-by-visit, and stratification factors.

[2] For binary endpoints, computation was based on Cochran-Mantel-Haenszel (CMH) test adjusted by prior biologic or tofacitin b failure (yes/no), baseline corticosteroid use (yes/no), baseline disease activity (mMS: <7 or ≥7), and region (North America/Europe/Other). For the continuous endpoint, computation was based on a mixed model with repeated measures including treatment, baseline value, visit, interaction of baseline value-by-visit, interaction of treatment-by-visit, prior biologic or tofacitin b failure (yes/no), baseline corticosteroid use (yes/no), baseline disease activity (mMS: <7 or ≥7), and region (North America/Europe/Other) as covariates.

[3] The endpoint was tested at an alpha level of 0.00125.

[4] This endpoint will be called "endoscopic improvement" in the label.

Abbreviations: N, number of subjects in treatment group; Q4W, once every 4 weeks; IV, intravenous; CI, confidence interval; NRS, Numeric Rating Scale; LSMEAN, least squares mean; SE, standard error; N_{obs}, number of observed values.

Discussion of Primary and Secondary Endpoints Proposed for Labeling

Clinical Remission and Alternate Clinical Remission

The Applicant's proposed definition of clinical remission differs from the Agency's preferred definition of clinical remission due to the requirement for subjects to demonstrate at least 1-point decrease from baseline in the SFS. The definition of the term "alternate clinical remission", proposed by the Applicant, is the Agency's preferred definition of clinical remission. The efficacy results on the two endpoints were similar and both were significant. Although the two endpoints are slightly different in terms of definition, they provide redundant information. Therefore, the team concluded that "alternate clinical remission" will be included in the label as the primary efficacy endpoint of "clinical remission;" (b) (4)

(b) (4)

(b) (4)

Endoscopic Improvement

The Applicant's proposed definition of "endoscopic remission" is the same as the Agency's preferred definition of "endoscopic improvement", which is a centrally read endoscopy subscore of 0 or 1 (score of 1 modified to exclude friability). The definition of endoscopic remission recommended by the Agency is a centrally read endoscopy subscore of 0. Therefore, alternative terminology will be utilized to describe this endpoint in the label.

Histologic-Endoscopic Mucosal Improvement

The Applicant utilized a definition of endoscopic improvement (ES of 0 or 1-exclusing friability) and histologic improvement defined by the Geboes scoring system with neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue (Geboes score of ≤3.1).

The Applicant proposed that the clinical relevance of this definition is supported by the following:

- "As demonstrated by (Bryant et al. 2016 and Christensen et al. 2017) the improvement, and resolution, of inflammation in UC, as measured by a histologic assessment and endoscopic measures [respectively], compared to endoscopic measures alone, is associated with lower rates of clinical relapse, corticosteroid use, hospitalization, and colectomy. The mirikizumab UC program included endpoint definitions that combined histologic and endoscopic evaluations according to the available literature (Gupta et al. 2007; Bryant et al. 2016; Zenlea et al. 2016; Yoon et al. 2020). Additionally, the definition of histologic-endoscopic mucosal improvement was similar to other approved labeling (e.g., Rinvoq, Zeposia)"

Although the review team agrees with this justification, there were some important limitations to the histologic evaluation in this program. Some subjects (approximately 6.6%) entered the induction study with a Geboes score of ≤3.1 on the baseline biopsy, thus meeting the histologic component of the endpoint definition. Therefore, it was unclear whether achieving histologic-endoscopic mucosal improvement represents an improvement from baseline in all subjects. The review team conducted a sensitivity analysis in which this endpoint was reanalyzed only in the subgroup of subjects with a baseline Geboes score of >3.1. Results were consistent with those obtained in the FDA preferred analysis population, and therefore the team concluded that it is reasonable to include this endpoint in the label. See Section 16.7.4.

Additionally, although investigators were instructed to perform biopsies on the mucosa most representative of the inflammation seen in the region, there may be variation in histologic findings due to sampling. UC is generally considered to involve continuous segments of the GI tract; however, discontinuous patterns of inflammation may also be observed, particularly in subjects with a prior history of treatment (Bernstein et al. 1995). Furthermore, the clinical significance of achieving "histologic improvement" (in addition to endoscopic improvement) has not been well characterized and is limited by the various definitions used in the literature to define this concept (Battat et al. 2019).

Bowel urgency (b) (4)

Bowel urgency is a common symptom of UC and is associated with reduced quality of life (Dubinsky et al. 2022). The Applicant assessed bowel urgency severity with the Urgency Numeric Rating Scale (NRS) patient-reported outcome measure, a single-item PRO measure assessing severity of a subject's urgency (the sudden or immediate need) to have a bowel movement within the past 24 hours using an 11-point NRS ranging from 0 ("No urgency") to 10 ("Worst possible urgency"). Daily total scores were recorded using the Urgency NRS and weekly Urgency NRS scores are calculated as the mean score over a 7-day period. If there are fewer than 4 available daily Urgency NRS scores over the relevant 7-day period, then the Urgency NRS score is recorded as missing.

Based on FDA's comprehensive quantitative anchor-based analyses and qualitative assessment, the review team does not agree with the Applicant's proposed clinically meaningful within-subject change threshold range for the Urgency NRS score for both Studies AMAN and AMBG. Despite the statistically significant results reported on the multiplicity controlled secondary endpoint of change from baseline in the Urgency NRS score at Week 12 (AMAN) or Week 40 (AMBG), data collected from AMAN and AMBG do not provide strong evidence to support the meaningfulness of the observed improvement in urgency severity for subjects with higher severity at baseline, given that the difference between mirikizumab and placebo groups was modest. Thus, the review team concluded that the evaluation of this multiplicity controlled secondary endpoint for AMAN and AMBG did not demonstrate that subjects treated with mirikizumab had meaningful improvement compared to those treated with placebo. Refer to Section 16.4 and Section 16.5 for further details regarding the Urgency NRS PRO, and Section

16.6 for further details regarding the interpretation of change from baseline in the Urgency NRS.

Discussion of Additional Endpoints

Urgency NRS 0 or 1

The Applicant assessed the proportion of subjects with Urgency NRS 0 or 1 at Week 12 of AMAN and Week 40 of AMBG. The Applicant supported the clinical relevance of an Urgency NRS 0 or 1 with qualitative data as described in Section 16.5. The Urgency NRS 0 or 1 endpoint was a pre-specified, non-multiplicity-controlled secondary endpoint at Week 12 and a multiplicity-controlled secondary endpoint at Week 40. At Week 12 of AMAN, Urgency NRS 0 or 1 was achieved by 131/728 (18.0%) of subjects treated with mirikizumab compared to 24/245 (9.8%) of subjects on placebo. The review team agrees that urgency is an important symptom in UC as described above. Given that the Urgency NRS 0 or 1 endpoint was not multiplicity-controlled for AMAN, the label will include language indicating that a greater proportion of subjects achieved an Urgency NRS 0 or 1 in the mirikizumab group compared to placebo, (b) (4). Refer to Section 8.1.4 regarding the inclusion of Urgency NRS 0 or 1 in labeling for AMBG.

(b) (4)

Dose/Dose Response

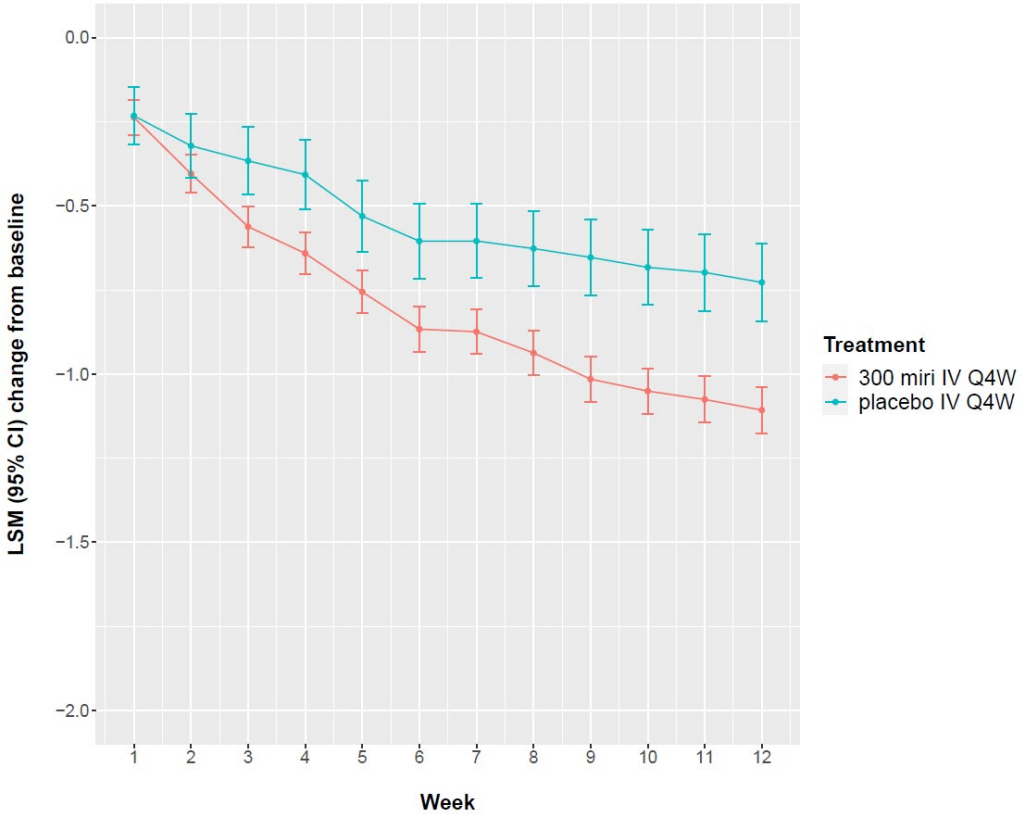
AMAN evaluated a single dose level of mirikizumab 300 mg IV Q4W for the induction period and the dose was selected based on a phase 2 dose-ranging trial (AMAC). In AMAC, three doses of mirikizumab (600, 200, and 50 mg IV Q4W) or placebo were administered to a total of 249 subjects with moderately to severely active UC. Subjects in the 600 mg IV Q4W mirikizumab cohort did not respond better to treatment than subjects in the 200 mg IV Q4W exposure-based (overall average dose level of 250 mg) mirikizumab cohort. Thus, the 300 mg IV Q4W induction dose was selected for Study AMAN. Refer to the Clinical pharmacology in Section 6.3.

Persistence of Effect

Individual analyses of the SFS and RBS of the mMS in AMAN showed evidence that mirikizumab provides symptomatic relief after only a few weeks of induction dosing. Subjects in the

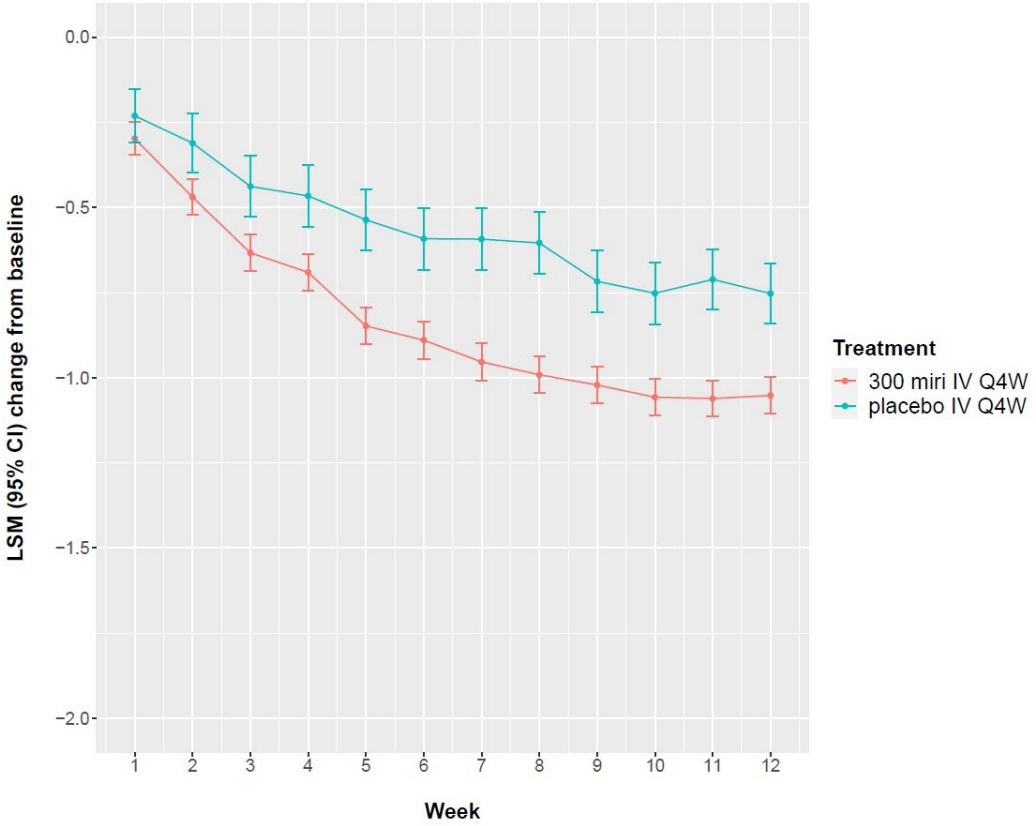
mirikizumab treatment group showed a greater mean reduction in SFS as early as Week 3 and in RBS as early as Week 2 compared to the placebo (Figure 13 and Figure 14).

Figure 13. Stool Frequency Subscore Change from Baseline, FDA Preferred Analysis Population, AMAN



Source: Reviewer generated figure based on Applicant submitted data admayo.xpt, and adsl.xpt.
Abbreviations: LSM, least-square mean; CI, confidence interval.

Figure 14. Rectal Bleeding Subscore Change from Baseline, FDA Preferred Analysis Population, AMAN



Source: Reviewer generated figure based on Applicant submitted data admayo.xpt, and adsl.xpt.
Abbreviations: LSM, least-square mean; CI, confidence interval.

Additional Analyses Conducted on the Individual Trial

Efficacy results were investigated by prior biologic or JAKi failure status for important efficacy endpoints in AMAN (Table 34). Although the study was not powered to detect a significant difference for each subgroup, the group of subjects who were naïve to biologic and JAKi showed numerically higher clinical remission, alternate clinical remission, endoscopic remission, and histologic-endoscopic mucosal improvement treatment difference compared to the group with prior biologic or JAKi failure. The mirikizumab groups consistently showed higher remission and response rates compared to the placebo across all subgroups.

Table 34. Subgroup Analyses, Biologic/JAKi Naïve Versus Prior Biologic or JAKi Failed, FDA Preferred Analysis Population, Study AMAN

	Mirikizumab 300 mg IV Q4W (N=795)		Placebo (N=267)		Treatment difference (95% CI)[1]
Endpoints	**n/N**	**%**	**n/N**	**%**	
Clinical remission at Week 12					
Biologic and JAKi naïve	137/450	30.4	26/155	16.8	13.7 (6.4, 20.9)
Prior biologic or JAKi failed	47/331	14.2	9/107	8.4	5.8 (-0.7, 12.2)

	Mirikizumab 300 mg IV Q4W (N=795)		Placebo (N=267)		Treatment difference (95% CI)[1]
Endpoints	**n/N**	**%**	**n/N**	**%**	
Alternate clinical remission at Week 12					
Biologic and JAKi naïve	140/450	31.1	28/155	18.1	13.1 (5.6, 20.5)
Prior biologic or JAKi failed	48/331	14.5	9/107	8.4	6.1 (-0.4, 12.6)
Clinical response at Week 12					
Biologic and JAKi naïve	320/450	71.1	80/155	51.6	19.5 (10.6, 28.4)
Prior biologic or JAKi failed	185/331	55.9	33/107	30.8	25.0 (14.8, 35.3)
Endoscopic remission at Week 12					
Biologic and JAKi naïve	198/450	44.0	43/155	27.7	16.3 (7.8, 24.7)
Prior biologic or JAKi failed	72/331	21.8	11/107	10.3	11.5 (4.2, 18.7)
Symptomatic remission at Week 12					
Biologic and JAKi naïve	228/450	50.7	54/155	34.8	15.8 (7.0, 24.6)
Prior biologic or JAKi failed	126/331	38.1	19/107	17.8	20.3 (11.4, 29.2)
Histologic-Endoscopic Mucosal Improvement at Week 12					
Biologic and JAKi naïve	153/450	34.0	29/155	18.7	15.3 (7.8, 22.8)
Prior biologic or JAKi failed	44/331	13.3	8/107	7.5	5.8 (-0.4, 12.0)
Symptomatic remission at Week 4					
Biologic and JAKi naïve	107/450	23.8	23/155	14.8	8.9 (2.1, 15.8)
Prior biologic or JAKi failed	54/331	16.3	8/107	7.5	8.8 (2.5, 15.2)

Source: Reviewer generated table based on Applicant submitted data admayo.xpt, adsl.xpt, and adhist.xpt.
[1] The 95% confidence intervals of the treatment effects were constructed by Wald approach.
Abbreviations: N, number of subjects in treatment group; Q4W, once every 4 weeks; IV, intravenous; CI, confidence interval.

Efficacy results were evaluated by the status of corticosteroids use at induction baseline for important efficacy endpoints in AMAN (Table 35). Although the mirikizumab groups showed higher remission and response rates compared to the placebo across all subgroups, the treatment difference is small in the group with use of corticosteroids at baseline compared to the group who did not use corticosteroids at baseline. The smaller treatment difference is due to both a numerically lower response rate in mirikizumab subjects who used corticosteroids at baseline compared to those who did not use corticosteroids at baseline and a higher response rate for placebo subjects who used corticosteroids at baseline compared to those who did not use corticosteroids at baseline. It is possible that corticosteroid usage impacted the efficacy of mirikizumab during the induction study. However, a much larger benefit was demonstrated in the subgroup with baseline corticosteroids use at Week 40 of the maintenance study (Table 45), indicating long-term benefit of mirikizumab in subjects who used corticosteroids at baseline.

Table 35. Subgroup Analyses, Use of Corticosteroids at Baseline, FDA Preferred Analysis Population, Study AMAN

	Mirikizumab 300 mg IV Q4W (N=795)		Placebo (N=267)		Treatment difference (95% CI)[1]
Endpoints	**n/N**	**%**	**n/N**	**%**	
Clinical remission at Week 12					
Corticosteroids at baseline	66/331	19.9	19/100	19.0	0.9 (-7.9, 9.8)
No corticosteroids at baseline	121/464	26.1	18/167	10.8	15.3 (9.1, 21.5)
Alternate clinical remission at Week 12					
Corticosteroids at baseline	68/331	20.5	20/100	20.0	0.5 (-8.4, 9.5)
No corticosteroids at baseline	123/464	26.5	19/167	11.4	15.1 (8.9, 21.4)
Clinical response at Week 12					
Corticosteroids at baseline	196/331	59.2	50/100	50.0	9.2 (-1.9, 20.4)
No corticosteroids at baseline	318/464	68.5	66/167	39.5	29.0 (20.5, 37.5)
Endoscopic remission at Week 12					
Corticosteroids at baseline	100/331	30.2	28/100	28.0	2.2 (-7.9, 12.3)
No corticosteroids at baseline	174/464	37.5	28/167	16.8	20.7 (13.6, 27.9)
Symptomatic remission at Week 12					
Corticosteroids at baseline	134/331	40.5	36/100	36.0	4.5 (-6.3, 15.3)
No corticosteroids at baseline	227/464	48.9	40/167	24.0	25.0 (17.1, 32.9)
Histologic-Endoscopic Mucosal Improvement at Week 12					
Corticosteroids at baseline	73/331	22.1	18/100	18.0	4.0 (-4.7, 12.8)
No corticosteroids at baseline	127/464	27.4	20/167	12.0	15.4 (9.0, 21.8)
Symptomatic remission at Week 4					
Corticosteroids at baseline	57/331	17.2	15/100	15.0	2.2 (-5.9, 10.3)
No corticosteroids at baseline	106/464	22.8	18/167	10.8	12.1 (6.0, 18.1)

Source: Reviewer generated table based on Applicant submitted data admayo.xpt, adsl.xpt, and adhist.xpt.
[1] The 95% confidence intervals of the treatment effects were constructed by Wald approach.
Abbreviations: N, number of subjects in treatment group; Q4W, once every 4 weeks; IV, intravenous; CI, confidence interval.

Efficacy results were investigated by baseline mMS category (<5, ≥5) for important efficacy endpoints in AMAN (Table 36). The study enrolled subjects with baseline mMS of 4 to 9 while FDA preferred analysis population is subjects with baseline mMS of 5 to 9. The mirikizumab group consistently showed higher remission and response rates compared to the placebo group across all subgroups. Treatment differences were generally larger in the mMS of 4 subgroup. For the mirikizumab arm, the group of baseline mMS of 4 showed numerically higher response rates compared to the group of baseline mMS of 5 to 9 in most of the endpoints listed in Table 36. However, for the placebo arm, the group of baseline mMS of 4 generally had lower response rates compared to the group of baseline mMS of 5 to 9. The interpretation of these subgroup results is limited by the small number of subjects with baseline mMS of less than 5.

Table 36. Subgroup Analyses, Baseline Modified Mayo Score (<5, ≥5), MITT Population, Study AMAN

	Mirikizumab 300 mg IV Q4W (N=868)		Placebo (N=294)		Treatment difference (95% CI)[1]
Endpoints **Baseline Modified Mayo Score (mMS)**	**n/N**	**%**	**n/N**	**%**	
Clinical remission at Week 12					
mMS <5	23/73	31.5	2/26	7.7	23.8 (9.0, 38.6)
mMS ≥5	187/795	23.5	37/267	13.9	9.7 (4.6, 14.8)
Alternate clinical remission at Week 12					
mMS <5	31/73	42.5	4/26	15.4	27.1 (9.2, 45.0)
mMS ≥5	191/795	24.0	39/267	14.6	9.4 (4.2, 14.6)
Clinical response at Week 12					
mMS <5	37/73	50.7	8/26	30.8	19.9 (-1.2, 41.0)
mMS ≥5	514/795	64.7	116/267	43.4	21.2 (14.4, 28)
Endoscopic remission at Week 12					
mMS <5	41/73	56.2	6/26	23.1	33.1 (13.3, 52.9)
mMS ≥5	274/795	34.5	56/267	21.0	13.5 (7.6, 19.4)
Symptomatic remission at Week 12					
mMS <5	34/73	46.6	6/26	23.1	23.5 (3.7, 43.3)
mMS ≥5	361/795	45.4	76/267	28.5	16.9 (10.5, 23.4)
Histologic-Endoscopic Mucosal Improvement at Week 12					
mMS <5	35/73	47.9	3/26	11.5	36.4 (19.6, 53.2)
mMS ≥5	200/795	25.2	38/267	14.2	10.9 (5.8, 16.1)
Symptomatic remission at Week 4					
mMS <5	26/73	35.6	5/26	19.2	16.4 (-2.3, 35.1)
mMS ≥5	163/795	20.5	33/267	12.4	8.1 (3.3, 13.0)

Source: Reviewer generated table based on Applicant submitted data admayo.xpt, adsl.xpt, and adhist.xpt.
[1] The 95% confidence intervals of the treatment effects were constructed by Wald approach.
Abbreviations: MITT, modified intent-to-treat; N, number of subjects in treatment group; Q4W, once every 4 weeks; IV, intravenous; CI, confidence interval.

8.1.3. I6T-MC-AMBG

Trial Design

AMBG was a multicenter, randomized, double-blind, parallel-arm, placebo-controlled study designed to evaluate the safety and efficacy of mirikizumab, compared with placebo, in achieving remission of UC at Week 40 in subjects who completed the 12-week induction trial AMAN. A total of 1177 subjects entered AMBG and were assigned to one of three cohorts, as explained below. The primary efficacy analysis of the maintenance trial was conducted in the cohort described in #1 below (mirikizumab responders from AMAN). The overall trial design for AMBG is shown in Figure 15.

- **Mirikizumab responders from AMAN:**
  A total of 544 subjects who achieved clinical response to blinded mirikizumab in AMAN were randomized to receive blinded 200 mg mirikizumab Q4W SC or blinded placebo SC

Q4W in a 2:1 ratio. Randomization was stratified by prior biologic or JAKi failure status (yes/no), baseline corticosteroid use (yes/no) at AMAN baseline, region (North America/Europe/Other), and AMAN clinical remission status (yes/no). Subjects continued on the randomized treatment assignment for the remainder of AMBG unless they developed loss of response (LOR)[8]. The Applicant's primary efficacy population for maintenance was this cohort (mITT population). The FDA's preferred analysis population (N=506) was the subset of the mITT population who also had induction baseline mMS of at least 5.

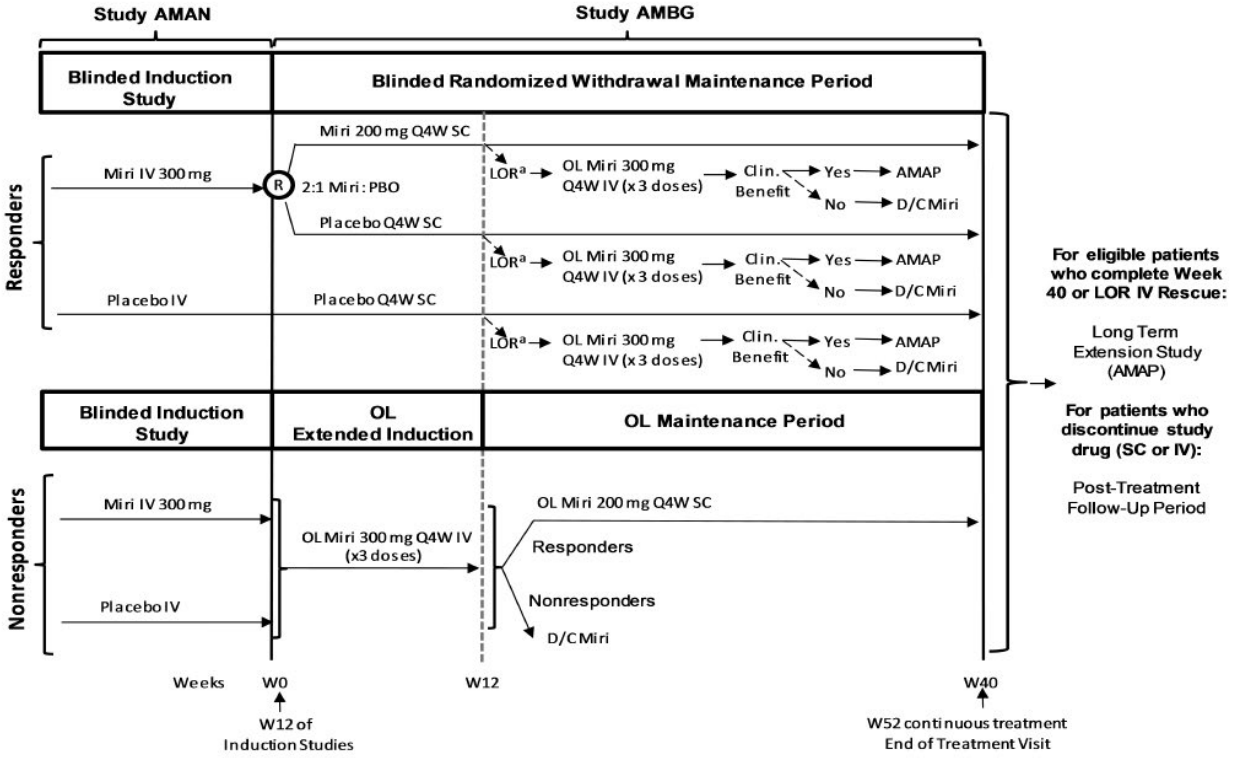
Subjects who experienced LOR during maintenance could receive open-label rescue therapy with mirikizumab 300 mg IV Q4W for 12 weeks. A total of 59 subjects received LOR rescue therapy during AMBG. (b) (4)

- **Placebo responders from AMAN:**
  A total of 135 subjects who achieved clinical response to blinded placebo in the induction study continued to receive blinded placebo for the remainder of the maintenance study. Placebo SC injections were administered Q4W to maintain study blind. If LOR was confirmed, subjects would be rescued with open-label mirikizumab 300 mg Q4W IV for 3 doses.

- **Mirikizumab and placebo nonresponders from AMAN:**
  A total of 405 subjects who did not achieve clinical response to blinded mirikizumab or blinded placebo in AMAN received open-label extended induction treatment with 300 mg mirikizumab IV Q4W for 12 weeks. Subjects who achieved clinical response with extended mirikizumab induction therapy were not randomized into AMBG but could subsequently receive open-label maintenance treatment with 200 mg mirikizumab Q4W SC starting at Week 12. (b) (4)

[8] Loss of response was defined as ≥2-point increase from Study AMBG baseline in the combined SF + RB scores AND combined SF + RB score of ≥4, on 2 consecutive visits (≥7 days apart, and with confirmation of negative C. difficile testing), AND confirmed by centrally read endoscopic subscore (ES) of 2 or 3.

Figure 15. Trial Design for AMBG



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

Note: LOR is defined as an at least 2-point increase from maintenance baseline in the combined SF + RB scores, AND combined SF + RB score of at least 4 on 2 consecutive visits, AND an ES of 2 (moderate disease – marked erythema, absent vascular pattern, erosions, and friability) or 3 (severe disease – spontaneous bleeding, ulceration), AND with confirmation of negative C. difficile testing.

[a] LOR at or after Week 12 and up to and including Week 28.

Source: Applicant's BLA 761279 submission, Module 2.7.3 Summary of Clinical Efficacy, Figure 2.7.3.3.

Study Endpoints

The primary efficacy endpoint was the proportion of subjects in clinical remission at Week 40. The multiplicity-controlled secondary efficacy endpoints are shown in Table 37 and were subject to overall type I error control (tested in graphical testing procedure, refer to Section 16.7.1).

Table 37. Multiplicity-Controlled Secondary Efficacy Endpoints for Study AMBG

Secondary Endpoint	Definition
Alternate clinical remission at Week 40	SFS = 0 or 1, and RBS = 0, and ES = 0 or 1 (excluding friability)
Endoscopic remission at Week 40	ES = 0 or 1 (excluding friability)
Histologic-Endoscopic Mucosal Remission at Week 40	Geboes scoring system subscores of 0 for grades 2b, 3, 4, and 5, PLUS ES = 0 or 1 (excluding friability)
Change from baseline in the Urgency NRS score at Week 40	
Corticosteroid-free remission[1] without surgery at Week 40	Clinical remission at Week 40, and symptomatic remission at Week 28, and no corticosteroid use for ≥12 weeks prior to Week 40
Urgency remission at Week 40 among subjects had Urgency NRS ≥3 at induction baseline	Urgency NRS = 0 or 1
Clinical remission at Week 40 among subjects in clinical remission at Week 12[2] in Study AMAN	

Source: Reviewer's table.
[1] The definition of this endpoint is different from FDA recommended definition of corticosteroid-free remission which is alternate clinical remission (FDA preferred definition of clinical remission) at Week 40, and no corticosteroid use for at least 12 weeks prior to Week 40.
[2] The definition of this endpoint is different from FDA recommended definition which is alternate clinical remission (FDA preferred definition of clinical remission) at Week 40 among subjects in alternate clinical remission at Week 12 in AMAN.
Abbreviations: SFS, stool frequency subscore; RBS, rectal bleeding subscore; ES, endoscopic subscore; NRS, Numeric Rating Scale.

Statistical Analysis Plan

Populations

The Applicant's specified primary efficacy analysis population was modified Intent-to-Treat (mITT) population defined as all randomized subjects who received any amount of study treatment excluding subjects impacted by the eCOA transcription error in Poland and Turkey. For analyses of efficacy outcomes, subjects were classified by their treatment assignment, prior biologic of JAKi failure status, baseline corticosteroid use, region, and AMAN clinical remission status stratum. The safety population included all randomized subjects who received any amount of study treatment, which is used for safety-related analysis. As previously discussed, the review will focus on assessment of the FDA preferred analysis population.

Sample Size

The study was powered based on assumed clinical remission rates at Week 40 for mirikizumab versus placebo to be 47% versus 27%. It was expected that approximately 470 subjects who completed Study AMAN would enter Study AMBG as clinical responders to mirikizumab. A sample size of 470 subjects was expected to provide >95% power to demonstrate that mirikizumab is superior to placebo in achieving the primary efficacy endpoint, as assessed using a chi-square test with a 2-sided significance level of 0.05.

Calculation of SF and RB Subscore

Similar to the induction trial, AMAN, the primary efficacy endpoint for AMBG was evaluated using the mMS, which contains three components: SFS, RBS, and ES. For the SFS and RBS, the most recent 3 non-missing days of the 7-day period were averaged and rounded to the nearest integer to calculate the weekly score for each subject. Subjects with less than 3 measurements in the 7-day period were considered missing.

Analyses of Efficacy Endpoints

For assessments of the primary efficacy endpoint and other categorical multiplicity-controlled efficacy endpoints, the estimated difference in proportions between arms and the corresponding 95% confidence interval were computed based on the stratified risk difference using the CMH weights. The analyses adjusted for the following randomization stratification factors: prior biologic or JAKi failure status (yes/no), baseline corticosteroid use (yes/no), region (North America/Europe/Other) and AMAN clinical remission status (yes/no).

For assessments of continuous efficacy endpoints with multiple postbaseline time points, the estimated least squares (LS) means, and the corresponding 95% confidence interval were computed using mixed-effects model for repeated measures (MMRM) analysis. The MMRM included the following effects and covariates: treatment group, prior biologic or JAKi failure status (yes/no), corticosteroid use (yes/no), AMAN clinical remission status (yes/no), region (North America/Europe/Other), baseline value, visit, and the interactions of treatment-by-visit and baseline by- visit as fixed factors. The covariance structure to model the within-subject errors was unstructured.

Estimands

The estimand corresponding to the primary efficacy endpoint evaluated the difference in the proportion of subjects in clinical remission at Week 40 for mirikizumab 200 mg SC versus placebo among mITT subjects who achieved clinical response on mirikizumab in AMAN. For the intercurrent events of premature treatment discontinuation and use of rescue medication, subjects were considered non-responders. Other binary multiplicity-controlled efficacy endpoints used the same estimand as the primary endpoint.

Handling of Missing Data

For analyses of the primary efficacy endpoint and other categorical multiplicity-controlled efficacy endpoints, missing data were imputed using nonresponder imputation. For continuous variables, the primary analysis was MMRM with the missing at random (MAR) assumption for handling missing data. For missing data at baseline of the induction study, the Applicant's pre-specified analyses used a subject's first available post-baseline value to impute the missing baseline value. The review team requested that the Applicant re-analyze multiplicity-controlled

continuous endpoints instead using multiple imputation to impute the missing values at induction baseline based on a linear model with stratification factors as predictors.

As a sensitivity analysis for the primary endpoint and all multiplicity-controlled binary secondary endpoints except the endpoint of Histologic-Endoscopic improvement, an mNRI approach was used to handle missing data. For subjects impacted by the eCOA transcription error, subjects who discontinued treatment due to COVID-19-related reasons, lost to follow-up, or a protocol deviation were imputed based on multiple imputation. The modified mayo subscores for all scheduled visits were imputed under the multivariate normal assumption. Indicator variables for treatment and for all stratification factors were included in the model. Subjects who discontinued from the study treatment period for other reasons such as an AE or lack of efficacy were categorized as non-responders.

Multiplicity Adjustment

A graphical multiple testing approach was specified to control the overall type I error rate at 2-sided alpha of 0.05, for all primary and major secondary endpoints. Refer to Figure 53 in Section 16.7.1 for the final proposed graphical testing procedure. This testing procedure controls the family-wise error rate across all endpoints, and any hypothesis with a multiple testing adjusted p-value of less than 0.05 was considered statistically significant.

Protocol Amendment

The original study protocol (dated March 13, 2018) had 1 amendment and 1 addendum.

On September 12, 2019, in order to align with recent external biologic clinical trials in UC, primary endpoint changed to clinical remission among responders, and clinical remission among remitters moved to a major secondary endpoint. To assess the stability of efficacy with mirikizumab throughout the maintenance period, an endpoint "*The proportion of patients in symptomatic remission defined as being in symptomatic remission for at least 7 out of 9 visits from Week 4 to Week 36 and in symptomatic remission at Week 40 among patients in symptomatic remission at Week 12 of AMAN*" added to Major Secondary Objective/Endpoints. Improvement in bowel urgency endpoint has moved to a Major secondary endpoint, given that it is one of the most bothersome symptoms experienced by subjects with UC. In order to align with recent UC clinical trials and FDA guidance, protocol definition of mucosal healing was updated to include histologic and endoscopic healing.

On September 11, 2020, a protocol addendum (16) was submitted with additional options for mitigation of the disruption and to enable the safe conduct of the clinical trial during the COVID-19 public health emergency. The changes included the following, which are aligned with

the guidance for industry FDA Guidance on Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency (July 2020).

- Increasing visit windows
- Local laboratory option
- Telemedicine and alternative site visits
- Home administration of subcutaneous study drug
- Missing endoscopy; subjects who are impacted by COVID-19 restrictions and are unable to complete scheduled endoscopies to be assessed for Clinical Benefit instead of Clinical Response/Remission.
- None of the changes had a major impact on the overall study design, efficacy assessments, or negatively impacted collection of safety data.

8.1.4. Study Results (AMBG)

Compliance with Good Clinical Practices

The study was performed in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki, and the International Conference on Harmonization guidelines for Good Clinical Practice, all applicable laws, rules, and regulations.

Data Quality and Integrity

The data was of sufficient quality to permit a substantive review.

Financial Disclosure

There were no new investigators for study AMBG. Refer to the Financial Disclosure in Section 8.1.2 and the Appendix Section 16.2.

Subject Disposition

A total of 1178 subjects entered AMBG, and one subject discontinued prior to randomization. A total of 1177 subjects were assigned to one of four cohorts, 1) mirikizumab induction responders randomized to mirikizumab 200 mg SC Q4W (n=389), 2) mirikizumab induction responders randomized to placebo (n=192), 3) placebo induction responders continued on placebo (n=135), and 4) induction nonresponders (n=461). The primary efficacy analysis of the maintenance study was conducted in the cohorts of mirikizumab induction responders randomized to mirikizumab 200 mg SC Q4W (hereafter “mirikizumab 200 mg SC Q4W”) and mirikizumab induction responders randomized to placebo (hereafter “placebo”). Induction nonresponders were eligible to receive open-label extended induction with mirikizumab 300 mg IV Q4W and were analyzed separately.

Overall, more subjects had a premature discontinuation from the placebo group as compared to the mirikizumab group during AMBG, 74 (38.5%) versus 42 (10.8%), respectively. The most frequently reported reason for discontinuation from study treatment were loss of response (defined as an at least 2-point increase from AMBG baseline in the combined SFS + RBS and combined SFS + RBS score of at least 4, on 2 consecutive visits [at least 7 days apart, and with confirmation of negative C. difficile testing], AEs, withdrawal by subject, and lack of efficacy), and all were reported more frequently by subjects in the placebo group than mirikizumab treatment group.

Table 38. Subject Disposition, AMBG, 40 Week Maintenance Period

Disposition Outcome	Mirikizumab Responders to Mirikizumab 200 mg SC Q4W N=389 n (%)	Mirikizumab Responders to Placebo N=192 n (%)	Placebo Responders to Placebo N=135 n (%)
Subjects enrolled	389	192	135
ITT population	389	192	135
mITT population	365	179	124
FDA preferred analysis population	337	169	116
Safety population	389	192	135

Source: adds.xpt and adsl.xpt; Software: R
Abbreviations: ITT intent-to-treat; mITT, modified intent-to-treat; n, number of subjects in specified population or group; N, number of subjects in treatment arm; Q4W, once every 4 weeks; SC, subcutaneous
Refer to refer to Table 26 for the population definitions.

Table 39. Subject Disposition, Safety Population, Study AMBG, 40 Week Maintenance Period

Disposition Outcome	Mirikizumab Responders to Mirikizumab 200 mg SC Q4W N=389 n (%)	Mirikizumab Responders to Placebo N=192 n (%)	Risk Difference (%) (95% CI)	Placebo Responders to Placebo N=135 n (%)
Discontinued study drug	42 (10.8)	74 (38.5)	-27.7 (-35.3, -20.2)	45 (33.3)
Adverse event	6 (1.5)	18 (9.4)	-7.8 (-12.1, -3.5)	1 (0.7)
Lack of efficacy	8 (2.1)	10 (5.2)	-3.2 (-6.6, 0.3)	8 (5.9)
Lost to follow-up	1 (0.3)	0	0.3 (-0.2, 0.8)	0
Other[1]	15 (3.9)	38 (19.8)	-15.9 (-21.9, -10.0)	28 (20.7)
Physician decision	1 (0.3)	0	0.3 (-0.2, 0.8)	0
Pregnancy	1 (0.3)	0	0.3 (-0.2, 0.8)	1 (0.7)
Protocol deviation	1 (0.3)	0	0.3 (-0.2, 0.8)	1 (0.7)
Withdrawal by subject	9 (2.3)	8 (4.2)	-1.9 (-5.1, 1.3)	6 (4.4)

Source: adds.xpt and adsl.xpt; Software: R
Risk difference (with 95% confidence interval) is shown between mirikizumab responders to mirikizumab and mirikizumab responders to placebo.
[1]Other: Per protocol treatment discontinuation due to loss of response, defined as a ≥2-point increase from AMBG baseline in the combined SF + RB scores and combined SF + RB score of ≥4, on 2 consecutive visits ≥7 days apart, and with confirmation of negative C. difficile testing
Abbreviations: CI, confidence interval; n, number of subjects in specified population or group; N, number of subjects in treatment arm; NA, not applicable; Q4W, once every 4 weeks; SC, subcutaneous

Protocol Violations/Deviations

In mITT population of AMBG, important protocol deviations were reported in 42 (23.5%) subjects in the placebo group and 65 (17.8%) subjects in the mirikizumab group.

For subjects in the mirikizumab group, the most frequent protocol deviation categories were missing laboratory data (e.g., hematology/chemistry laboratories were not obtained); not having at least 3 of 7 days of SF, or RB data, when required for mMS calculation at week 40. For subjects in the placebo group, the most frequent protocol deviation categories were missing laboratory data (e.g., hematology/chemistry laboratories were not obtained); not having endoscopy score available and use of prohibited medications.

The important protocol violations were reported by higher proportion of subjects in the placebo group.

Demographic Characteristics

Among mirikizumab induction responders who were re-randomized to either mirikizumab 200 mg SC or placebo in AMBG, the majority of subjects were male (58.9%), and most subjects were White (73.3%) and not Hispanic or Latino (75.1%). The mean age was 43.3 years with a range from 18 to 79 years, and the majority (91.8%) of subjects were younger than 65 years of age. Demographic characteristics were similar across the mirikizumab and placebo arms.

There were no notable differences in baseline demographic characteristics between the safety population and the FDA preferred analysis population. Refer to Table 122 of Section 16.7.2 of the Appendix.

Table 40. Baseline Demographic Characteristics, AMBG, 40 Week Maintenance Period (Safety Population)

Characteristic	Mirikizumab Responders to Mirikizumab 200 mg SC Q4W N=389	Mirikizumab Responders to Placebo N=192	Mirikizumab Responders in Total N=581	Placebo Responders to Placebo N=135
Sex, n (%)				
Female	160 (41.1)	78 (40.6)	238 (41.0)	61 (45.2)
Male	229 (58.9)	114 (59.4)	343 (59.0)	74 (54.8)
Age, years				
Mean (SD)	43.3 (14.1)	41.2 (12.9)	42.6 (13.8)	40.8 (13.4)
Median (min, max)	41 (18, 79)	39 (20, 77)	40 (18, 79)	38 (19, 72)
Age group, years, n (%)				
<65	357 (91.8)	181 (94.3)	538 (92.6)	126 (93.3)
≥65	32 (8.2)	11 (5.7)	43 (7.4)	9 (6.7)
Age group ≥75, years, n (%)				
≥75	4 (1.0)	1 (0.5)	5 (0.9)	0
Weight, kg				
Mean (SD)	72 (17.3)	72.3 (17)	72 (17)	71.1 (17.7)
Median (min, max)	70 (34, 151.5)	71.2 (38, 129.5)	70 (34, 152)	68 (39, 124)

Characteristic	Mirikizumab Responders to Mirikizumab 200 mg SC Q4W N=389	Mirikizumab Responders to Placebo N=192	Mirikizumab Responders in Total N=581	Placebo Responders to Placebo N=135
Weight group, kg, n (%)				
<80	275 (70.7)	135 (70.3)	410 (71)	99 (73.3)
≥80	114 (29.3)	57 (29.7)	171 (29)	36 (26.7)
BMI, kg/m^2				
Mean (SD)			25 (5,2)	24.6 (5.2)
		24.7 (5.1)		
Median (min, max)	24.8 (5.4)	23.6 (13.8,	24 (14.1,	
	24.1 (14.6, 53.5)	43.3)	53.0)	24.1 (14.5, 42.7)
Race, n (%)				
White	285 (73.3)	138 (71.9)	423 (72.8)	103 (76.3)
Asian	93 (23.9)	51 (26.6)	144 (24.8)	28 (20.7)
Black or African American	6 (1.5)	0	6 (1.0)	0
American Indian/Alaska Native	3 (0.8)	1 (0.5)	4 (0.7)	2 (1.5)
Multiple	0	0	0	2 (1.5)
Missing	2 (0.5)	2 (1.0)	4 (0.7)	0
Ethnicity, n (%)				
Not Hispanic or Latino	292 (75.1)	145 (75.5)	437 (75.2)	115 (85.2)
Hispanic or Latino	17 (4.4)	3 (1.6)	20 (3.4)	2 (1.5)
Not Reported	80 (20.6)	44 (22.9)	124 (21.3)	18 (13.3)
Region of participation, n (%)				
Eastern Europe	82 (21)	47 (24)	129 (22)	35 (26)
Asia	88 (23)	50 (26)	138 (24)	26 (19)
Rest of the World	90 (23)	41 (21)	131 (23)	39 (29)
Western Europe	71 (18)	28 (15)	99 (17)	21 (16)
North America	50 (13)	24 (13)	74 (13)	12 (9)
Central America/South America	8 (2)	2 (1)	10 (2)	2 (1)

Source: adsl.xpt; Software: R
Abbreviations: N, number of subjects in treatment group; n, number of subjects with given characteristic; Q4W, once every 4 weeks; SC, subcutaneous; SD, standard deviation.
Region of participation: Eastern Europe: Czech Republic, Hungary, Latvia, Lithuania, Poland, Romania, Slovakia; Asia: China, India, Japan, South Korea, Malaysia, Taiwan; Rest of the world: Australia, Israel, Russian Federation, Serbia, Turkey, Ukraine; Western Europe: Austria, Belgium, Denmark, France, Germany, Ireland, Italy, Netherlands, Spain, Switzerland, United Kingdom; North America: Canada, United States of America; Central/South America: Argentina, Mexico

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Other baseline characteristics (measured prior to randomization into induction AMAN), including baseline mMS, prior biologic or tofacitinib failure, and baseline corticosteroid use, are presented in Table 41. The treatment arms were generally balanced with respect to these baseline factors. Of note, in AMBG, the mirikizumab responders to mirikizumab SC treatment group had a higher proportion of subjects with moderate baseline mMS (46.5% versus 40.1%). This small imbalance did not impact efficacy results because baseline disease severity was a stratification factor and was accounted for in the primary efficacy analysis.

Table 41. Other Baseline Characteristics, AMBG, 40 Week Maintenance Period (Safety Population)

Characteristic	Mirikizumab Responders to Mirikizumab 200 mg SC Q4W N=389	Mirikizumab Responders to Placebo N=192	Mirikizumab Responders in Total N=581	Placebo Responders to Placebo N=135
Prior biologic or tofacitinib failure, n (%)				
Failed	131 (33.7)	65 (33.9)	196 (33.7)	38 (28.1)
Not failed	258 (66.3)	127 (66.1)	385 (66.3)	97 (71.9)
Modified Mayo score category at induction baseline, n(%)				
Mild [1-4]	28 (7.2)	10 (5.2)	38 (6.5)	8 (5.9)
Moderate [5-6]	153 (39.3)	67 (34.9)	220 (37.9)	58 (43.0)
Severe [7-9]	184 (47.3)	102 (53.1)	286 (49.2)	58 (43.0)
Missing[1]	24 (6.2)	13 (6.8)	37 (6.4)	11 (8.1)
Modified Mayo score at induction baseline				
Mean[2] (SD)	6.5 (1.3)	6.6 (1.3)	6.5 (1.3)	6.5 (1.3)
Median (min, max)	7 (4, 9)	7 (4, 9)	7 (4, 9)	6 (4, 9)
Corticosteroid use at induction baseline, n (%)				
Yes	151 (38.8)	76 (39.6)	227 (39.1)	59 (43.7)
No	238 (61.2)	116 (60.4)	354 (60.9)	76 (56.3)

Source: adsl.xpt; Software: R
[1]: All missing values of modified Mayo score at induction baseline were due to eCOA transcription error
[2]: Missing values were removed
Abbreviations: N, number of subjects in treatment group; n, number of subjects with given characteristic; Q4W, once every 4 weeks; SC, subcutaneous; SD, standard deviation

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

For AMBG, 97.8% subjects in the placebo group and 99.2% subjects in the mirikizumab treatment group were compliant with treatment. Compliance was similar across treatment arms. The compliance in the placebo group was a slightly lower than that in the mirikizumab treatment group. No obvious differential compliance between treatment groups was identified.

Efficacy Results – Primary Endpoint

The main analyses for the primary endpoint of clinical remission at Week 40 and secondary endpoint of alternate clinical remission at Week 40 in the FDA preferred analysis population (defined as subset of the mITT population with an mMS score of 5 to 9 at baseline of the induction studies) are displayed in Table 42.

For the primary endpoint of clinical remission at Week 40, subjects who received mirikizumab 200 mg SC had a statistically significantly higher rate of clinical remission than subjects who received placebo SC. The estimated difference in clinical remission rate for mirikizumab 200 mg versus placebo SC was 22.7% (95% CI: 14.3%, 31.0%), with a p-value less than 0.001.

The results for the secondary endpoint of alternate clinical remission (equivalent to the FDA preferred definition of clinical remission) at Week 40 were similar to the primary endpoint. The estimated treatment difference was 22.4% (95% CI: 14.1%, 30.8%), which was statistically

significant with a p-value less than 0.001. Overall, the efficacy results for clinical remission at Week 40 and alternate clinical remission at Week 40 are consistent in terms of treatment difference, 95% confidence interval, and statistical significance.

The percentage of subjects with missing data for the primary endpoint was 13.9% in the mirikizumab 200 mg SC arm, and 40.8% in the placebo arm. Most of the missing data were due to dropout, with a higher dropout rate in the placebo group. The most common reason for dropout was lack of efficacy, loss of response, and AEs, which occurred more in the placebo group compared to the mirikizumab group. Because UC is a chronic condition requiring long-term treatment and subjects who prematurely discontinued study drug would not receive a long-term benefit from the assigned study drug, using non-responder imputation to handle missing data due to dropout was considered reasonable. The treatment differences (24.0% and 23.7% for clinical remission and alternate clinical remission, respectively) and their 95% CIs ([15.5, 32.5] for clinical remission and [15.4, 32.1] for alternate clinical remission) from the pre-specified mNRI missing data sensitivity analyses (described in Section 8.1.3) supported the conclusions of the primary analysis.

Table 42. Clinical Remission at Week 40, FDA Preferred Analysis Population, Study AMBG

Parameter	Mirikizumab 200 mg SC Q4W (N=337)	Placebo SC (N=169)
Clinical remission at Week 40, n (%)	170 (50.4)	44 (26.0)
Treatment Difference[1], (95% CI)	22.7 (14.3, 31.0)	
P-value[2]	<0.001	
Alternate clinical remission at Week 40, n (%)	171 (50.7)	45 (26.6)
Treatment Difference[1], (95% CI)	22.4 (14.1, 30.8)	
P-value[2]	<0.001	
Missing data, n (%)	47 (13.9)	69 (40.8)

Source: Reviewer analysis using Applicant submitted data admayo.xpt; based on Clinical Summary of Efficacy Appendix (Table APP.2.7.3.6.138, P 1342 - P 1345)
[1] The common risk difference is the difference in proportions adjusted for the stratification factors: prior biologic or tofacitinib failure (yes/no), baseline corticosteroid use (yes/no), AMAN clinical remission status (yes/no), and region (North America/Europe/Other), where the confidence intervals are calculated using Mantel-Haenszel-Sato method.
[2] Cochran-Mantel-Haenszel (CMH) test adjusted by prior biologic or tofacitinib failure (yes/no), baseline corticosteroid use (yes/no), AMAN clinical remission status (yes/no), and region (North America/Europe/Other).
Abbreviations: N, number of subjects in treatment group; Q4W, once every 4 weeks; SC, subcutaneous; CI, confidence interval.

Efficacy Results – Secondary and other relevant endpoints

The analyses for all multiplicity-controlled secondary endpoints in AMBG other than alternate clinical remission are displayed in Table 43. The treatment differences between the mirikizumab **arm and the placebo arm were statistically significant for all the multiplicity-controlled secondary endpoints, with most p-values less than 0.001 and all p-values less than 0.003.**

Table 43. **Results for Secondary Efficacy Endpoints,** FDA Preferred Analysis Population, AMBG

Endpoints	Parameter	Mirikizumab 200 mg SC Q4W (N=337)	Placebo SC (N=169)	Treatment Difference[1] versus Placebo (95% CI)	P-value[2]
Clinical remission at Week 40 among subjects in clinical remission at Week 12 in AMAN, FDA preferred definition	(N)	(128)	(62)		
	%	65.6	40.3	22.7 (7.7, 37.6)	0.003
Clinical remission at Week 40 among subjects in clinical remission at Week 12 in AMAN, Applicant's definition	(N)	(127)	(59)		
	%	65.4	39.0	24.0 (8.7, 39.2)	0.003
Endoscopic remission at Week 40	%	57.9	29.6	27.2 (18.6, 35.8)	<0.001
Corticosteroid-free remission at Week 40, FDA preferred definition	%	50.1	26.6	21.8 (13.5, 30.2)	<0.001
Corticosteroid-free remission at Week 40, Applicant's definition	%	46.3	22.5	21.6 (13.5, 29.7)	<0.001
Histologic-endoscopic mucosal remission at Week 40	%	43.0	21.9	19.4 (11.4, 27.4)	<0.001
Urgency NRS score of 0 or 1 among subjects with baseline urgency NRS score ≥3	(N)	(307)	(160)		
	%	38.8	23.1	16.0 (7.6, 24.4)	<0.001
Change from AMAN baseline in urgency NRS score	(N_{obs}) LSMEAN (SE)	(291) -3.91 (0.147)	(97) -2.82 (0.212)	-1.09 (-1.55, -0.62)	<0.001

Source: Reviewer analysis using Applicant submitted data admayo.xpt and addd4.xpt; based on Clinical Summary of Efficacy Appendix (Table APP.2.7.3.6.140 – Table APP.2.7.3.6.143, P 1347 – P 1354) and Applicant's response to information request submitted on 09/23/2022.

[1] For binary endpoints, the common risk difference is the difference in proportions adjusted for the stratification factors: previous biologic therapy failure status (yes/no), baseline corticosteroid use (yes/no), region (North America/Europe/Other) and AMAN clinical remission status (yes/no), where the confidence intervals are calculated using Mantel-Haenszel-Sato method; for continuous endpoint, the treatment difference, 95% CI, and p-value were calculated using a mixed model with repeated measures including treatment, baseline value, visit, interaction of baseline value-by-visit, interaction of treatment-by-visit, and stratification factors.

[2] For binary endpoints, Cochran-Mantel-Haenszel (CMH) test adjusted by prior biologic or tofacitinib failure (yes/no), baseline corticosteroid use (yes/no), AMAN clinical remission status (yes/no), and region (North America/Europe/Other).

Abbreviations: N, number of subjects in treatment group; Q4W, once every 4 weeks; SC, subcutaneous; CI, confidence interval; NRS, Numeric Rating Scale; LSMEAN, least squares mean; SE, standard error; N_{obs}, number of observed values.

Discussion of Secondary Endpoints Proposed for Labeling

Clinical remission at Week 40 Among Subjects in Clinical Remission at Week 12 in AMAN

The Applicant assessed clinical remission at Week 40 in subjects who had achieved clinical remission at Week 12 at the end of AMAN. This endpoint represents the maintenance of clinical remission in subjects who achieved clinical remission at Week 12. The Applicant's definition of clinical remission is slightly different from the Agency's preferred definition of clinical remission, as discussed previously. Therefore, the maintenance of clinical remission, where clinical remission is defined according to the Agency's preferred definition, in subjects who achieved clinical remission at Week 12 will be described in labeling.

Endoscopic Improvement

Similar to AMAN, the Applicant's proposed definition of "endoscopic remission" for AMBG is the same as the Agency's preferred definition of "endoscopic improvement," which is a centrally read endoscopy subscore of 0 or 1 (score of 1 modified to exclude friability). The definition of endoscopic remission recommended by the Agency is a centrally read endoscopy subscore of 0. Therefore, alternative terminology will be utilized to describe this endpoint in the label.

Corticosteroid-Free Remission

The Applicant proposed definition of corticosteroid-free remission is clinical remission at Week 40, symptomatic remission at Week 28, and no corticosteroid use for at least 12 weeks prior to Week 40, among subjects in clinical response at start of maintenance treatment. This definition is slightly different from the Agency's preferred definition where symptomatic remission at an earlier timepoint is not required. A sensitivity analysis was conducted based on the Agency's preferred definition of corticosteroid-free remission on mITT population mMS of 5 to 9. The treatment difference (22.1%) and its 95% CI ([13.7, 30.4]) in the sensitivity analysis results were consistent with the main analysis on the endpoint of corticosteroid-free remission.

Histologic-Endoscopic Mucosal Remission

Some subjects (approximately 3.2%) entered the maintenance study with a Geboes score of <2.0 during the biopsy at induction baseline, thus meeting the histologic component of the endpoint definition. Therefore, it was unclear whether achieving histologic-endoscopic mucosal remission represented an improvement from baseline in all subjects. The review team conducted a sensitivity analysis in which this endpoint was reanalyzed only in the subgroup of subjects with a baseline Geboes score of ≥2.0 (refer to Section 16.7.4). Results were consistent with those obtained in the FDA preferred analysis population, and therefore the team concluded that it is reasonable to include this endpoint in the label.

The considerations for the other secondary endpoints (e.g., Urgency NRS 0 or 1) are similar to those described in AMAN (discussed previously in this document).

Discussion of Additional Endpoints

Endoscopic Remission

The Applicant defined "endoscopic normalization" as an endoscopic subscore of 0. This definition is consistent with the Agency's preferred definition of "endoscopic remission." As stated previously (refer to the discussion regarding histologic-endoscopic mucosal improvement), endoscopic remission represents a clinically relevant endpoint that prescribers utilize as a treatment target as part of clinical practice. The Applicant assessed endoscopic remission in study AMAN; however, the results were not statistically significantly different

between mirikizumab and placebo (refer to Section 8.1.2). In AMBG, endoscopic remission was achieved by 74/337 (22.0%) of subjects treated with mirikizumab compared to 23/169 (13.6%) of subjects on placebo, which was statistically significantly different (p=0.0397). Language describing the results of endoscopic remission at Week 40 will be included in labeling.

Dose/Dose Response

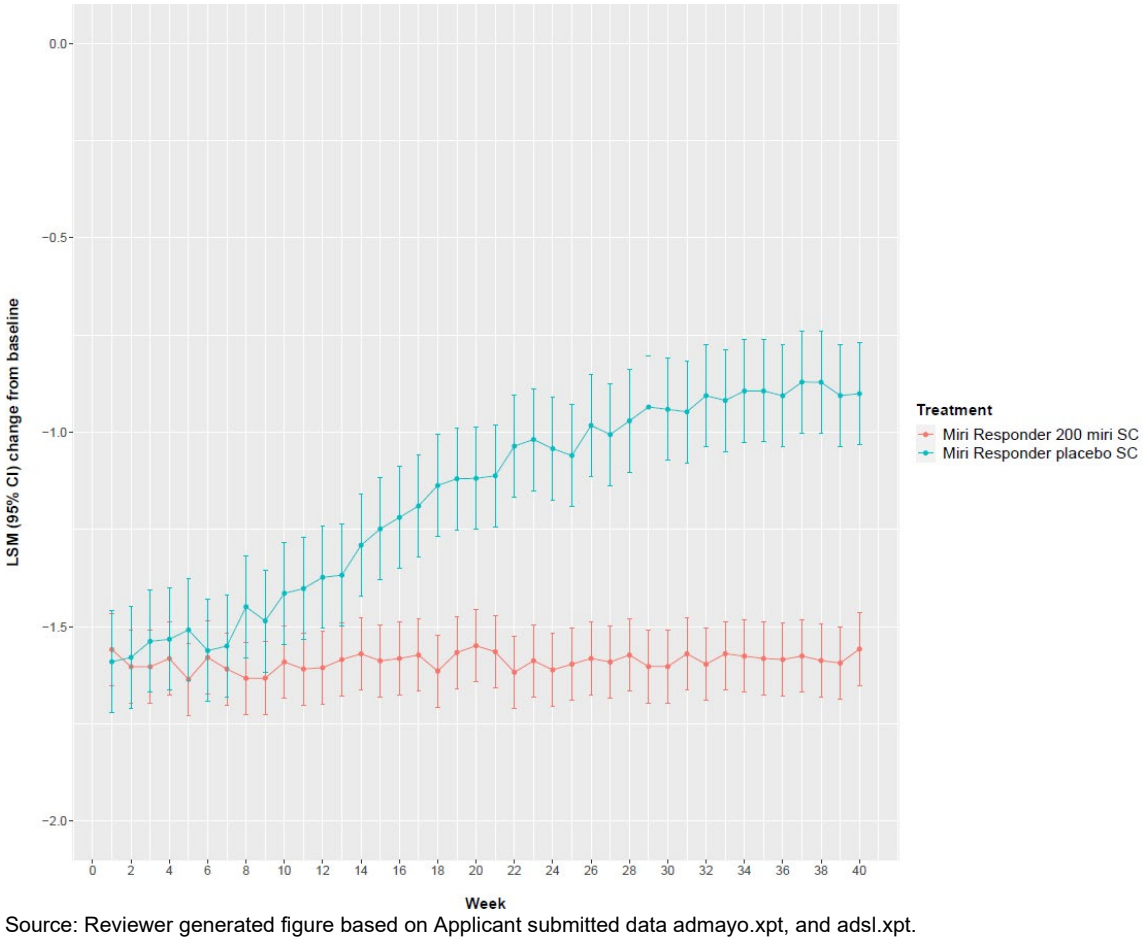
AMBG evaluated a single dose level mirikizumab 200 mg SC Q4W for the maintenance period based on data from AMAC. AMAC, was a phase 2 dose-ranging study, evaluated mirikizumab 200 mg Q4W and 200 md Q12W. Mirikizumab Q4W dose regimen provided more consistent efficacy compared to the 200 mg Q12W regimen. Thus, the 200 mg SC Q4W maintenance dose was selected for Study AMBG. Refer to the Clinical pharmacology in Section 6.3.

Persistence of Effect

Individual analyses of the SFS and RBS of the mMS in AMAN showed evidence that mirikizumab provides symptomatic relief after only a few weeks of induction dosing. Subjects in the mirikizumab treatment group showed a greater mean reduction in SFS as early as Week 3 and in RBS as early as Week 2 compared to the placebo (Figure 13 and Figure 14).

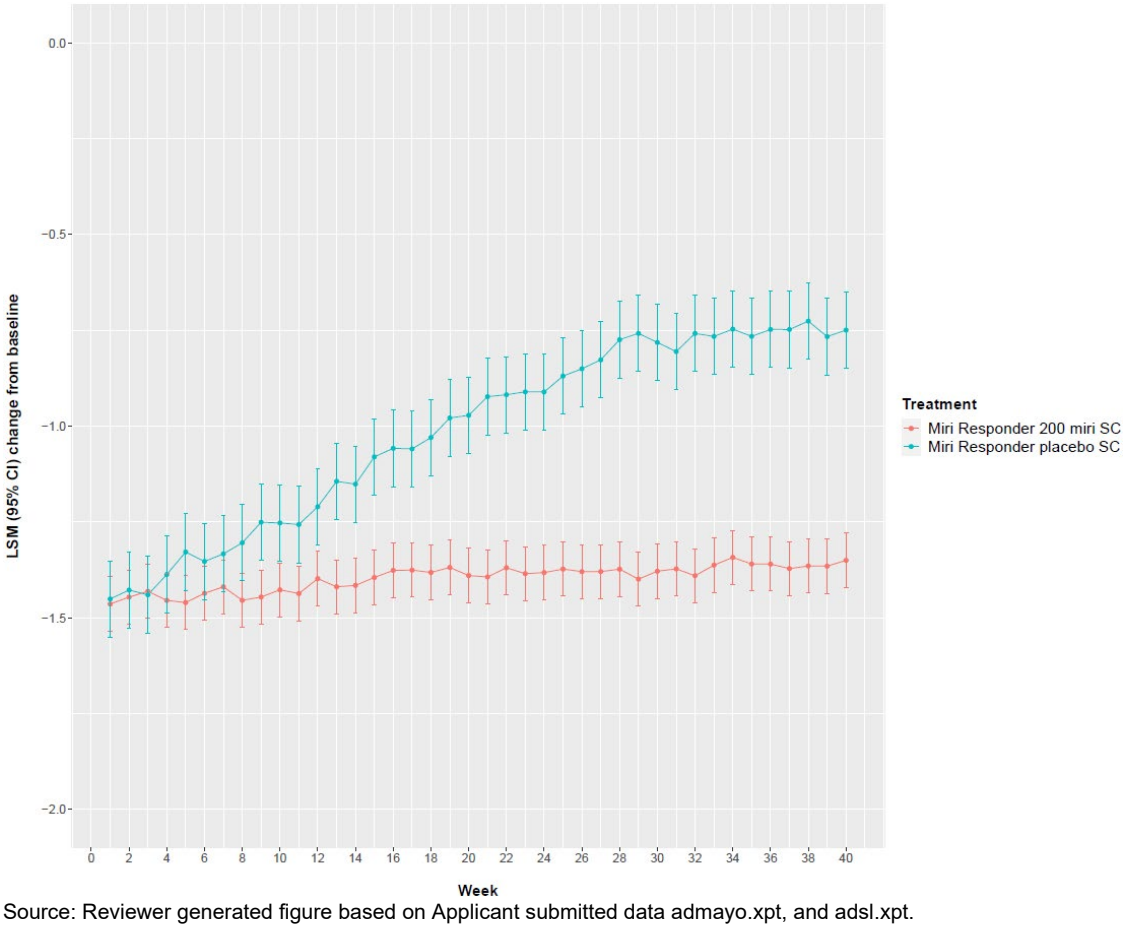
Individual analyses of the SFS and RBS of the mMS in AMBG showed that improvements in SFS and RBS were sustained during the maintenance treatment period. Subjects who were mirikizumab induction responders and received placebo in AMBG had worsening of their stool frequency and rectal bleeding after mirikizumab withdrawal. However, the improvement from induction baseline in SFS and RBS was sustained in the mirikizumab group throughout the maintenance period (Figure 16 and Figure 17)**.**

Figure 16. Stool Frequency Subscore Change from Baseline, FDA Preferred Analysis Population, AMBG



Source: Reviewer generated figure based on Applicant submitted data admayo.xpt, and adsl.xpt.
Abbreviations: LSM, least-square mean; CI, confidence interval.

Figure 17. Rectal Bleeding Subscore Change from Baseline, FDA Preferred Analysis Population, AMBG



Source: Reviewer generated figure based on Applicant submitted data admayo.xpt, and adsl.xpt.
Abbreviations: LSM, least-square mean; CI, confidence interval.

Additional Analyses Conducted on the Individual Trial

Efficacy results were investigated by prior biologic or JAKi failure status for important efficacy endpoints in Study AMBG (Table 44). Although the study was not powered to detect a significant difference for each subgroup, the treatment differences were consistent with the primary analysis. The mirikizumab groups consistently showed higher remission rates compared to the placebo across all subgroups. The group of subjects who were naïve to biologic and JAKi showed numerically smaller treatment difference for all endpoints compared to the group with prior biologic or JAKi failure.

Table 44. Subgroup Analyses, Biologic/JAKi Naïve Versus Prior Biologic or JAKi Failed, FDA Preferred Analysis Population, AMBG

	Mirikizumab responders Mirikizumab 200 mg SC Q4W (N=337)		Mirikizumab responders Placebo SC (N=169)		Treatment difference (95% CI)[1]
Endpoints	n/N	%	n/N	%	
Clinical remission at Week 40					
Biologic and JAKi naïve	110/208	52.9	35/109	32.1	20.8 (9.7, 31.9)
Prior biologic or JAKi failed	55/121	45.5	9/59	15.3	30.2 (17.4, 43.0)
Alternate clinical remission at Week 40					
Biologic and JAKi naïve	111/208	53.4	36/109	33.0	20.3 (9.2, 31.5)
Prior biologic or JAKi failed	55/121	45.5	9/59	15.3	30.2 (17.4, 43.0)
Endoscopic remission at Week 40					
Biologic and JAKi naïve	129/208	62.0	38/109	34.9	27.2 (16.0, 38.3)
Prior biologic or JAKi failed	60/121	49.6	12/59	20.3	29.2 (15.7, 42.8)
Clinical remission at Week 40 among subjects in clinical remission at Week 12 in AMAN	(N = 128)		(N = 62)		
Biologic and JAKi naïve	60/91	65.9	23/48	47.9	18.0 (0.9, 35.2)
Prior biologic or JAKi failed	22/34	64.7	2/14	14.3	50.4 (26.0, 74.8)
Corticosteroid-free remission at Week 40					
Biologic and JAKi naïve	109/208	52.4	36/109	33.0	19.4 (8.2, 30.5)
Prior biologic or JAKi failed	55/121	45.5	9/59	15.3	30.2 (17.4, 43.0)
Histologic-endoscopic mucosal remission at Week 40					
Biologic and JAKi naïve	97/208	46.6	29/109	26.6	20.0 (9.3, 30.7)
Prior biologic or JAKi failed	44/121	36.4	8/59	13.6	22.8 (10.6, 35.0)

Source: Reviewer generated table based on Applicant submitted data admayo.xpt, adsl.xpt, and adhist.xpt.
[1] The 95% confidence intervals of the treatment effects were constructed by Wald approach.
Abbreviations: N, number of subjects in treatment group; Q4W, once every 4 weeks; SC, subcutaneous; CI, confidence interval.

Efficacy results were evaluated by use of corticosteroids at induction baseline for important efficacy endpoints in Study AMBG (Table 45). The mirikizumab groups showed higher remission rates compared to the placebo across all subgroups. The estimated treatment effects for the two subgroups were similar.

Table 45. Subgroup Analyses, Use of Corticosteroids at Baseline, FDA Preferred Analysis Population, AMBG

	Mirikizumab responders Mirikizumab 200 mg SC Q4W (N=337)		Mirikizumab responders Placebo SC (N=169)		Treatment difference (95% CI)[1]
Endpoints	**n/N**	**%**	**n/N**	**%**	
Clinical remission at Week 40					
Corticosteroids at baseline	58/128	45.3	12/65	18.5	26.9 (14.1, 39.6)
No corticosteroids at baseline	112/209	53.6	32/104	30.8	22.8 (11.7, 34.0)
Alternate clinical remission at Week 40					
Corticosteroids at baseline	58/128	45.3	12/65	18.5	26.9 (14.1, 39.6)
No corticosteroids at baseline	113/209	54.1	33/104	31.7	22.3 (11.1, 33.5)
Endoscopic remission at Week 40					
Corticosteroids at baseline	69/128	53.9	14/65	21.5	32.4 (19.2, 45.6)
No corticosteroids at baseline	126/209	60.3	36/104	34.6	25.7 (14.4, 37.0)
Clinical remission at Week 40 among subjects in clinical remission at Week 12 in AMAN	(N = 128)		(N = 62)		
Corticosteroids at baseline	30/48	62.5	7/20	35.0	27.5 (2.5, 52.5)
No corticosteroids at baseline	54/80	67.5	18/42	42.9	24.6 (6.5, 42.8)
Corticosteroid-free remission at Week 40					
Corticosteroids at baseline	57/128	44.5	12/65	18.5	26.1 (13.3, 38.8)
No corticosteroids at baseline	112/209	53.6	33/104	31.7	21.9 (10.6, 33.1)
Histologic-endoscopic mucosal remission at Week 40					
Corticosteroids at baseline	49/128	38.3	10/65	15.4	22.9 (10.7, 35.1)
No corticosteroids at baseline	96/209	45.9	27/104	26.0	20.0 (9.2, 30.8)

Source: Reviewer generated table based on Applicant submitted data admayo.xpt, adsl.xpt, and adhist.xpt.
[1] The 95% confidence intervals of the treatment effects were constructed by Wald approach.
Abbreviations: N, number of subjects in treatment group; Q4W, once every 4 weeks; SC, subcutaneous; CI, confidence interval.

Efficacy results were investigated by baseline mMS category (<5, ≥5) for important efficacy endpoints in Study AMBG (Table 46). The mirikizumab groups consistently showed higher remission rates compared to the placebo across all subgroups. The interpretation of these subgroup results is limited by the small number of subjects with baseline mMS of less than 5.

Table 46. Subgroup Analyses, Baseline Modified Mayo Score (<5, ≥5), MITT Population, Study AMBG

	Mirikizumab responders Mirikizumab 200 mg SC Q4W (N=337)		Mirikizumab responders Placebo SC (N=169)		Treatment difference (95% CI)[1]
Endpoints **Baseline Modified Mayo Score (mMS)**	**n/N**	**%**	**n/N**	**%**	
Clinical remission at Week 40					
mMS <5	12/28	42.0	1/10	10.0	32.9 (6.8, 59.0)
mMS ≥5	170/337	50.4	44/169	26.0	24.4 (15.9, 32.9)
Alternate clinical remission at Week 40					
mMS <5	18/28	64.3	2/10	20.0	44.3 (13.8, 74.8)
mMS ≥5	171/337	50.7	45/169	26.6	24.1 (15.6, 32.6)
Endoscopic remission at Week 40					
mMS <5	19/28	67.9	2/10	20.0	47.9 (17.6, 78.1)
mMS ≥5	195/337	57.9	50/169	29.6	28.3 (19.6, 37.0)
Clinical remission at Week 40 among subjects in clinical remission at Week 12 in AMAN	(N = 151)		(N = 69)		
mMS <5	15/23	65.2	2/7	28.6	36.6 (-2.1, 75.4)
mMS ≥5	84/128	65.6	25/62	40.3	25.3 (10.6, 40.0)
Corticosteroid-free remission at Week 40					
mMS <5	16/28	57.1	2/10	20.0	37.1 (6.3, 68.0)
mMS ≥5	169/337	50.1	45/169	26.6	23.5 (15.0, 32.1)
Histologic-endoscopic mucosal remission at Week 40					
mMS <5	13/28	46.4	2/10	20.0	26.4 (-4.5, 57.4)
mMS ≥5	145/337	43.0	37/169	21.9	21.1 (13.0, 29.3)

Source: Reviewer generated table based on Applicant submitted data admayo.xpt, adsl.xpt, and adhist.xpt.
[1] The 95% confidence intervals of the treatment effects were constructed by Wald approach.
Abbreviations: MITT, modified intent-to-treat; N, number of subjects in treatment group; Q4W, once every 4 weeks; SC, subcutaneous; CI, confidence interval.

8.1.5. Integrated Assessment of Effectiveness

Overall, the submission contains substantial evidence of effectiveness for mirikizumab 300 mg induction administered by intravenous infusion every 4 weeks for 12 weeks. Although there was only a single induction trial, multiplicity-controlled endpoints were tested at an alpha level of 0.00125 which is the same statistical evidence against the null hypothesis as achieving statistical significance on two independent induction studies that are each tested at a 2-sided alpha level of 0.05. The results of the single induction trial were statistically and clinically significant compared to placebo on the primary and multiple major secondary endpoints. Similarly, the single phase 3 trial AMBG provided evidence of the effectiveness for mirikizumab 200 mg maintenance administered by subcutaneous injection every 4 weeks for additional 40 weeks. The results for the maintenance trial were statistically and clinically significant compared to placebo on the primary and multiple major secondary endpoints. The results of both trials were robust to subgroup analyses, including for subjects with prior biologic or JAKi failure, baseline corticosteroid use, and mMS greater than 5, supporting that clinical benefit was observed among the trial population.

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety review of this application focused on the data from the randomized, double-blind, placebo-controlled studies AMAN (the 12-week induction study) and AMBG (the 40-week maintenance study). Analyses of the randomized placebo-controlled arms of AMAN and AMBG represent adverse events that occurred through 52-weeks of total treatment. Of note, the randomized placebo-controlled arm of AMBG consisted of subjects who were mirikizumab responders during AMAN and were subsequently re-randomized to either mirikizumab or placebo. Subjects who responded to placebo in AMAN were continued on blinded placebo in AMBG. Results for this separate cohort are presented side by side with the data from the randomized controlled portion as they represent a "true placebo" group (no exposure to mirikizumab in any treatment period).

Supportive safety information for this application included data from open-label portions of AMBG. During AMBG, subjects who were nonresponders during AMAN could receive open-label extended induction with mirikizumab 300 mg IV Q4W for 12 weeks. Subjects who received open-label extended induction and achieved clinical response could subsequently receive open-label maintenance with mirikizumab 200 mg SC Q4W. Furthermore, during AMBG, subjects that experienced a loss-of-response could receive open-label mirikizumab 300 mg IV Q4W for 3 doses (i.e., a second induction dose) for a loss of response rescue period. Subjects who received open-label mirikizumab for a loss of response were either enrolled in the open-label extension AMAP or discontinued from the study if they did or did not report a clinical benefit, respectively.

Additional supportive safety information included pooled data from the mirikizumab UC development program. Data from AMAC[9] and AMAP[10] were pooled with data from AMAN and AMBG to generate an "All UC Mirikizumab Integrated Analysis Set." These pooled data were reviewed to assess for rare events or events with a delayed onset of action; however, the interpretation of the pooled data is limited by differences in the individual study designs, which includes different dosages, different durations of treatment, and lack of a comparator (AMAP). The Applicant also submitted a summary of the available safety information from ongoing programs in other indications (i.e., psoriasis and Crohn's disease); however, the interpretability of those data is also limited due to differences in the dosages and indications.

Clinical trial data were analyzed using R, JMP and JMP Clinical software. All safety assessments and conclusions are those of the clinical review team unless otherwise specified. The review

[9] A phase 2 dose ranging study, refer to Section 7.1 for additional information.

[10] A phase 3 open-label extension study, refer to Section7.1 for additional information.

team did not identify any major data quality or integrity issues that precluded performing a thorough safety review.

8.2.2. Review of the Safety Database

Overall Exposure

The induction safety database (AMAN) included 958 subjects who received mirikizumab induction therapy (mirikizumab 300 mg IV Q4W) and 321 subjects who received placebo. The maximum duration of study AMAN was 12 weeks; 725 (75.7%) subjects in the mirikizumab group and 211 (65.7%) subjects in the placebo group completed 12 weeks of induction treatment. Table 47 summarize the **duration of exposure for study AMAN.**

Table 47. Duration of Exposure, AMAN, 12 Week Induction Period (Safety Population)

Parameter	Mirikizumab 300 mg IV Q4W N=958 n (%)	Placebo N=321 n (%)
Duration of treatment, weeks		
Mean (SD)	12.1 (1.4)	11.7 (2.1)
Median (Q1, Q3)	12.1 (12, 12.4)	12.1 (11.7, 12.4)
Min, Max	1, 17.7	1, 16
Total exposure (person years)	222	72
Subjects treated, by duration, n (%)		
≥4 weeks	952 (99.4)	315 (98.1)
≥8 weeks	938 (97.9)	301 (93.7)
≥12 weeks	725 (75.7)	211 (65.7)

Source: adex.xpt and adsl.xpt; Software: R
Abbreviations: IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with given treatment duration; Q1, first quartile; Q3, third quartile; Q4W, once every 4 weeks; SD, standard deviation

The maintenance safety database (AMBG) included 389 subjects who responded to mirikizumab induction and received mirikizumab maintenance therapy (mirikizumab 200 mg SC Q4W) and 192 subjects who responded to mirikizumab induction and received placebo during maintenance. The maximum duration of study AMBG was 40 weeks; 263 (67.6%) subjects in the mirikizumab group and 91 (47.4%) subjects in the placebo group completed 40 weeks of maintenance treatment. Of note, subjects who completed 40 weeks of maintenance treatment received 52 weeks of total treatment (induction + maintenance). Table 48 summarizes the exposure period for study AMBG.

Table 48. Duration of Exposure, Study AMBG, 40 Week Maintenance Period (Safety Population)

Parameter	Mirikizumab Responders to Mirikizumab 200 mg SC Q4W N=389 n (%)	Mirikizumab Responders to Placebo N=192 n (%)	Placebo Responders to Placebo N=135 n (%)
Duration of treatment, weeks			
Mean (SD)	38.4 (7.1)	32.5 (11.6)	33.7 (11)
Median (Q1, Q3)	40.1 (39.6, 40.9)	39.9 (24, 40.5)	40 (25.2, 40.4)
Min, Max	4.7, 49.1	1.1, 44	3.1, 49
Total exposure (person years)	286	119	87
Subjects treated, by duration, n (%)			
≥4 weeks	389 (100)	187 (97.4)	134 (99.3)
≥8 weeks	386 (99.5)	185 (96.4)	133 (98.5)
≥12 weeks	383 (98.7)	178 (92.7)	131 (97.0)
≥24 weeks	360 (92.5)	144 (75.0)	103 (76.3)
≥40 weeks	263 (67.6)	91 (47.4)	68 (50.4)

Source: adex.xpt and adsl.xpt; Software: R
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given treatment duration; Q1, first quartile; Q3, third quartile; Q4W, once every 4 weeks; SC, subcutaneous; SD, standard deviation

Adequacy of the safety database:

In AMAN, 725 (75.7%) of subjects had a total duration of mirikizumab exposure ≥12 weeks. In AMBG, 263 (67.6 %) subjects had a total duration of mirikizumab exposure ≥40 weeks (i.e., 52 weeks of total exposure). Given the duration of exposures in the induction and maintenance studies, the safety database is deemed sufficient to characterize the safety of mirikizumab in adults with moderately to severely active UC when used through 52 weeks. It is acknowledged that a pre-market database in UC contains limited data to fully assess the potential for rare events, particularly those of long latency (e.g., malignancy). Nevertheless, the size and scope of the submitted safety database is acceptable to inform a risk-benefit assessment for the proposed indication of the treatment of moderately to severely active UC.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

No issues regarding data integrity or submission quality were identified.

Categorization of Adverse Events

A treatment emergent adverse event (TEAE) was defined as an event that first occurred or worsened in severity after baseline. The MedDRA Lowest Level Term (LLT) was used in the treatment emergent assessment.

For study AMAN, the baseline period was the Screening period. AEs that occurred after the Screening period until a subject completed AMAN and enrolled in AMBG or completed the post-treatment follow-up period of 16 weeks, were reported as TEAEs. For study AMBG, baseline AEs were defined as events which were ongoing at the start of study AMBG. AEs that occurred after the start of AMBG until a subject completed AMBG and enrolled in AMAP or completed the post-treatment follow-up period of 16 weeks, were reported as TEAEs.

Serious adverse events (SAEs) were appropriately defined consistent with 21 CFR 32.32(a) and reported as required.

All AEs, including SAEs, were monitored until the subject discontinued and/or completed the study. Any SAEs or AEs that were medically important or considered related to the investigational product or the study, or that caused the subject to discontinue the investigational product before completing the study, were followed by the investigator until the event had resolved, stabilized, or was reasonably explained.

All AEs were graded as mild, moderate, or severe as per the Investigator's judgement. The causal relationship between the investigational drug and the AE was characterized by the Investigator as related or not related, according to definitions outlined in the study protocol.

Adverse events of special interest (AESIs) were specified as being of special interest based on safety findings from previous studies in the development program, potential risks associated with biologic immunomodulators as noted in product labels and published literature, and comorbidities and risk factors prevalent in the studied populations. The AESIs for studies AMAN and AMBG were:

- Infections, including opportunistic infections
    - Treatment-emergent infections were analyzed for all infections (by maximum severity), serious infections and opportunistic infections.
    - The Applicant defined opportunistic infections based upon Winthrop et al. 2015) and they were defined in the statistical analysis plan (refer to Table 133 in Section 16.7.6).
- Hypersensitivity events, including anaphylaxis
    - Potential hypersensitivity reactions were categorized as immediate (i.e., occurring within 24 hours) or non-immediate (i.e., occurring after the day of study drug administration but prior to subsequent drug administration) based on the timing of the reaction.
- Infusion and injection site events
- Cerebro-cardiovascular events
    - Treatment-emergent, serious, and nonserious cardiovascular, cerebrovascular, and peripheral vascular AEs including major adverse cerebro-cardiovascular events were reviewed by an independent, external adjudication committee to adjudicate reported cerebro-cardiovascular AEs in a blinded manner during the study.

- Categories of events included: Cardiovascular, Cerebrovascular and Peripheral Vascular Events. The categories are further categorized into subcategories.

- Malignancies
- Depression, or suicidal ideation and behavior
- Hepatic adverse events included hepatic disorder related PTs and hepatic enzyme abnormalities (e.g., alanine aminotransferase [ALT], aspartate transaminase [AST], total bilirubin [TBL] and serum alkaline phosphatase [ALP]).

Routine Clinical Tests

For each subject, the Applicant collected laboratory tests, radiologic tests, and electrocardiograms (ECGs) according to the Schedule of Activities defined in the study protocol.

The Applicant assessed clinical laboratory testing as detailed in Appendix 16.7.6. Hematology, chemistry, and urinalysis testing samples were analyzed by Applicant-designated laboratory and confirmed by the central laboratory. The criteria for determining whether an abnormal laboratory test finding should be reported as an AE included the following:

- The test finding results in a diagnosis
- The test result requires medical or surgical intervention
- The test finding results in discontinuation from the study

8.2.4. Safety Results During Induction (AMAN)

Overview of Adverse Events

A summary of AEs reported during AMAN is provided in Table 49. Overall, a greater proportion of subjects who received placebo reported SAEs, AEs leading to study drug discontinuation, severe TEAEs, and TEAEs compared to subjects who received mirikizumab.

Table 49. Overview of Adverse Events, Safety Population, Study AMAN, 12 Week Induction Period

Event Category	Mirikizumab 300 mg IV Q4W N=958 n (%)	Placebo N=321 n (%)	Risk Difference (%) (95% CI)
SAE	27 (2.8)	17 (5.3)	-2.5 (-5.1, 0.2)
SAEs with fatal outcome	0	0	0 (0, 0)
AE leading to permanent discontinuation of study drug	15 (1.6)	23 (7.2)	-5.6 (-8.5, -2.7)*
AE leading to interruption of study drug	7 (0.7)	6 (1.9)	-1.1 (-2.7, 0.4)
TEAEs	428 (44.7)	149 (46.4)	-1.7 (-8.0, 4.6)
Severe	22 (2.3)	23 (7.2)	-4.9 (-7.8, -1.9)*
Moderate	143 (14.9)	48 (15.0)	-0.0 (-4.5, 4.5)

Event Category	Mirikizumab 300 mg IV Q4W N=958 n (%)	Placebo N=321 n (%)	Risk Difference (%) (95% CI)
Mild	263 (27.5)	78 (24.3)	3.2 (-2.3, 8.6)

Source: adae.xpt and adsl.xpt; Software: R
Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CI, confidence interval; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with at least one event; Q4W, once every 4 weeks; SAE, serious adverse event; TEAEs, Treatment emergent adverse events

8.2.4.1. *Deaths*

There were no deaths during study AMAN. However, the Applicant reported 2 deaths that occurred during the follow-up period of AMAN, . One subject had a sudden cardiac death (SCD) and one subject had disseminated intravascular coagulation (DIC) caused by infection and sepsis. The two deaths are described in detail below:

Sudden cardiac death: A 68-year-old male with history of atrial fibrillation, hypercholesterolemia, dual chamber pacer who completed study AMAN, underwent colorectal surgery for adenocarcinoma of the rectum and died of sudden cardiac death (SCD) on post-operative day 5. The death occurred 117 days after the subject's last dose of mirikizumab. The subject did not continue in study AMBG because of the adenocarcinoma diagnosis that was made 32 days after the last dose of mirikizumab 300 mg IV Q4W (induction). The cause of death was reported as "not related" to the study drug by the Investigator. The SCD was probably due to post-operative complications that occurred in a subject with several cardiovascular risk factors. Refer to the Adverse Events of Special Interest 8.2.4.4 for additional information regarding the AE of adenocarcinoma of the rectum.

Disseminated intravascular coagulation (DIC): A 50-year-old female with a history of type 2 diabetes mellitus (DM-2) and obesity died of DIC in the setting of systemic sepsis (cytomegalovirus [CMV] colitis and systemic candidiasis). The subject discontinued study drug after the second dose of mirikizumab 300 mg IV (51 days after starting treatment and 22 days after the last dose) because of an exacerbation of UC and worsening GI symptoms. Relevant concomitant medications include oral corticosteroids. Following discontinuation of study treatment, the subject was admitted to the hospital with a diagnosis of severe UC exacerbation and sepsis (88 days after starting treatment and 59 days since the last dose) for treatment with IV steroids and possible surgery. The subject underwent subtotal colectomy and developed an SAE of DIC on the same day after the surgery. The postoperative recovery was further complicated by severe sepsis and severe systemic candidiasis that lasted for 76 days after the surgery. The subject died 147 days after the last dose of mirikizumab. The cause of death was reported as "not related" to the study drug. Of note, the subject may have been immunocompromised due to her underlying DM-2 and IV steroids that were used to treat an exacerbation of UC. Although it appears unlikely that mirikizumab directly caused DIC, due to the long

half-life of mirikizumab, the immunosuppressive effects of IL-23 inhibition, and the increased risk of infection, mirikizumab may have contributed to the subject's risk of infection.

8.2.4.2. *Serious Adverse Events*

Serious adverse events (SAEs) for AMAN are shown in Table 50. Overall, SAEs were reported at a higher frequency in the placebo group (17 subjects, 5.3%) than the mirikizumab group (27 subjects, 2.8%); however, the overall SAE rates were low.

Table 50. Subjects With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Study AMAN, 12 Week Induction Period

System Organ Class (SOC) Preferred Term (PT)	Mirikizumab 300 mg IV Q4W N=958 n (%)	Placebo N=321 n (%)	Risk Difference (%) (95% CI)
Any SAE	27 (2.8)	17 (5.3)	-2.5 (-5.1, 0.2)
Blood and lymphatic system disorders	1 (0.1)	1 (0.3)	-0.2 (-0.9, 0.4)
Anemia	1 (0.1)	1 (0.3)	-0.2 (-0.9, 0.4)
Cardiac disorders	0	1 (0.3)	-0.3 (-0.9, 0.3)
Acute myocardial infarction	0	1 (0.3)	-0.3 (-0.9, 0.3)
Ear and labyrinth disorders	1 (0.1)	0	0.1 (-0.1, 0.3)
Vertigo	1 (0.1)	0	0.1 (-0.1, 0.3)
Gastrointestinal disorders	9 (0.9)	10 (3.1)	-2.2 (-4.2, -0.2)*
Lower gastrointestinal hemorrhage	1 (0.1)	0	0.1 (-0.1, 0.3)
Colitis ulcerative	8 (0.8)	10 (3.1)	-2.3 (-4.3, -0.3)*
Infections and infestations	7 (0.7)	2 (0.6)	0.1 (-0.9, 1.1)
Pneumonia	2 (0.2)	0	0.2 (-0.1, 0.5)
Cytomegalovirus colitis	1 (0.1)	0	0.1 (-0.1, 0.3)
Gastroenteritis viral	1 (0.1)	0	0.1 (-0.1, 0.3)
Intestinal sepsis	1 (0.1)	0	0.1 (-0.1, 0.3)
Klebsiella infection	1 (0.1)	0	0.1 (-0.1, 0.3)
Listeria sepsis	1 (0.1)	0	0.1 (-0.1, 0.3)
Viral infection	1 (0.1)	0	0.1 (-0.1, 0.3)
Acute sinusitis	0	1 (0.3)	-0.3 (-0.9, 0.3)
Sinusitis	0	1 (0.3)	-0.3 (-0.9, 0.3)
Injury, poisoning and procedural complications	2 (0.2)	0	0.2 (-0.1, 0.5)
Spinal compression fracture	1 (0.1)	0	0.1 (-0.1, 0.3)
Spinal fracture	1 (0.1)	0	0.1 (-0.1, 0.3)
Metabolism and nutrition disorders	2 (0.2)	1 (0.3)	-0.1 (-0.8, 0.6)
Diabetes mellitus	1 (0.1)	0	0.1 (-0.1, 0.3)
Type 2 diabetes mellitus	1 (0.1)	0	0.1 (-0.1, 0.3)
Malnutrition	0	1 (0.3)	-0.3 (-0.9, 0.3)
Musculoskeletal and connective tissue disorders	1 (0.1)	0	0.1 (-0.1, 0.3)
Ankylosing spondylitis	1 (0.1)	0	0.1 (-0.1, 0.3)
Neoplasms benign, malignant, and unspecified (cysts and polyps)	2 (0.2)	0	0.2 (-0.1, 0.5)
Adenocarcinoma of colon	1 (0.1)	0	0.1 (-0.1, 0.3)
Uterine leiomyoma	1 (0.1)	0	0.1 (-0.1, 0.3)
Renal and urinary disorders	0	1 (0.3)	-0.3 (-0.9, 0.3)
Renal colic	0	1 (0.3)	-0.3 (-0.9, 0.3)

System Organ Class (SOC) Preferred Term (PT)	Mirikizumab 300 mg IV Q4W N=958 n (%)	Placebo N=321 n (%)	Risk Difference (%) (95% CI)
Reproductive system and breast disorders	1 (0.1)	1 (0.3)	-0.2 (-0.9, 0.4)
Ovarian enlargement	1 (0.1)	0	0.1 (-0.1, 0.3)
Penile vein thrombosis	0	1 (0.3)	-0.3 (-0.9, 0.3)
Vascular disorders	3 (0.3)	1 (0.3)	0.0 (-0.7, 0.7)
Arteriosclerosis	1 (0.1)	0	0.1 (-0.1, 0.3)
Hypertension	1 (0.1)	0	0.1 (-0.1, 0.3)
Deep vein thrombosis	1 (0.1)	1 (0.3)	-0.2 (-0.9, 0.4)

Source: CDS safety tables and figures for I6T-MC-AMAN, adae.xpt; Software: R
Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Abbreviations: CI, confidence interval; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; Q4W, once every 4 weeks; SOC, system organ class

The most frequently reported SAE was “colitis ulcerative,” which was reported more frequently in the placebo group, 10 subjects (3.1%), than the mirikizumab treatment group, 8 subjects (0.8%). Of note, 4 (0.4%) subjects in the mirikizumab treatment group that reported SAE of “colitis ulcerative” were withdrawn due to lack of efficacy and worsening UC symptoms.

SAEs that occurred in at least 2 subjects in the mirikizumab group and not reported in the placebo group:

One SAE was reported by at least 2 subjects (0.2%) in the mirikizumab group and not reported in the placebo group, pneumonia. Given that IL-23 inhibition has immunosuppressive effects and mirikizumab may increase the risk of infection, the SAEs of pneumonia may possibly be related to mirikizumab. Pneumonia was also considered an adverse event of special interest (AESIs) and are described in the Adverse Events of Special Interest Section 8.2.4.4.

- Pneumonia: Two subjects reported SAEs of pneumonia. One subject, a 37-year-old white female, was hospitalized 84 days after starting treatment with mirikizumab 300 mg IV Q4W and 28 days after the last dose of mirikizumab 300 mg IV Q4W. The subject was treated with antibiotics, recovered, and was discharged in 5 days. The other subject, a 48-year-old Asian male with history of smoking and concomitant steroid use, was hospitalized 23 days after starting treatment with mirikizumab 300 mg IV Q4W and 22 days after the last dose of mirikizumab 300 mg IV Q4W. The subject was treated with antibiotics, recovered, and was discharged in 10 days. For both cases, no change was made to the study drug and the events were reported as “not related” to the study drug by the Investigators. However, given that IL-23 inhibition has immunosuppressive effects and mirikizumab may increase the risk of infection, the SAEs of pneumonia may be related to mirikizumab.

SAEs that led to discontinuation

There were 2 SAEs in 2 subjects that received mirikizumab (1 subject reported UC exacerbation, and 1 subject reported deep vein thrombosis) that led to discontinuation from the study. Additionally, 1 SAE in 1 subject that received mirikizumab (adenocarcinoma of colon) led to the

subject not continuing on to AMBG according to the protocol. Since these SAEs that led to discontinuation occurred in one subject each, there is uncertainty whether the SAEs are related to mirikizumab. Each SAE that led to discontinuation are described in greater detail below.

- UC exacerbation: A 57-year-old White female experienced an SAE of UC exacerbation that resulted in hospitalization 83 days after starting treatment with mirikizumab 300 mg IV Q4W and 25 days after the last dose of mirikizumab. The subject discontinued the study due to UC exacerbation. The subject was on mesalamine, azathioprine, methylprednisolone, and pancreatic enzyme for ulcerative colitis at the time of hospitalization. During the hospitalization the subject was diagnosed with Klebsiella infection, which was reported as an SAE by the Applicant (verbatim term “Klebsiella pneumoniae colonization”), that was detected in the stool and was considered colonization (which may occur in subjects with UC); therefore, no therapy was administered. Four days after the hospitalization the subject experienced another SAE of listeria sepsis (verbatim term "*listeria monocytogenes sepsis*") of severe severity that was also defined as an adverse event of special interest (AESI) under the category of opportunistic infection. The subject was treated with antibiotics, approximately 2 weeks later (101 days after starting treatment, 43 days after the last dose of study drug), the subject recovered from the SAE of listeria sepsis. The subject was discontinued from the study due to SAE of UC exacerbation after completing the induction treatment with the study drug, 234 days after starting treatment, 176 days after last dose of study drug. The subject did not continue to study AMBG. The SAEs of colitis ulcerative and severe klebsiella infection were not recovered at the time of study discontinuation. The UC exacerbation is likely due to lack of the drug effectiveness. However, the causality for klebsiella and listeria may possibly relate to the study treatment since the study drug has immunosuppressive effects and may have the potential to increase infection and serious infections.

- Deep vein thrombosis (DVT): 50-year-old Asian female subject with no significant risk factors for thrombosis, experienced a SAE of DVT that resulted in hospitalization. The subject reported pain and swelling on lower extremities that started 10 days after the first dose of the drug and was later hospitalized (21 days after initiation of mirikizumab 300 mg IV Q4W). The subject treated with anticoagulant and discharged 10 days later. The subject was discontinued the study drug due to SAE of DVT, and the subject was discontinued from the trial. The event was reported as “related” to the study drug. The causal role of mirikizumab cannot be excluded, and it may possibly be related to the study treatment. However, subjects with UC are at increased risk of DVT and this was the only vascular event reported in the mirikizumab treatment group. Analysis of the AESI of “cerebro-cardiovascular events", and peripheral vascular event data at the population level did not show significant changes, between treatment and placebo arm.

- Adenocarcinoma of colon: A 39-year-old American Indian female with 17 years history

of UC, experienced a SAE of adenocarcinoma of the colon during colonoscopy corresponding to Week 12, which was 92 days after starting treatment with mirikizumab 300 mg IV Q4W and 28 days since the last dose of mirikizumab 300 mg IV Q4W. The subject was asymptomatic at the time of the diagnosis. The subject was discontinued from the study because of the adenocarcinoma diagnosis. The event was reported as "not related" to the study drug. Of note, subjects with UC have higher risk for developing colorectal cancers such as adenocarcinoma, and the risk increases with the duration of the disease. It is unlikely that a short exposure to mirikizumab caused adenocarcinoma of colon in this subject, who has a long-standing history of UC.

SAEs that were considered AESIs

There was 1 SAE (cytomegalovirus [CMV] colitis) reported by 1 subject that was considered an AESI, and not already discussed above. Mirikizumab may increase the risk of infection; however, the event of CMV colitis is likely not related to the study drug since it was reported before the initiation of the study drug, as explained below.

- CMV Colitis: A 42-year-old white male subject experienced an SAE of CMV colitis of severe severity that resulted in hospitalization, which was 14 days after starting mirikizumab 300 mg IV Q4W. The subject was previously treated with prednisone; and biologic therapy included infliximab, adalimumab, and vedolizumab for UC. The subject was on mesalazine and loperamide at the time of hospitalization. The subject reported having fever, increased number of stools, vomiting, abdominal pain, and distension at the time of admission. During the hospitalization the results of the screening colonoscopy biopsies (collected prior to initiating treatment with mirikizumab) were made available and showed CMV. The subject was treated with rehydration and ganciclovir. The subject continued the study drug. The subject recovered from the event approximately 7 weeks later. The event of CMV colitis was likely not related to the study drug since the biopsies that confirmed CMV infection were obtained before the initiation of the study drug. The subject's immunocompromised state secondary to underlying UC and previous treatment with immunosuppressive therapy placed the subject at increased risk for CMV colitis.

8.2.4.3. *Discontinuation due to Adverse Events*

Adverse events that led to study discontinuation for AMAN are shown in Table 51. Overall, study discontinuation due to AEs was rare and reported by a higher proportion of subjects in the placebo group, 23 subjects (7.2%), than the mirikizumab treatment group, 15 subjects (1.6%).

Table 51. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, AMAN – 12 Week Induction Period

System Organ Class (SOC) Preferred Term (PT)	Mirikizumab 300 mg IV Q4W N=958 n (%)	Placebo N=321 n (%)	Risk Difference (%) (95% CI)
AE leading to discontinuation of study drug	15 (1.6)	23 (7.2)	-5.6 (-8.5, -2.7)
Blood and lymphatic system disorders	2 (0.2)	0	0.2 (-0.1, 0.5)
Lymphopenia	2 (0.2)	0	0.2 (-0.1, 0.5)
Cardiac disorders	0	1 (0.3)	-0.3 (-0.9, 0.3)
Acute myocardial infarction	0	1 (0.3)	-0.3 (-0.9, 0.3)
Eye disorders	0	1 (0.3)	-0.3 (-0.9, 0.3)
Conjunctivitis allergic	0	1 (0.3)	-0.3 (-0.9, 0.3)
Gastrointestinal disorders	5 (0.5)	19 (5.9)	-5.4 (-8.0, -2.8)*
Colitis ulcerative	5 (0.5)	19 (5.9)	-5.4 (-8.0, -2.8)*
Immune system disorders	3 (0.3)	0	0.3 (-0.0, 0.7)
Infusion-related hypersensitivity reaction	4 (0.4)	0	0.4 (0.0, 0.8)
Infections and infestations	1 (0.1)	1 (0.3)	-0.2 (-0.9, 0.4)
Intestinal sepsis	1 (0.1)	0	0.1 (-0.1, 0.3)
Sinusitis	0	1 (0.3)	-0.3 (-0.9, 0.3)
Injury, poisoning and procedural complications	1 (0.1)	0	0.1 (-0.1, 0.3)
Spinal fracture	1 (0.1)	0	0.1 (-0.1, 0.3)
Musculoskeletal and connective tissue disorders	0	1 (0.3)	-0.3 (-0.9, 0.3)
Arthritis	0	1 (0.3)	-0.3 (-0.9, 0.3)
Skin and subcutaneous tissue disorders	2 (0.2)	0	0.2 (-0.1, 0.5)
Pyoderma gangrenosum	1 (0.1)	0	0.1 (-0.1, 0.3)
Rash pruritic	1 (0.1)	0	0.1 (-0.1, 0.3)
Skin ulcer	1 (0.1)	0	0.1 (-0.1, 0.3)
Vascular disorders	1 (0.1)	0	0.1 (-0.1, 0.3)
Deep vein thrombosis	1 (0.1)	0	0.1 (-0.1, 0.3)

Source: I6T-MC-AMAN, adae.xpt; Software: R
Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Treatment-emergent adverse events defined as an event that first occurred or worsened in severity after baseline and on or prior to the date of the last visit within the blinded treatment dosing period.
Abbreviations: CI, confidence interval; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; Q4W, once every 4 weeks; SOC, system organ class

The most frequently reported AE that led to study discontinuation was “colitis ulcerative” which was reported more frequently in the placebo group (19 subjects, 5.9%) than the mirikizumab group (5 subjects, 0.5%). Infusion-related hypersensitivity reactions that led to study discontinuation were reported by 4 subjects (0.3%) in the mirikizumab group and 0 subjects in the placebo group; infusion-related hypersensitivity reactions were considered an AESI.

The AEs that led to study discontinuation that were reported by at least 2 subjects in the mirikizumab group and higher than placebo or were considered related to the study drug are discussed in more detail below.

- Lymphopenia: Two subjects in the mirikizumab treatment group discontinued the study treatment due to lymphopenia. One subject is a 35-year-old White male with baseline lymphocyte count of 0.24 and 0.8 (10^9/L) 3 and 4 weeks prior to the treatment (respectively) and decreased to 0.18 (10^9/L) after receiving the first dose of the study

drug. The AE of severe severity lymphopenia occurred 1 day after starting treatment with mirikizumab 300 mg IV Q4W, lasted 61 days and was listed as not resolved at the time of database lock. The event reported as "not related" to the study drug. The other subject is a 47-year-old White male with baseline lymphocyte count of 1.09 (10^9/L) 3 weeks prior to the treatment and decreased to 1.4 (10^9/L) after receiving the first dose of the study drug and decreased further to 0.45 (10^9/L) after receiving the second dose of the study drug. The AE of moderately severe lymphopenia occurred 48 days after starting treatment with mirikizumab 300 mg IV Q4W, lasted 367 days and was listed as resolving at the time of database lock. The event reported as "not related" to the study drug. Of note, subjects with UC have an increased risk of lymphopenia. Given that both subjects had a low baseline lymphocyte count, the further decline could potentially have been due to underlying active UC. Additionally, analysis of the hematology safety data at the population level did not show significant changes in these assessments, between treatment and placebo group, nor in the mirikizumab treated group pre- and post-dose.

- Infusion-related hypersensitivity reaction: Four subjects experienced AE of infusion-related hypersensitivity. The first subject was a 42-year-old White female who reported a mild severity reaction that occurred 29 days after starting treatment with mirikizumab 300 mg IV Q4W and 1 day since the last dose. The subject experienced mucocutaneous erythema of face and neck, elevated BP, dyspnea, abdominal pain, and panic. The second subject was a 49-year-old White male who reported a moderate severity reaction that occurred 1 day after starting treatment with mirikizumab 300 mg IV Q4W. The subject experienced sweating, hyperventilation, vertigo, and low BP. The third subject was a 26-year-old White male who reported a moderate severity reaction that occurred 29 days after starting treatment with mirikizumab 300 mg IV Q4W and 1 day since the last dose. The subject experienced red flushing of skin over the face, chest, and neck. The fourth subject was a 60-year-old White female who experienced mucocutaneous erythema and pruritis on arms, back, chest, face, and leg, and panic within 3 hours after the third dose of mirikizumab 300 mg IV Q4W. In all four subjects, the infusion-related hypersensitivity reaction lasted 1 day, and the subjects were discontinued from the study due to the hypersensitivity AE. Of note, the protocol specified that subjects who experienced an infusion-related hypersensitivity reaction would be discontinued from the trial. These events were reported as "related" to the study drug. Given that the hypersensitivity reaction occurred immediately after infusion, the event was likely related to the study drug. Serious hypersensitivity reactions, including anaphylaxis and infusion-related hypersensitivity reactions, will be included in the Warnings and Precautions section of the label.

- Skin ulcer: A 51-year-old Asian female subject experienced AE of skin ulcer and pruritic rash on hands and feet of moderate severity. The subject noticed a small blister located on left medial ankle that occurred 34 days after starting treatment with mirikizumab 300 mg IV Q4W and 5 days since the last dose of mirikizumab 300 mg IV Q4W. A couple

of days later the subject reported itchy rash on feet and then hands. The adverse events lasted 150 days and was listed as not resolved at the time of database lock. The subject reported as discontinued from the study due to AE. The event reported as "related" to the study drug. It is unclear whether the subject's AE of skin ulcer was a manifestation of a hypersensitivity reaction, given the description of the symptoms, and the subject later developed a pruritic rash on hands and feet. The reported AEs were possibly related to the study drug given no additional risk factors or previous skin disorders were reported. Serious hypersensitivity reactions, including anaphylaxis and infusion-related hypersensitivity reactions, will be included in the Warnings and Precautions section of the label.

8.2.4.4. *Adverse Events of Special Interest*

Adverse events of special interest (AESIs) were defined in the study protocol based on safety findings from previous studies in the development program, potential risks associated with biologic immunomodulators as noted in product labels and published literature, and comorbidities and risk factors prevalent in the studied populations. Refer Section 8.2.3, "Categorization of Adverse Events."

AESIs for study AMAN are shown in Table 52. Overall, a greater proportion of subjects in the mirikizumab group reported at least one AESI compared to placebo. Hypersensitivity reactions, infusion site reactions, opportunistic infections, malignant tumors, and hepatic adverse events were reported by a greater proportion of subjects in the mirikizumab treatment group than the placebo group.

Table 52. Subjects With Adverse Events of Special Interest, AMAN – 12 Week Induction Period (Safety Population)

Adverse Event of Special Interest Preferred Term	Mirikizumab 300 mg IV Q4W N=958 n (%)	Placebo N=321 n (%)	Risk Difference (%) (95% CI)
Any AESI	193 (20.1)	58 (18.1)	2.1 (-2.8, 7.0)
Cerebro-cardiovascular events	2 (0.2)	2 (0.6)	-0.4 (-1.3, 0.5)
Hospitalization for hypertension	1 (0.1)	0	0.1 (-0.1, 0.3)
Deep vein thrombosis	1 (0.1)	0	0.1 (-0.1, 0.3)
Acute myocardial infarction	0	1 (0.3)	-0.3 (-0.9, 0.3)
Atrial fibrillation	0	1 (0.3)	-0.3 (-0.9, 0.3)
Depression and suicide/self-injury	4 (0.4)	2 (0.6)	-0.2 (-1.2, 0.7)
Depressed mood	2 (0.2)	1 (0.3)	-0.1 (-0.8, 0.6)
Depression	2 (0.2)	1 (0.3)	-0.1 (-0.8, 0.6)
Hepatic events	16 (1.7)	6 (1.9)	-0.2 (-1.9, 1.5)
Transaminase increased^	8 (0.8)	3(0.9)	-0.1 (-1.3, 1.1)
Blood bilirubin increased	4 (0.4)	0	0.4 (0.0, 0.8)
Gamma-glutamyltransferase increased	4 (0.4)	2 (0.6)	-0.2 (-1.2, 0.7)
Hepatomegaly	0	1 (0.3)	-0.3 (-0.9, 0.3)
Hypoalbuminaemia	0	1 (0.3)	-0.3 (-0.9, 0.3)
Blood alkaline phosphatase increased	1 (0.1)	2 (0.6)	-0.5 (-1.4, 0.4)

Adverse Event of Special Interest Preferred Term	Mirikizumab 300 mg IV Q4W N=958 n (%)	Placebo N=321 n (%)	Risk Difference (%) (95% CI)
Hypersensitivity reactions (≤24 hours after drug administration)	10 (1.0)	1 (0.3)	0.7 (-0.2, 1.6)
Infusion-related reaction[1]	3 (0.3)	0	0.3 (-0.0, 0.7)
Infusion-related hypersensitivity reaction[1]	4 (0.4)	1 (0.3)	0.1 (-0.6, 0.8)
Dermatitis acneiform	1 (0.1)	0	0.1 (-0.1, 0.3)
Swelling face	1 (0.1)	0	0.1 (-0.1, 0.3)
Eczema	1 (0.1)	0	0.1 (-0.1, 0.3)
Hypersensitivity reactions (>24 hours after drug administration)	24 (2.6)	7 (2.2)	0.4 (-1.5, 2.3)
Rash^	12 (1.3)	3 (0.9)	0.4 (-0.9, 1.6)
Urticaria^	5 (0.5)	1 (0.3)	0.2 (-0.6, 1.0)
Rash pustular	2 (0.2)	0	0.2 (-0.1, 0.5)
Drug hypersensitivity	1 (0.1)	0	0.1 (-0.1, 0.3)
Dermatitis^	3 (0.3)	1 (0.3)	0.0 (-0.7, 0.7)
Conjunctivitis allergic	2 (0.2)	1 (0.3)	-0.1 (-0.8, 0.6)
Eczema	1 (0.1)	1 (0.3)	-0.2 (-0.9, 0.4)
Infections	145 (15.1)	45 (14.0)	1.1 (-3.3, 5.5)
Opportunistic infections	6 (0.6)	1 (0.3)	0.3 (-0.5, 1.1)
Cytomegalovirus colitis	2 (0.2)	0	0.2 (-0.1, 0.5)
Listeria Sepsis	1 (0.1)	0	0.1 (-0.1, 0.3)
Intestinal tuberculosis	1 (0.1)	0	0.1 (-0.1, 0.3)
Esophageal candidiasis	1 (0.1)	0	0.1 (-0.1, 0.3)
Herpes zoster	1 (0.1)	1 (0.3)	-0.2 (-0.9, 0.4)
Infusion site reactions	4 (0.4)	1 (0.3)	0.1 (-0.6, 0.8)
Infusion site erythema	1 (0.1)	0	0.1 (-0.1, 0.3)
Infusion site pain	1 (0.1)	0	0.1 (-0.1, 0.3)
Infusion site pruritus	1 (0.1)	0	0.1 (-0.1, 0.3)
Infusion site paresthesia	1 (0.1)	1 (0.3)	-0.2 (-0.9, 0.4)
Malignant tumors	2 (0.2)	0	0.2 (-0.1, 0.5)
Adenocarcinoma of colon	2 (0.2)	0	0.2 (-0.1, 0.5)

Source: adae.xpt; Software: R
Risk difference (with 95% confidence interval) is shown between mirikizumab and placebo.
Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
^Grouped query, refer to Table 136, Appendix 16.7.
[1] Infusion-related reactions were not identified as hypersensitivity reactions by the Investigator; however, the Applicant grouped infusion-related reactions as an AESI of "hypersensitivity reactions." All of the infusion-related reactions were mild, and subjects continued in the study, whereas subjects with infusion-related hypersensitivity reactions were discontinued from the study.
Abbreviations: AESI, adverse event of special interest; CI, confidence interval; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; Q4W, once every 4 weeks
Subjects may count more than one for each PT.

AESIs that were reported by a greater proportion of subjects in the mirikizumab group than placebo are described in more detail below.

Infections and Opportunistic infections

One hundred forty-five subjects (15.1%) in the mirikizumab group and 45 subjects (14.0%) in the placebo group reported an AESI of infection. The majority of the infections were mild or moderate in severity. The proportion of subjects with a severe infection was slightly higher in the mirikizumab group (5/145, 3.4%) compared to the placebo group (1/45 subject, 2.2%), and one TEAE of severe severity was reported "related" to the study drug in the mirikizumab group.

The most common infection was upper respiratory tract infections, which were reported more frequently in the mirikizumab group (72 subjects, 7.5%) as compared to placebo (20 subjects, 6.2 %). Other types of infection reported in the mirikizumab group included urinary tract infection (UTI), Clostridioides difficile infection, viral gastroenteritis, and tinea; however, these infections were reported in less than 1% of subjects and/or were reported by a similar proportion of subjects in the mirikizumab and placebo groups.

Six subjects (0.6%) in the mirikizumab group and 1 subject (0.3%) in the placebo group reported opportunistic infections. CMV colitis and listeria sepsis (discussed previously in Section 8.2.4.2.) were reported severe in severity, the other opportunistic infections were mild or moderate in severity. Intestinal tuberculosis, esophageal candidiasis and herpes zoster were reported as "related" to the study drug. These opportunistic infections may possibly be related to the study treatment, given the study drug has immunosuppressive effects and may have the potential to increase infection/opportunistic infections. However, no subjects were discontinued from study treatment due to opportunistic infections and the rate of opportunistic infections was low. Additionally, the Applicant defined opportunistic infection based upon Winthrop et al. 2015, which includes herpes zoster (refer to Table 133 in Section 16.7.6). However, it is uncertain whether herpes zoster should be considered an opportunistic infection, as it occurs in patients who are immunocompetent in addition to those who are immunosuppressed. Given the increased occurrence of infections, a Warnings and Precautions will describe the potentially increased risk of infection in the label.

Hypersensitivity reactions, including anaphylaxis

Hypersensitivity reactions that occurred within 24 hours of study drug administration were reported in 10 subjects (1.0%) in the mirikizumab group and 1 subject (0.3%) in the placebo group. None of the hypersensitivity events were reported as SAEs. Four subjects (0.5%) in the mirikizumab group discontinued study treatment due to an infusion-related hypersensitivity reaction. The subjects reported erythema, flushing on face and chest, dyspnea, low blood pressure, and pruritis on arms, chest, and face. All these events were reported as "related" to the study. Given that these events occurred within 24 hours of treatment with mirikizumab they were likely related to the study drug.

Hypersensitivity reactions that occurred more than 24 hours after study drug administration were reported by 24 subjects (2.6%) in mirikizumab treatment group, and 7 subjects (2.2%) in the placebo group. Rash, urticaria and dermatitis were more frequently reported in mirikizumab treatment group. None of the events were reported as SAEs. One subject from each group discontinued the treatment due to the hypersensitivity reaction.

Given the immune-mediated mode of action of mirikizumab and the observed frequency of the hypersensitivity events, such as infusion-related hypersensitivity reaction, rash, and urticaria, these AEs are likely related to the study drug. Serious hypersensitivity reactions, including anaphylaxis and infusion-related hypersensitivity reactions, will be included in the Warnings and Precautions section of the label.

Malignancies

Two subjects (0.2%) in the mirikizumab treatment group reported malignant tumors (adenocarcinoma of colon and adenocarcinoma of rectum) and no subjects in the placebo group. In both subjects a colonoscopy was performed, and no malignancy was reported prior to enrollment. Both subjects were diagnosed during the follow up endoscopy (one had flexible sigmoidoscopy and one had colonoscopy) at the end of the induction period. As per the AMAN protocol, subjects with malignancy were not eligible to continue to AMBG and were discontinued from the study. Based on the short duration of exposure to mirikizumab, it is unlikely that these malignancies were related to mirikizumab. Of note, subjects with UC have higher risk for developing colorectal adenocarcinoma (Eaden et al. 2001). Additionally, it is possible that chronic inflammation in moderately to severe UC would make it more difficult to see these lesions during pretreatment endoscopy. Although the Applicant reported that the incidence rate (IR) of colon/rectum adenocarcinoma was consistent with the background cancer risk of subjects with UC, due to the small sample size and short duration of exposure, a relationship between mirikizumab and malignancy cannot be ruled out.

8.2.4.5. *Treatment Emergent Adverse Events*

An overview of treatment emergent adverse events (TEAEs) for AMAN is shown in Table 53. Overall, the proportion of subjects with at least one TEAE was similar in the placebo group, 149 subjects (46.4%), compared to mirikizumab treatment group, 428 subjects (44.7%). The majority of the TEAEs were mild or moderate in severity. The proportion of subjects with a severe TEAE was higher in the placebo group (7.2%) compared to mirikizumab treatment group (2.3%).

Table 53 summarize the common TEAEs reported at a frequency of at least 1% of subjects in the mirikizumab treatment group and greater than placebo in Study AMAN. The most common TEAEs were upper respiratory tract infections, headache, and arthralgia.

Table 53. Subjects With Common Adverse Events Occurring at ≥1% Frequency and Greater Than Placebo, Safety Population, AMAN, 12 Week Induction Period

Preferred Term	Mirikizumab 300 mg IV Q4W N=958 n (%)	Placebo N=321 n (%)	Risk Difference (%) (95% CI)
TEAE	**428 (44.7)**	**149 (46.4)**	**-1.7 (-8.0, 4.6)**
Upper respiratory tract infections^	72 (7.5)	20 (6.2)	1.3 (-1.8, 4.4)
Arthralgia	20 (2.1)	4 (1.2)	0.8 (-0.7, 2.4)
Fatigue	12 (1.3)	2 (0.6)	0.6 (0.5, 1.7)
Headache	32 (3.3)	9 (2.8)	0.5 (-1.6, 2.7)
Rash^	11 (1.1)	2 (0.6)	0.5 (-0.6, 1.6)
Herpes simplex infections^	13 (1.4)	3 (0.9)	0.4 (-0.9, 1.7)
Pyrexia^	14 (1.5)	4 (1.2)	0.3 (-1.2, 1.7)
Hypertension^	13 (1.4)	4 (1.2)	0.2 (1.5, 1.3)

Source: adae.xpt; Software: R
Gray shading reflects what will be included in the label as the most common adverse reactions
^ Grouped query, refer to Table 136, Appendix 16.7
Abbreviations: AE, adverse event; CI, confidence interval; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; Q4W, once every 4 weeks
Subjects may count more than one for each PT.

Upper Respiratory Tract Infections

Upper respiratory tract infections (URI) group query included preferred terms of acute sinusitis, COVID-19, nasopharyngitis, pharyngitis, rhinitis, rhinovirus, sinusitis, tonsillitis, upper respiratory tract infection, and viral upper respiratory tract infection (Table 136).

URIs were reported more frequently in the mirikizumab treatment group (72 subjects, 7.5%) as compared to placebo group (20 subjects, 6.2%). The most frequently reported URI was nasopharyngitis and reported more frequently in mirikizumab treatment group (45 subjects, 62.5 % in mirikizumab, and 11 subjects, 55.5 % in placebo). URIs were reported as mild or moderate in severity and no subjects were discontinued from study treatment due to URIs in mirikizumab treatment group. URIs may possibly be related to the study treatment, given the imbalance observed during AMAN and AMBG and the study drug has immunosuppressive effects that may increase the risk of infection.

Upper respiratory tract infections including related terms (e.g., COVID-19, nasopharyngitis, pharyngitis, rhinitis, sinusitis, and upper respiratory tract infection) will be included in the Adverse Reactions section of the label.

Arthralgia

Arthralgia was reported more frequently in the mirikizumab treatment group (20 subjects, 2.1%) as compared to placebo (4 subjects, 1.2%). Arthralgia was reported as mild or moderate in severity and no subject was discontinued from study treatment due to arthralgia in both groups.

Arthralgia can be extraintestinal manifestation of UC, and it improves with treatment of UC. However, arthralgia reported more frequently in the mirikizumab treatment arm in AMAN. Additionally, arthralgia adverse events have been observed with monoclonal antibodies, including other IL-23 antagonists, in IBD (e.g., Skyrizi [risankizumab]). The pathogenesis of arthralgia associated with IL-23 antagonists is not well characterized; however, immune-complex deposition and/or direct antibody binding in joints may play a role in monoclonal antibody-associated arthralgia/arthritis. Risk of arthralgia to be included in the Adverse Reactions section of the label.

Fatigue, headache, rash, herpes simplex infection, pyrexia, and hypertension: The TEAEs headache, rash, herpes simplex infection, and pyrexia were reported in at least 1% of subjects in the mirikizumab group and greater than placebo; however, these PTs are not recommended to be included in labeling because these TEAEs were reported in similar proportions of subjects between mirikizumab and placebo. Additionally, the majority of these TEAEs were reported in the setting of other TEAEs (e.g., URI, infusion reaction, nervousness, nausea, abdominal pain), such that they are unlikely to be related to mirikizumab.

Laboratory Findings

Routine hematology and chemistry clinical laboratory testing were performed during Screening, at Baseline, and at Weeks 4, 8, 12, early termination visit, and/or end of treatment visit during AMBG according to the Schedule of Activities (Table 133, and Table 135). No clinically meaningful differences between mirikizumab and placebo were observed in hematology and chemistry parameters except for the hepatic enzyme elevations as discussed in 8.2.6.1.

Vital Signs

Routine vital signs that included temperature, blood pressure and pulse rate were performed during Screening, at Baseline, and at Weeks 4, 8, 12, and early termination visit, and/or end of treatment visit during AMAN according to the Schedule of Activities. No clinically meaningful differences between mirikizumab and placebo were observed in vital signs during AMAN.

Electrocardiograms (ECGs)

The potential for mirikizumab to alter QRS, PR, or RR intervals was investigated in 2 clinical pharmacology studies of mirikizumab (AMAA and AMAD). No clinically significant ECG findings or TEAEs related to ECGs were identified in Studies AMAA or AMAD or in other studies comprising the complete integrated clinical pharmacology safety database.

In AMAN, a single 12-lead ECG was collected at baseline, and at Week 12 or at the end of treatment visit (if the subjects discontinued before Week 12). Inspection of the ECG data from these individual study reports did not reveal any clinically significant changes in ECG parameters.

QT

The potential for mirikizumab to alter the QT interval was assessed in studies AMAA and AMAD. No dose relationship in the incidence of QTcF >450 msec was observed, with the incidence in the placebo group comparable with mirikizumab.

Immunogenicity

The frequency of hypersensitivity reactions, infusion site reactions, and injection site reactions did not significantly differ between TE ADA positive and TE ADA negative subjects. Refer to the Clinical Pharmacology Section 6.2.1.3 for further details.

8.2.5. Safety Results During Maintenance (AMBG)

Overview of Adverse Events

Subjects who achieved clinical response with mirikizumab treatment during AMAN (i.e., induction) were re-randomized 2:1 to 200 mg mirikizumab Q4W SC or blinded placebo. Subjects who responded to placebo during AMAN remained on blinded placebo. In this section, the "mirikizumab group" refers to subjects who were mirikizumab responders during AMAN and received mirikizumab during AMBG. The "placebo group" refers to subjects who were mirikizumab responders during AMAN and received placebo during AMBG.

Table 54 provides a summary of AEs reported during AMBG. Overall, a greater proportion of subjects in the placebo group reported SAEs, AEs leading to study drug discontinuation, severe TEAEs, and TEAEs compared to subjects in the mirikizumab group.

Table 54. Overview of Adverse Events, Safety Population, AMBG, 40 Week Maintenance Period

Event Category	Mirikizumab Responders to Mirikizumab 200 mg SC Q4W N=389 n (%)	Mirikizumab Responders to Placebo N=192 n (%)	Risk Difference (%) (95% CI)	Placebo Responders to Placebo N=135 n (%)
SAE	13 (3.3)	15 (7.8)	-4.5 (-8.7, -0.3)*	7 (5.2)
SAEs with fatal outcome	0	1 (0.5)	-0.5 (-1.5, 0.5)	0
AE leading to permanent discontinuation of study drug	6 (1.5)	16 (8.3)	-6.8 (-10.9, -2.7)*	1 (0.7)
AE leading to interruption of study drug	5 (1.3)	2 (1.0)	0.2 (-1.6, 2.1)	1 (0.7)
TEAEs	251 (64.5)	132 (68.8)	-4.2 (-12.3, 3.9)	82 (60.7)
Severe	16 (4.1)	12 (6.2)	-2.1 (-6.1, 1.8)	11 (8.1)
Moderate	87 (22.4)	49 (25.5)	-3.2 (-10.6, 4.3)	32 (23.7)

Event Category	Mirikizumab Responders to Mirikizumab 200 mg SC Q4W N=389 n (%)	Mirikizumab Responders to Placebo N=192 n (%)	Risk Difference (%) (95% CI)	Placebo Responders to Placebo N=135 n (%)
Mild	148 (38.0)	71 (37.0)	1.1 (-7.3, 9.4)	39 (28.9)

Source: adae.xpt and adsl.xpt; Software: R
Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Events that occurred only in the Placebo Responders to Placebo group are not included.
Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with at least one event; Q4W, once every 4 weeks; SAE, serious adverse event; SC, subcutaneous; TEAE, Treatment emergent adverse event

8.2.5.1. *Deaths*

The Applicant reported 1 death during AMBG due to COVID-19 infection. The subject was a mirikizumab responder during AMAN and randomized to placebo during study AMBG. The death occurred while the subject was receiving placebo. The case is described in detail below:

- COVID-19 infection: A 53-year-old white male who responded to mirikizumab during AMAN and then entered AMBG and received placebo, was hospitalized with an SAE of COVID-19 infection 288 days after starting treatment with mirikizumab 300 mg IV Q4W (induction), 190 days since the first dose of placebo (maintenance), and 226 days since the last dose of mirikizumab 300 mg IV Q4W (induction). COVID-19 infection was complicated by secondary bacterial pneumonia and respiratory failure. Two weeks after the hospitalization, the subject developed acute cerebral ischemia (ischemic stroke) and ten days later, the subject died of cardiogenic shock due to hypercoagulation and thrombosis of the mesenteric arteries of the abdomen. Given that the COVID-19 infection occurred while the subject was receiving placebo and more than 6 months after the last exposure to mirikizumab, it is likely not related to mirikizumab.

8.2.5.2. *Serious Adverse Events*

Serious adverse events (SAEs) for AMBG are shown in Table 55. Overall, SAEs were reported at a higher frequency in the placebo group (15 subjects, 7.8%) than the mirikizumab group (13 subjects, 3.3%); however, the overall SAE rates were low.

Table 55. Subjects With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, AMBG, 40 Week Maintenance Period

System Organ Class (SOC) Preferred Term (PT)	Mirikizumab Responders to Mirikizumab 200 mg SC Q4W N=389 n (%)	Mirikizumab Responders to Placebo N=192 n (%)	Risk Difference (%) (95% CI)	Placebo Responders to Placebo N=135 n (%)
Serious Adverse Events (SAE)	13 (3.3)	15 (7.8)	-4.5 (-8.7, -0.3)*	7 (5.2)
Endocrine disorders	0	1 (0.5)	-0.5 (-1.5, 0.5)	0
Autoimmune thyroiditis	0	1 (0.5)	-0.5 (-1.5, 0.5)	0
Eye disorders	1 (0.3)	0	0.3 (-0.2, 0.8)	0
Retinal detachment	1 (0.3)	0	0.3 (-0.2, 0.8)	0
Gastrointestinal disorders	1 (0.3)	8 (4.2)	-3.9 (-6.8, -1.0)*	1 (0.7)
Inguinal hernia	1 (0.3)	0	0.3 (-0.2, 0.8)	0
Rectal hemorrhage	0	1 (0.5)	-0.5 (-1.5, 0.5)	0
Rectal polyp	0	1 (0.5)	-0.5 (-1.5, 0.5)	0
Colitis ulcerative	0	6 (3.1)	-3.1 (-5.6, -0.7)*	1 (0.7)
Immune system disorders	0	1 (0.5)	-0.5 (-1.5, 0.5)	0
Anaphylactic reaction	0	1 (0.5)	-0.5 (-1.5, 0.5)	0
Infections and infestations	3 (0.8)	3 (1.6)	-0.8 (-2.7, 1.2)	3 (2.2)
COVID-19 pneumonia	1 (0.3)	0	0.3 (-0.2, 0.8)	0
Diverticulitis	1 (0.3)	0	0.3 (-0.2, 0.8)	0
Gastroenteritis	1 (0.3)	0	0.3 (-0.2, 0.8)	1 (0.7)
COVID-19	0	1 (0.5)	-0.5 (-1.5, 0.5)	0
Large intestine infection	0	1 (0.5)	-0.5 (-1.5, 0.5)	0
Subcutaneous abscess	0	1 (0.5)	-0.5 (-1.5, 0.5)	0
Injury, poisoning and procedural complications	1 (0.3)	0	0.3 (-0.2, 0.8)	1 (0.7)
Spinal compression fracture	1 (0.3)	0	0.3 (-0.2, 0.8)	0
Investigations	1 (0.3)	0	0.3 (-0.2, 0.8)	0
Blood glucose increased	1 (0.3)	0	0.3 (-0.2, 0.8)	0
Metabolism and nutrition disorders	1 (0.3)	1 (0.5)	-0.3 (-1.4, 0.9)	0
Hypokalemia	1 (0.3)	0	0.3 (-0.2, 0.8)	0
Hypoglycemia	0	1 (0.5)	-0.5 (-1.5, 0.5)	0
Musculoskeletal and connective tissue disorders	1 (0.3)	0	0.3 (-0.2, 0.8)	1 (0.7)
Back pain	1 (0.3)	0	0.3 (-0.2, 0.8)	0
Neoplasms benign, malignant, and unspecified (cysts and polyps)	2 (0.5)	0	0.5 (-0.2, 1.2)	0
Gastric cancer	1 (0.3)	0	0.3 (-0.2, 0.8)	0
Lipoma-vocal fold	1 (0.3)	0	0.3 (-0.2, 0.8)	0
Nervous system disorders	1 (0.3)	2 (1.0)	-0.8 (-2.3, 0.7)	0
Headache	1 (0.3)	0	0.3 (-0.2, 0.8)	0
Ischemic stroke	0	1 (0.5)	-0.5 (-1.5, 0.5)	0
Presyncope	0	1 (0.5)	-0.5 (-1.5, 0.5)	0
Psychiatric disorders	1 (0.3)	0	0.3 (-0.2, 0.8)	0
Depression suicidal	1 (0.3)	0	0.3 (-0.2, 0.8)	0
Reproductive system and breast disorders	1 (0.3)	0	0.3 (-0.2, 0.8)	0
Rectocele	1 (0.3)	0	0.3 (-0.2, 0.8)	0

System Organ Class (SOC) Preferred Term (PT)	Mirikizumab Responders to Mirikizumab 200 mg SC Q4W N=389 n (%)	Mirikizumab Responders to Placebo N=192 n (%)	Risk Difference (%) (95% CI)	Placebo Responders to Placebo N=135 n (%)
Respiratory, thoracic, and mediastinal disorders	0	1 (0.5)	-0.5 (-1.5, 0.5)	0
Asthma	0	1 (0.5)	-0.5 (-1.5, 0.5)	0
Surgical and medical procedures	1 (0.3)	0	0.3 (-0.2, 0.8)	0
Retinopexy	1 (0.3)	0	0.3 (-0.2, 0.8)	0

Source: adae.xpt; Software: R
Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Events that occurred only in the Placebo Responders to Placebo group are not included.
Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; Q4W, once every 4 weeks; SAE, serious adverse event; SC, subcutaneous; SOC, system organ class

The most frequently reported SAE was “colitis ulcerative,” which was reported by 6 subjects (3.1%) in the placebo group versus none in the mirikizumab group. There was one SAE that led to study discontinuation (“gastric cancer”) which was also considered an AESI. There were 2 SAEs that were considered AESIs reported in the mirikizumab group. One subject (0.3%) reported gastric cancer and one subject (0.3%) reported suicidal depression. SAEs that were AESIs are described in more detail below.

SAEs that were considered AESIs

- COVID-19 pneumonia: A 64-year-old Caucasian male experienced an SAE of COVID-19 pneumonia. The SAE occurred 398 days after starting treatment with mirikizumab 300 mg IV Q4W (induction), 300 days since the first dose of mirikizumab 200 mg SC Q4W (maintenance), and 49 days since the last dose of mirikizumab 200 mg SC Q4W (maintenance). At the time of the SAE, the subject had completed AMBG and was in the process of rolling over to AMAP. The subject presented to the emergency department due to decreased oxygen saturation at home. The subject tested positive for COVID-19 and was admitted to the hospital. He was subsequently admitted to the intensive care unit and intubated. He received broad spectrum antibiotics and mechanical ventilation for 15 days. He eventually recovered and was discharged from the hospital after 6 weeks. The subject did not continue into AMAP. Given that the SAE occurred 49 days since the last dose of mirikizumab (nearly 5 half-lives), it is likely not related to the drug. However, given the immunosuppressive effects of the mechanism of action and increased rate of infection observed in the trials, a relationship to the drug cannot be excluded.

- Gastric cancer: A 48-year-old Asian female, experienced an SAE of gastric cancer and discontinued the study drug, which was 257 days after starting treatment with mirikizumab 300 mg IV Q4W (induction), 166 days since the first dose of mirikizumab 200 mg SC Q4W (maintenance), and 20 days since the last dose of

mirikizumab 200 mg SC Q4W (maintenance). The subject reported to the study investigator that she was diagnosed with gastric cancer as a result of medical surveillance, which the subject received due to a family history of gastric cancer. The subject underwent endoscopic submucosal dissection (ESD) that revealed "gastric cancer type 0-IIb (superficial flat type)". The subject had uneventful postoperative course and follow up upper endoscopy showed occlusion of the ulcer after ESD, and the gastric cancer was reported as "resolved". The event of gastric cancer was reported "not related" to the study drug by the investigator. Given that the subject has family history of gastric cancer and was under surveillance, the event of gastric cancer is probably not related to the study drug.

- Suicidal depression: A 59-year-old white female with medical history of depression and 2 suicidal attempts, was hospitalized with an SAE of suicidal attempt due to depression, by intentionally taking 90 capsules of alprazolam 1 mg, which was 111 days after starting treatment with mirikizumab 300 mg IV Q4W (induction), 8 days since the first dose of mirikizumab 200 mg SC Q4W (maintenance), and 8 days since the last dose of mirikizumab 200 mg SC Q4W (maintenance). No adverse event (AE) due to intentional overdose was reported. The investigator discussed with the psychiatrist and confirmed that the subject's status was appropriate to remain in the study. Additional safety measures were instituted including site calls to the subject every 2-3 days to ensure subject was feeling well, and the subject's psychiatrist had increased follow up visits. No change was made to the study drug and the event was reported "not related" to the study drug. Given that SAE of suicidal depression occurred in a subject with a history of depression and suicidal attempts and the symptoms were reported to be resolved at the last study assessment, the event of suicidal depression is probably not related to the study drug.

8.2.5.3. *Discontinuation due to Adverse Events*

Adverse events (AEs) that led to study discontinuation for AMBG are shown in Table 56. Overall, study discontinuation due to TEAEs was rare and reported by a greater proportion of subjects in the placebo group (16 subjects, 8.3%) than the mirikizumab group (6 subjects, 1.5%).

Table 56. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, AMBG, 40 Week Maintenance Period

System Organ Class (SOC) Preferred Term (PT)	Mirikizumab Responders to Mirikizumab 200 mg SC Q4W N=389 n (%)	Mirikizumab Responders to Placebo N=192 n (%)	Risk Difference (%) (95% CI)	Placebo Responders to Placebo N=135 n (%)
TEAE leading to Study Discontinuation	6 (1.5)	16 (8.3)	-6.8 (-10.9, -2.7)*	1 (0.7)
Gastrointestinal disorders	2 (0.5)	11 (5.7)	-5.2 (-8.6, -1.9)*	1 (0.7)
Colitis ulcerative	2 (0.5)	11 (5.7)	-5.2 (-8.6, -1.9)*	1 (0.7)

System Organ Class (SOC) Preferred Term (PT)	Mirikizumab Responders to Mirikizumab 200 mg SC Q4W N=389 n (%)	Mirikizumab Responders to Placebo N=192 n (%)	Risk Difference (%) (95% CI)	Placebo Responders to Placebo N=135 n (%)
General disorders and administration site conditions	2 (0.5)	0	0.5 (-0.2, 1.2)	0
Injection site hypersensitivity	1 (0.3)	0	0.3 (-0.2, 0.8)	0
Oedema peripheral	1 (0.3)	0	0.3 (-0.2, 0.8)	0
Hepatobiliary disorders	1 (0.3)	0	0.3 (-0.2, 0.8)	0
Autoimmune hepatitis	1 (0.3)	0	0.3 (-0.2, 0.8)	0
Immune system disorders	0	1 (0.5)	-0.5 (-1.5, 0.5)	0
Anaphylactic reaction	0	1 (0.5)	-0.5 (-1.5, 0.5)	0
Infections and infestations	0	1 (0.5)	-0.5 (-1.5, 0.5)	0
COVID-19	0	1 (0.5)	-0.5 (-1.5, 0.5)	0
Musculoskeletal and connective tissue disorders	0	1 (0.5)	-0.5 (-1.5, 0.5)	0
Arthralgia	0	1 (0.5)	-0.5 (-1.5, 0.5)	0
Neoplasms benign, malignant, and unspecified (cysts and polyps)	1 (0.3)	0	0.3 (-0.2, 0.8)	0
Gastric cancer	1 (0.3)	0	0.3 (-0.2, 0.8)	0
Nervous system disorders	0	1 (0.5)	-0.5 (-1.5, 0.5)	0
Presyncope	0	1 (0.5)	-0.5 (-1.5, 0.5)	0
Vascular disorders	0	1 (0.5)	-0.5 (-1.5, 0.5)	0
Hypotension	0	1 (0.5)	-0.5 (-1.5, 0.5)	0

Source: adae.xpt; Software: R
Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; Q4W, once every 4 weeks; SC, subcutaneous; SOC, system organ class

The most commonly reported AE that led to discontinuation was “colitis ulcerative” which was reported more frequently in the placebo group (11 subjects, 5.7%) than the mirikizumab group (2 subjects, 0.5%). There were three AEs that led to discontinuation that were considered AESIs. These were hypersensitivity and injection site reaction (1 subject with injection site hypersensitivity), malignancy (1 subject with gastric cancer) and hepatic event (1 subject with autoimmune hepatitis).

AEs that led to discontinuation and considered AESIs

- Injection site hypersensitivity: A 29-year-old Asian female, discontinued the study drug due to the adverse event of “injection site hypersensitivity” which occurred 128 days after starting treatment with 300 mg mirikizumab Q4W IV (induction), 33 days since the first dose of 200 mg mirikizumab Q4W SC (maintenance), and 5 days since the last dose of 200 mg mirikizumab Q4W SC (maintenance). The TEAE of mild severity lasted for 4 days and resolved. Overall, injection site reactions were reported more frequently in the mirikizumab group (8.7%) than the placebo group (4.2%) during AMBG (Refer to Table 57). Given the immune-mediated mode of action of mirikizumab, the event of injection

site hypersensitivity reaction is probably likely related to the study drug. A Warnings and Precautions regarding hypersensitivity reactions will be included in the label.

- Autoimmune hepatitis: A 21-year-old white female, discontinued the study drug due to "autoimmune hepatitis" which started 211 days after starting treatment with mirikizumab 300 mg Q4W IV (induction), 123 days after starting treatment with mirikizumab 200 mg Q4W SC (maintenance), and 7 days since the last dose of 200 mg mirikizumab Q4W SC (maintenance). No relevant medical history, pre-existing condition or family history of liver diseases were reported. The diagnosis of autoimmune hepatitis was made by blood tests because of persistently elevated AST/ALT. The subject was found to have positive pANCA, ANA, and anti-actin antibody. The event was reported "related" to the study drug. Of note, autoimmune hepatitis occurs with increased frequency (up to 16%) in subjects with underlying UC (Saich and Chapman 2008); however, contribution of study drug cannot be excluded.

- Gastric cancer: The SAE of gastric cancer led to discontinuation from the study as per protocol; this SAE is described in more detail in previous section.

8.2.5.4. *Adverse Events of Special Interest*

Adverse events of special interest (AESIs) were defined in the study protocol based on safety findings from previous studies in development program, potential risks associated with biologic immunomodulators as noted in product labels and published literature, and comorbidities and risk factors prevalent in the studied populations. Refer to the in Section 8.2.3, "Categorization of Adverse Events."

AESIs for AMBG are shown in Table 57. Overall, a higher proportion of subjects in the mirikizumab group (141 subjects, 36.2%) reported at least one AESI compared to the placebo group (61 subjects, 31.8%). Hypersensitivity reactions, injection site reactions, opportunistic infections, depression, and hepatic adverse events were reported more frequently in the mirikizumab group than the placebo group.

Table 57. Subjects With Adverse Events of Special Interest, Safety Population, Study AMBG – Maintenance Period

Adverse Event of Special Interest Preferred Term	Mirikizumab Responders to Mirikizumab 200 mg SC Q4W N=389 n (%)	Mirikizumab Responders to Placebo N=192 n (%)	Risk Difference (%) (95% CI)	Placebo Responders to Placebo N=135 n (%)
Any AESI	141 (36.2)	61 (31.8)	4.5 (-3.7, 12.6)	38 (28.1)
Anaphylactic reaction	0	1 (0.5)	-0.5 (-1.5, 0.5)	0
Anaphylactic reaction	0	1 (0.5)	-0.5 (-1.5, 0.5)	0
Cerebro-cardiovascular	1 (0.3)	2 (1.0)	-0.8 (-2.3, 0.7)	2 (1.5)
Ischemic stroke	0	1 (0.5)	-0.5 (-1.5, 0.5)	0
Depression and suicide/self-injury	5 (1.3)	0	1.3 (0.2, 2.4)*	0
Depressed mood	2 (0.5)	0	0.5 (-0.2, 1.2)	0
Depression	2 (0.5)	0	0.5 (-0.2, 1.2)	0
Depression suicidal	1 (0.3)	0	0.3 (-0.2, 0.8)	0
Hepatic events	14 (3.6)	6 (3.1)	0.5 (-2.6, 3.6)	4 (3.0)
Transaminase increased^	7 (1.8)	3 (1.6)	0.2 (-2.0, 2.4)	1 (0.7)
Blood bilirubin increased	2 (0.5)	0	0.5 (-0.2, 1.2)	1 (0.7)
Gamma-glutamyltransferase increased	4 (1.0)	1 (0.5)	0.5 (-0.9, 1.9)	2 (1.5)
Autoimmune hepatitis	1 (0.3)	0	0.3 (-0.2, 0.8)	0
Granulomatous liver disease	1 (0.3)	0	0.3 (-0.2, 0.8)	0
Nonalcoholic fatty liver disease	1 (0.3)	0	0.3 (-0.2, 0.8)	0
Hepatic steatosis	1 (0.3)	1 (0.5)	-0.3 (-1.4, 0.9)	0
Blood alkaline phosphatase increased	1 (0.3)	3 (1.6)	-1.3 (-3.1, 0.5)	0
Hypersensitivity reactions (≤24 hours after drug administration)	7 (1.8)	2 (1.0)	0.8 (-1.2, 2.7)	0
Hypersensitivity	4 (1.0)	0	1.0 (0.0, 2.0)	0
Injection site rash	2 (0.5)	0	0.5 (-0.2, 1.2)	0
Injection site urticaria	2 (0.5)	0	0.5 (-0.2, 1.2)	0
Rash	2 (0.5)	0	0.5 (-0.2, 1.2)	0
Anaphylactic reaction	0	1 (0.5)	-0.5 (-1.5, 0.5)	0
Dermatitis allergic	0	1 (0.5)	-0.5 (-1.5, 0.5)	0
Hypersensitivity reactions (>24 hours after drug administration)	27 (6.9)	5 (2.6)	4.3 (1.0, 7.7)*	4 (3.0)
Rash^	20 (5.1)	7 (3.6)	1.5 (-1.9, 4.9)	2 (1.5)
Dermatitis^	6 (1.5)	1 (0.5)	1.0 (-0.6, 2.6)	0
Hypersensitivity	2 (0.5)	0	0.5 (-0.2, 1.2)	1 (0.7)
Injection site hypersensitivity	3 (0.8)	0	0.8 (-0.1, 1.6)	1 (0.7)
Injection site urticaria	2 (0.5)	0	0.5 (-0.2, 1.2)	0
Conjunctivitis allergic	1 (0.3)	0	0.3 (-0.2, 0.8)	0
Eczema	1 (0.3)	0	0.3 (-0.2, 0.8)	0
Swelling of eyelid	1 (0.3)	0	0.3 (-0.2, 0.8)	0
Urticaria	1 (0.3)	0	0.3 (-0.2, 0.8)	0
Infections	93 (23.9)	44 (22.9)	1 (-6.3, 8.3)	30 (22.2)
Opportunistic infections	5 (1.3)	0	1.3 (0.2, 2.4)*	0
Herpes zoster	4 (1.0)	0	1.0 (0.0, 2.0)*	0
Oral candidiasis	1 (0.3)	0	0.3 (-0.2, 0.8)	0

Adverse Event of Special Interest Preferred Term	Mirikizumab Responders to Mirikizumab 200 mg SC Q4W N=389 n (%)	Mirikizumab Responders to Placebo N=192 n (%)	Risk Difference (%) (95% CI)	Placebo Responders to Placebo N=135 n (%)
Injection site reactions	34 (8.7)	8 (4.2)	4.6 (0.6, 8.6)*	3 (2.2)
Injection site reaction	10 (2.6)	1 (0.5)	2.0 (0.2, 3.9)*	1 (0.7)
Injection site pain	17 (4.4)	6 (3.1)	1.2 (-1.9, 4.4)	2 (1.5)
Injection site erythema	8 (2.1)	2 (1.0)	1.0 (-1.0, 3.0)	1 (0.7)
Injection site bruising	2 (0.5)	0	0.5 (-0.2, 1.2)	0
Injection site pruritus	2 (0.5)	0	0.5 (-0.2, 1.2)	0
Injection site dermatitis	1 (0.3)	0	0.3 (-0.2, 0.8)	0
Injection site hematoma	1 (0.3)	0	0.3 (-0.2, 0.8)	0
Injection site hypersensitivity	1 (0.3)	0	0.3 (-0.2, 0.8)	0
Injection site oedema	1 (0.3)	0	0.3 (-0.2, 0.8)	0
Injection site paresthesia	1 (0.3)	0	0.3 (-0.2, 0.8)	0
Injection site rash	1 (0.3)	0	0.3 (-0.2, 0.8)	0
Injection site urticaria	1 (0.3)	0	0.3 (-0.2, 0.8)	0
Malignant tumors	1 (0.3)	1 (0.5)	-0.3 (-1.4, 0.9)	0
Gastric cancer	1 (0.3)	0	0.3 (-0.2, 0.8)	0
Basal cell carcinoma	0	1 (0.5)	-0.5 (-1.5, 0.5)	0

Source: adae.xpt; Software: R
Risk difference (with 95% confidence interval) is shown between mirikizumab responders to mirikizumab and mirikizumab responders to placebo.
Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Events that occurred only in the Placebo Responders to Placebo group are not included.
Treatment-emergent adverse events defined as an event that first occurred or worsened in severity after baseline and on or prior to the date of the last visit within the blinded treatment dosing period. Duration is 40 weeks.
Abbreviations: AESI, adverse event of special interest; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; Q4W, once every 4 weeks; SARS, severe acute respiratory syndrome; SC, subcutaneous
^Grouped query, refer to Table 136, Appendix 16.7.
Subjects may count more than one for each PT.

AESIs that were reported by a greater proportion of subjects in the mirikizumab group than the placebo group is described in more detail below.

Infections and Opportunistic infections

Ninety-three subjects (23.9%) in the mirikizumab group and 44 subjects (22.9%) in the placebo group reported an infection. The majority of the infections were mild or moderate in severity. Infection related SAEs were rare but, reported at a higher frequency in the placebo group (3 subjects, 1.6%) than the mirikizumab group (3 subjects, 0.8%). No subject discontinued the study drug due to infection.

The most common infection was upper respiratory tract infections, which were reported more frequently in the mirikizumab group (53 subjects, 13.6%) compared to the placebo group (23 subjects, 11.9%). Other types of infections reported in the mirikizumab group included UTI, gastroenteritis, Clostridioides difficile infection, otitis media, and dental infections however, these infections were reported in less than 1% of subjects and/or were reported by a similar proportion of subjects in the mirikizumab and placebo groups.

Opportunistic infections were reported in 5 subjects (1.3%) in the mirikizumab group (4 subjects with herpes zoster and 1 subject with oral candidiasis), and no subject in the placebo group. No subject discontinued the study drug due to opportunistic infection. As stated previously, the Applicant defined opportunistic infection based upon Winthrop et al. 2015, which includes herpes zoster (refer to Table 133 in Section 16.8). However, it is uncertain whether herpes zoster should be considered an opportunistic infection, as it occurs in patients who are immunocompetent in addition to those who are immunosuppressed. Given the increased occurrence of infections, a Warnings and Precautions will describe the potentially increased risk of infection in the label.

Hypersensitivity reactions

Overall, hypersensitivity reactions (regardless of the timing of the reaction to study drug administration) were reported more frequently in the mirikizumab group. Thirty subjects (7.7%) in the mirikizumab group, and 7 subjects (3.6%) in the placebo group reported hypersensitivity reactions.

Hypersensitivity reactions that occurred within 24 hours of study drug administration were reported in 7 subjects (1.8%) in the mirikizumab group, and 2 subjects (1.0%) in the placebo group. Hypersensitivity, injection site rash, and urticaria were more frequently reported in the mirikizumab group. No subject reported anaphylaxis in the mirikizumab group.

Hypersensitivity reactions that occurred more than 24 hours after study drug administration were reported in 27 subjects (6.9%) in the mirikizumab group and 5 subjects (2.6%) in the placebo group. Rash, hypersensitivity, and dermatitis were more frequently reported in the mirikizumab group. No SAE of hypersensitivity reaction was reported. One subject discontinued the study drug because of injection site hypersensitivity rection in mirikizumab maintenance group, which was described in section 8.2.5.3.

Given the biologic plausibility of hypersensitivity reactions (e.g., ADAs, reaction to the size of the molecule) occurring with monoclonal antibodies and the observed frequency of the hypersensitivity events (e.g., rash, hypersensitivity, and injection site reactions), hypersensitivity AEs are likely related to the study drug. A Warnings and Precautions regarding hypersensitivity reactions will be included in the label.

Injection site reactions

Overall, injection site reactions were reported more frequently in the mirikizumab group. Thirty-four subjects (8.7%) in the mirikizumab group and 8 subjects (4.2%) in the placebo group had at least 1 injection site reaction. The most frequently reported injection site reactions were injection site reaction, injection site pain, injection site erythema, injection site pruritis, and injection site bruising. No SAEs of injection site reactions were reported. One subject in the mirikizumab group discontinued the study drug due to an injection site hypersensitivity reaction that was mild in severity, which was described previously (Section 8.2.5.3).

Two subjects in the mirikizumab group reported injection site pain of severe severity; however, the subjects continued the study drug. Given that injection site reactions occurred at the injection site, and the biologic plausibility for injection site reactions related to SC dosing of biologic agents, these AEs are likely related to the study drug. Injection site reactions including related terms (e.g., erythema, hypersensitivity, pain, reaction, and urticaria at the injection site) will be included in the "Adverse Reactions" section of the label.

Malignant tumors

Overall, the number of AEs related to malignancy was low. One subject (0.3%) in the mirikizumab group reported gastric cancer and 1 subject (0.5%) in the placebo group reported basal cell carcinoma. The subject with gastric cancer discontinued the study drug and was described in more detail in previous section (Section 8.2.5.3).

Depression, or suicidal ideation and behavior

Four subjects (1.0%) in the mirikizumab group, and no subjects in the placebo group reported AEs of depression and depressed mood. These events were mild or moderate severity, and one subject had a prior history of depression. No events were serious or led to treatment discontinuation. These events were reported as "not related" to the study drug. One subject (0.3%) in the mirikizumab group with medical history of depression and suicide attempts, reported a suicidal attempt and was hospitalized due to a drug overdose during AMBG. This case was described in more detail in previous section (Section 8.2.5.3)

Of note, during AMAN and AMBG, subjects were evaluated for worsening of depression based on the Quick Inventory of Depressive Symptomatology (QIDS). The Applicant reported that any worsening of depression severity category on the QIDS was reported more frequently in placebo than mirikizumab for both AMAN and AMBG (data not shown). Given that subjects with UC have an increased risk of depression and that the AEs of depression were rare, no clear increased risk of depression due to mirikizumab was observed. Furthermore, the QIDS data was supportive that worsening of depression is unlikely to be related to mirikizumab.

Subjects with UC are at increased risk of depression, and this was the only suicidal attempt event reported in a subject with history of previous depression and suicidal events.

Hepatic adverse events

Fourteen subjects (3.6%) in the mirikizumab group and 6 subjects (3.1%) in the placebo group reported hepatic adverse event. The most commonly reported hepatic AEs were transaminase (AST and ALT) and GGT elevation. None of these events were reported as SAEs or severe AEs. One subject with autoimmune hepatitis discontinued the study treatment. Of note, autoimmune hepatitis occurs with increased frequency in subjects with UC; however, contribution of study drug cannot be excluded. Refer to Section 8.2.6.1 for additional hepatotoxicity analyses.

8.2.5.5. *Treatment Emergent Adverse Events*

An overview of treatment emergent adverse events (TEAEs) for study AMBG is shown in Table 58. Overall, the proportion of subjects with at least one TEAE was higher in the placebo group (132 subjects, 68.8%) compared to the mirikizumab group (251 subjects, 64.5%). The majority of the TEAEs were mild or moderate in severity. The proportion of subjects with a severe TEAE was higher in the placebo group (12 subjects, 6.2%) compared to the mirikizumab group (16 subjects, 4.1%).

Table 58 summarize the common TEAEs reported at a frequency of at least 2% of subjects in the mirikizumab group and greater than placebo group. The most commonly reported TEAEs were upper respiratory infections, injections site reactions, arthralgia, headache, and rash.

Table 58. Subjects With Common Adverse Events Occurring at ≥2% Frequency, Safety Population, AMBG, 40 Week Maintenance Period

Preferred Term	Mirikizumab Responders to Mirikizumab 200 mg SC Q4W N=389 n (%)	Mirikizumab Responders to Placebo N=192 n (%)	Risk Difference (%) (95% CI)	Placebo Responders to Placebo N=135 n (%)
TEAE	251 (64.5)	132 (68.8)	-4.2 (-12.3, 3.9)	82 (60.7)
Upper respiratory tract infection^	53 (13.6)	23 (11.9)	1.6 (-4.1, 7.4)	20 (14.8)
Injection site reactions^	34 (8.7)	8 (4.2)	4.6 (0.6, 8.6)*	3 (2.2)
Headache	16 (4.1)	2 (1.0)	3.1 (0.6, 5.5)*	5 (3.7)
Rash^	16 (4.1)	2 (1.0)	3.1 (0.6, 5.5)*	2 (1.5)
Arthralgia	26 (6.7)	8 (4.2)	2.5 (1.2, 6.3)	4 (3.0)
Gastroesophageal reflux disease	10 (2.6)	1 (0.5)	2.0 (0.2, 3.9)*	0
Diarrhea	10 (2.6)	1 (0.5)	2.0 (0.2, 3.9)*	3 (2.2)
Hypertension	9 (2.3)	1 (0.5)	1.8 (0.0, 3.6)	1 (0.7)
Herpes viral infections^	9 (2.3)	1 (0.5)	1.8 (-0.0, 3.6)	2 (1.5)
Pyrexia	13 (3.3)	5 (2.6)	0.7 (-2.1, 3.6)	6 (4.4)
Abdominal pain	11 (2.8)	4 (2.1)	0.7 (-1.9, 3.4)	3 (2.2)
Fatigue	10 (2.6)	4 (2.1)	0.5 (-2.1, 3.0)	1 (0.7)

Source: adae.xpt; Software: R
Gray shading reflects what will be included in the label as the most common adverse reactions.
Risk difference (with 95% confidence interval) is shown between mirikizumab and placebo.
Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
^Grouped query, refer to Table 136 , Appendix 16.7.6
Adverse events are listed in decreasing order of the risk difference column.
Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; Q4W, once every 4 weeks; SARS, severe acute respiratory syndrome; SC, subcutaneous.
Subjects may count more than one for each PT.

Upper respiratory tract infections

Upper respiratory tract infection (URI) AEs were assessed as a group query that included preferred terms of acute sinusitis, COVID-19, nasopharyngitis, pharyngitis, rhinitis, rhinovirus,

sinusitis, tonsillitis, upper respiratory tract infection, and viral upper respiratory tract infection (Table 136). URIs were reported more frequently in the mirikizumab group (53 subjects, 13.6%) as compared to the placebo group (23 subjects, 11.9%). The most frequently reported URIs were nasopharyngitis, COVID-19, and rhinitis. All URIs were reported as mild or moderate in severity and no subjects were discontinued from study treatment due to URIs in the mirikizumab group. URIs may possibly be related to the study treatment, given the imbalance observed during AMAN and AMBG and the study drug has immunosuppressive effects that may increase the risk of infection. Upper respiratory infections including related terms (e.g., COVID-19, nasopharyngitis, pharyngitis, rhinitis, sinusitis, and upper respiratory tract infection) will be included in the "Adverse Reactions" section of the label.

Injection site reactions

Overall, injection site reactions were reported more frequently in the mirikizumab group compared to the placebo group. Thirty-four subjects (8.7%) in the mirikizumab group and 8 subjects (4.2%) in the placebo group had at least one injection site reaction. For additional details, refer to the AESI section of AMBG (Section 8.2.5.4). Injection site reactions including related terms (e.g., erythema, hypersensitivity, pain, reaction, and urticaria at the injection site) will be included in the "Adverse Reactions" section of the label.

Arthralgia

Arthralgia was reported more frequently in the mirikizumab group (26 subjects, 6.7%) as compared to the placebo group (8 subjects, 4.2%). All subjects with arthralgia reported severity as mild or moderate and no subject was discontinued from study treatment due to arthralgia in either group. Given that arthralgia was consistently reported more frequently in subjects who received mirikizumab for both trials (i.e., AMAN and AMBG) and potentially associated with mirikizumab treatment, arthralgia will be included in product labeling.

The pathogenesis of arthralgia associated with IL-23 antagonists is not well characterized; however, immune-complex deposition and/or direct antibody binding in joints may play a role in monoclonal antibody-associated arthralgia/arthritis (Chang and Nigrovic 2019). Additionally, arthralgia adverse events have been observed with monoclonal antibodies, including other IL-23 antagonists, in IBD (e.g., Skyrizi [risankizumab]). Arthralgia will be included in the "Adverse Reactions" section of the label.

Headache

Headache was reported more frequently in the mirikizumab treatment group (16 subjects, 4.1%) as compared to placebo (2 subjects, 1.0%). None of headache events were reported as SAEs or severe AE. The subjects with headache reported severity as mild or moderate, and no subject was discontinued from study treatment due to headache in both groups. Although there is no obvious biologic explanation, headache was reported more frequently in mirikizumab group and the risk difference 95% confidence interval excludes zero; therefore,

headache is an important adverse reaction to include in labeling to inform prescribers and subjects.

Rash

Rash AEs were assessed by a group query that included preferred terms of rash, rash macular, rash maculo-papular, rash papular, rash erythematous and rash pruritic (Table 136). Rash AEs were reported more frequently in the mirikizumab group (16 subjects, 4.1%) as compared to placebo (2 subjects, 1.0%). None of rash AEs were reported as SAEs or severe AEs. The subjects with rash reported severity as mild or moderate and no subject was discontinued from study treatment due to rash. Given that rash was reported more frequently in the mirikizumab group, and the risk difference 95% confidence interval excludes zero, there appears to be an increased risk of rash in subjects who received mirikizumab, which supports inclusion in labeling. Additionally, hypersensitivity reactions were observed, the most common of which was rash, further supporting inclusion of rash AEs in labeling.

Herpes viral infections

Herpes viral infections were assessed by a group query that included preferred terms of herpes zoster, oral herpes, genital herpes, herpes simplex, and herpes simplex reactivation. Herpes viral infections were reported more frequently in the mirikizumab group (9 subjects, 2.3%) as compared to placebo (1 subjects, 0.5%). Herpes zoster was the most common herpes viral infection, which occurred in 4 subjects (1.0%) in the mirikizumab group as compared to no subjects in the placebo group. None of the herpes viral infections were reported as SAEs or severe AEs; and no subject discontinued the study due to a herpes viral infection. Given the imbalance of herpes viral infections between mirikizumab and placebo and the potential increased risk of infection due to the immunosuppressive effects of mirikizumab, herpes viral infections will be included in labeling.

Pyrexia, abdominal pain, fatigue, gastroesophageal reflux disease, and diarrhea

The AEs pyrexia, abdominal pain, fatigue, gastroesophageal reflux disease and diarrhea were reported in at least 2% of subjects in the mirikizumab group and greater than placebo; however, these PTs are not recommended to be included in labeling because these AEs were reported in the setting of other AEs (e.g., UC exacerbation, gastroenteritis, gastritis, URI). Additionally, these AEs are commonly associated with UC or are symptoms of UC. This suggests that the AEs of pyrexia, abdominal pain, fatigue, gastroesophageal reflux disease, and diarrhea were likely related to factors other than the study drug.

Hypertension

Hypertension (HTN) was reported in 9 subjects (2.3%) in the mirikizumab group and 1 subject (0.5%) in the placebo group. In general, the blood pressure (BP) measurements corresponding to AEs of HTN were mildly elevated. In the placebo group, 1 subject (0.5%) subject reported potentially clinically significant (i.e., a systolic blood pressure of ≥160 and increase of ≥20

mmHg from baseline) HTN. In the mirikizumab group, 3 subjects (0.8%) subjects reported potentially clinically significant HTN. Of note, the study drug was not discontinued in any subject reported HTN. All but one subject in the mirikizumab group had normal baseline BP and all subjects had normal blood pressure measurements following the elevated measurements. Additionally, the review of BP readings throughout the study for these subjects did not reveal an increased trend of BP for these subjects.

Laboratory Findings

Routine hematology and chemistry clinical laboratory testing were performed at baseline, every 4 weeks until the end of treatment (Week 40), early termination visit, and end of treatment visit during AMBG according to the Schedule of Activities. No clinically meaningful differences between the mirikizumab group and the placebo group were observed in hematology and chemistry parameters except for the hepatic enzyme elevations as discussed in 8.2.6.1.

Vital Signs

Routine vital signs that included temperature, blood pressure, and pulse rate were performed at screening, every 4 weeks until the end of treatment (Week 40), early termination visit, and end of treatment visit during AMBG according to the Schedule of Activities. No clinically significant differences between mirikizumab and placebo were observed.

Electrocardiograms (ECGs)

The potential for mirikizumab to alter QRS, PR, or RR was investigated in 2 clinical pharmacology studies of mirikizumab (AMAA and AMAD). No clinically significant ECG findings or TEAEs related to ECGs were identified in Studies AMAA or AMAD or in other studies comprising the complete integrated clinical pharmacology safety database.

During AMBG, a single 12-lead ECGs were collected at baseline, Week 40, early termination visit, and end of treatment visit according to the Schedule of Activities. The ECG data from these individual study reports did not reveal any clinically significant changes in ECG parameters.

QT

The potential for mirikizumab to alter the QT interval was assessed in studies AMAA and AMAD. No dose relationship in the incidence of QTcF >450 msec was observed, with the incidence in the placebo group comparable with mirikizumab.

Immunogenicity

The frequency of hypersensitivity reactions and injection site reactions did not significantly differ between TE ADA positive and TE ADA negative subjects. Refer to the Clinical Pharmacology Section 6.2.1.3 for further details.

8.2.6. Analysis of Submission-Specific Safety Issues

8.2.6.1. *Hepatotoxicity Safety Assessment*

A risk of hepatotoxicity related to mirikizumab was observed during the safety review. Hepatic safety was evaluated based on treatment emergent hepatic events and analyses for abnormal hepatic laboratory parameters, including those that may indicate drug-induced hepatocellular or cholestatic liver injury. A summary of the drug-induced liver injury analysis is described below. Refer to the drug-induced liver injury consult review (memo by Paul Hayashi, MD, MPH date November 19, 2022) for additional analyses.

There were more aminotransaminase elevations with mirikizumab compared to placebo during AMBG (Table 59). However, there was no difference between mirikizumab and placebo in aminotransaminase elevations during AMAN. Overall, a small number of subjects reported aminotransaminase elevation.

Table 59. Hepatic Enzyme Elevations During AMAN and AMBG

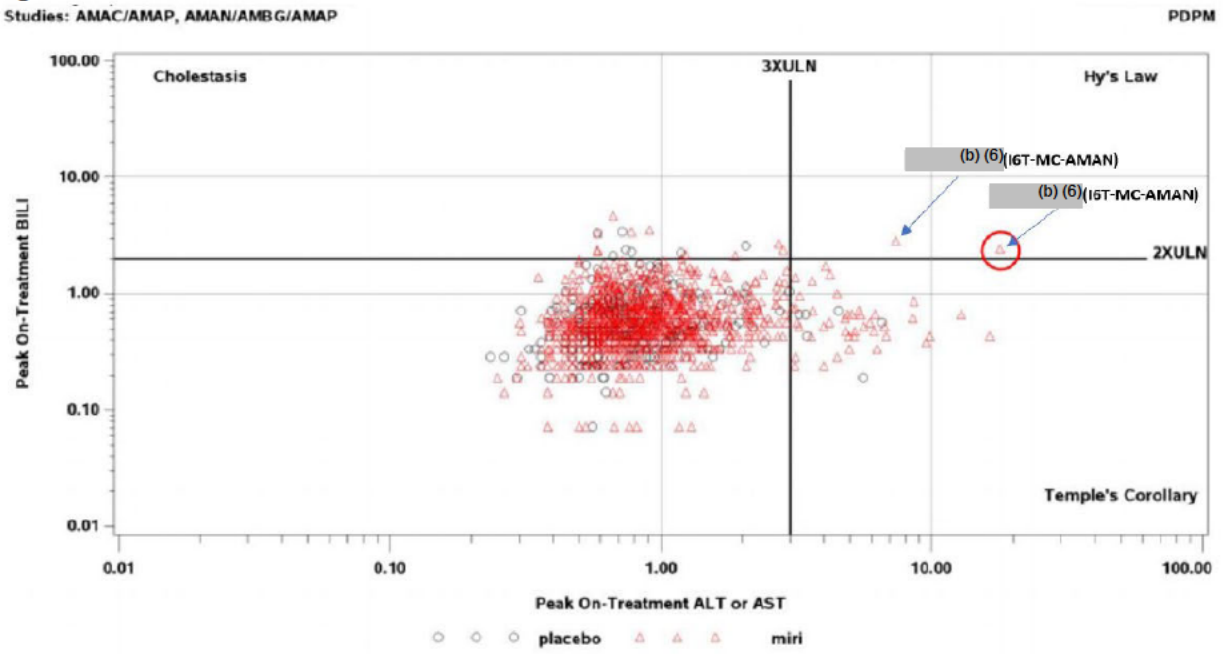
Maximum Postbaseline Category, n (%)	Induction (Weeks 0-12)		Maintenance (Weeks 12-52)	
	placebo IV Q4W N = 321 Nx = 312	miri 300 mg IV Q4W N = 958 Nx = 947	placebo SC Q4W N = 192 Nx = 191	miri 200 mg SC Q4W N = 389 Nx = 387
ALT				
≥3xULN	2 (0.6)	4 (0.4)	1 (0.5)	3 (0.8)
≥5xULN	1 (0.3)	1 (0.1)	0 (0)	3 (0.8)
≥10xULN	0 (0)	0 (0)	0 (0)	0 (0)
AST				
≥3xULN	0 (0)	4 (0.4)	1 (0.5)	4 (1.0)
≥5xULN	0 (0)	2 (0.2)	0 (0)	3 (0.8)
≥10xULN	0 (0)	0 (0)	0 (0)	0 (0)
ALP				
≥2xULN	2 (0.6)	2 (0.2)	4 (2.1)	2 (0.5)
Total Bilirubin				
≥2xULN	1 (0.3)	6 (0.6)	4 (2.1)	2 (0.5)

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; IV = intravenous; miri = mirikizumab; N = number of participants in the safety analysis set; n = number of participants in specified category; Nx = number of participants in the baseline category and that have at least 1 postbaseline measurement; Q4W = once every 4 weeks; SC = subcutaneous; UC = ulcerative colitis; ULN = upper limit of normal.

Source: Applicant's table, from Summary of clinical safety, section 2.7.4.6. Page 112/209

The eDISH plot for all UC trials identified two on-drug subjects in the Hy's Law quadrant (Figure 18). One subject ([redacted] (b) (6)) had alcohol-related liver injury. One subject ([redacted] (b) (6)) met Hy's Law criteria with no alternate etiology and was assessed as likely related to mirikizumab. The subject who met Hy's Law criteria is described in detail below.

Figure 18. eDISH Plot for AMAN, AMBG, and AMAP



- **Subject** (b) (6): A 37-year-old White female (mirikizumab induction nonresponder) with no reported significant risk factors for liver disease experienced hepatic enzymes elevation, cholestatic pruritis, and met criteria for Hy's Law (ALT or AST elevations ≥3× ULN with total serum bilirubin ≥2× ULN). The event occurred 122 days after starting treatment with mirikizumab 300 mg IV Q4W and 29 days since the first dose of open-label mirikizumab 300 mg IV Q4W as part of the open-label extended induction cohort. The subject initially reported pruritus that was treated with cetirizine. At day 136, ALT and AST peaked at an ALT of 609 U/L (17.9 x ULN), AST of 336 U/L (9.9 x ULN), and ALP of 167 U/L (1.6 x ULN). Total bilirubin at that time started to elevate and was 29 µmol/L (1.4 x ULN). Pruritis symptoms persisted and at day 150 the subject's total bilirubin (51 µmol/L; 2.4 x ULN) and ALP (187 U/L; 1.8 x ULN) reached their peak. On study day 85, 56 days since her last dose of 300 mg mirikizumab IV, laboratory values returned to normal without treatment. No alternative etiology was identified, and the event was reported as related to the study drug

Based on the hepatotoxicity analysis, mirikizumab carries a risk of hepatotoxicity likely due to immune-mediated liver injury. Assessment of liver injury in the UC population can be difficult because of frequent use of immunosuppressive agents for treatment of UC that may affect the presentation and course of liver injury by the study drug. However, the increase in elevated aminotransaminases reported in AMBG and the subject who met Hy's Law criteria are likely due to mirikizumab. Additionally, SKYRIZI (risankizumab-rzaa), a monoclonal antibody that shares a mechanism of action with mirikizumab (i.e., binds the p19 subunit of IL-23), has a Warnings and Precautions regarding hepatotoxicity in the treatment of Crohn's disease.

Based on these findings, close monitoring of subjects treated with mirikizumab will be recommended in labeling, a postmarketing requirement will be issued to further assess this risk post-approval of mirikizumab, and the Applicant will be recommended to perform enhanced pharmacovigilance for hepatotoxicity.

8.2.6.2. *Coronavirus Disease (COVID-2019)*

Studies AMAN and AMBG were performed during the COVID-19 pandemic. An analysis of COVID-19 related preferred terms (including "COVID-19," "SARS-Cov-2 test positive," and "COVID-19 pneumonia") was performed to assess the risk of COVID-19 in subjects who received mirikizumab compared to placebo.

The proportion of subjects who reported an AE of COVID-19 were similar between mirikizumab and placebo treatment groups during studies AMAN and AMBG. In study AMAN, 2 subjects (0.6%) in the placebo group, and 3 subjects (0.3%) in the mirikizumab group reported AEs of COVID-19, and in study AMBG, 4 subjects (2.1%) in the placebo group, and 9 subjects (2.3%) in the mirikizumab group reported of COVID-19.

Based on the COVID-19 safety assessment, there did not appear to be an increased risk of COVID-19 infection in subjects who received mirikizumab. COVID-19 was incorporated in the URI grouped term, which will be described in Section 6 of labeling.

8.2.6.3. *Safety in Non-randomized Study Cohorts*

8.2.6.3.1. *Open-label Extended Induction Period*

At the end of AMAN, subjects who did not experience clinical response ("placebo induction nonresponders" or "mirikizumab induction nonresponders") could receive 12 weeks of open-label mirikizumab 300 mg IV Q4W during an open-label extended induction (OLEI) period. The OLEI included 313 mirikizumab induction nonresponders and 148 placebo induction nonresponders. Safety information from the OLEI period was reviewed as supportive safety information; however, the results are limited by the lack of a comparator arm and the open-label nature of the OLEI period.

A summary of AEs reported during the OLEI period is provided in Table 60.

Table 60. Overview of Adverse Events: Open-label Extended Induction Period, Induction Nonresponders (Safety Population)

Event Category	Placebo Induction Nonresponder to Mirikizumab 300 mg IV Q4W N=148 n (%)	Mirikizumab Induction Nonresponder to Mirikizumab 300 mg IV Q4W N=313 n (%)
SAE	4 (2.7)	17 (5.4)
SAEs with fatal outcome	0	0
AE leading to permanent discontinuation of study drug	1 (0.7)	10 (3.2)
TEAEs	43 (29.1)	120 (38.3)
Severe	2 (1.4)	10 (3.2)
Moderate	13 (11.4)	47 (15.0)
Mild	35 (23.6)	92 (29.4)

Source: adae.xpt and adsl.xpt; Software: JMP
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with at least one event; Q4W, once every 4 weeks; SAE, serious adverse event; SC, subcutaneous; TEAE, Treatment emergent adverse event

Serious Adverse Events

Seventeen subjects (5.4%) who were mirikizumab induction nonresponders who received OLEI (i.e., subjects who received up to 24 weeks of mirikizumab 300 mg IV Q4W) reported an SAE, and 4 subjects (2.7%) who were placebo induction nonresponders who received OLEI reported an SAE. The types of SAEs that were reported in mirikizumab nonresponders who received OLEI were similar to those reported during study AMAN.

Adverse Events that Led to Study Discontinuation

Ten subjects (3.2%) subjects who were mirikizumab induction nonresponders who received OLEI, and 1 subject (0.7%) placebo induction nonresponder who received OLEI reported AEs leading to study drug discontinuation. Five AEs reported in 5 subjects (hypersensitivity, immune thrombocytopenia, hepatic enzyme increase, adenocarcinoma of colon, and rectal cancer) that led to study discontinuation were considered an AESIs. These cases are described in detail below:

- Immune thrombocytopenia (ITP): A 28-year-old White male (mirikizumab induction nonresponder) with a 7-year history of UC, experienced a SAE of ITP of severe severity that resulted in hospitalization for rectal bleeding, fatigue and petechial purpura. The SAE of ITP was reported on 104 days after starting treatment with mirikizumab 300 mg IV Q4W (induction) and 14 days after his first and last dose of mirikizumab 300 mg IV Q4W (OLEI). The subject initially reported petechial rash involving his trunk and all 4 extremities as well as increased frequency of bloody diarrhea on Study Day 11. On admission, the subject's platelet count was 3 (10^9/L), and concomitant medications included prednisone 5 mg/day, mesalazine, ferrous gluconate and diphenhydramine for rash on arms and legs. The subject was treated with intravenous immunoglobulin (IVIG) and dexamethasone 40 mg/day. Four days later the platelet count increased to 54

(10^9/L). The subject discontinued the study drug due to the adverse event of ITP. The event was reported as related to the study drug by the investigator; however, the Applicant reassessed the event as “not related” after drug-dependent platelet antibody test showed positive for IgG for non-drug IgG and negative for IgM for non-drug IgM. The lab interpretation of the result was "*Weak positive reactions in patient's serum by flow cytometry in the absence of drug which were not potentiated in the presence of drug. These results indicate the presence of platelet-reactive antibodies and/or immune complexes, but do not support a diagnosis of drug-induced Immune Thrombocytopenia. However, such a diagnosis cannot be completely ruled out*". It is possible that lack of mirikizumab efficacy and worsening UC symptoms may have triggered ITP. Additionally, ITP has been rarely reported in the literature and it resolves with treatment of UC flare. However, given the rapid response to steroid treatment (i.e., 4 days), drug-induced ITP cannot be excluded, and it may be possibly caused by mirikizumab.

- Drug induced liver injury (DILI) /Hy’s Law case: This case was described in more detail in hepatic safety assessment section 8.2.6.1.

- Adenocarcinoma of colon: A 53-year-old Asian male (mirikizumab induction nonresponder) experienced a SAE of "ascending colon tubular adenocarcinoma" of moderate severity that resulted in hospitalization. The SAE of adenocarcinoma of colon was reported 120 days after starting treatment with mirikizumab 300 mg IV Q4W (induction) and 29 days after his first and last dose of mirikizumab 300 mg IV Q4W (OLEI). The subject was asymptomatic at the time of the diagnosis. The event was reported as “not related” to the study drug. Subjects with UC have higher risk for developing colorectal cancer and the risk increases with the duration of the disease. It is unlikely that a relatively short exposure to mirikizumab caused adenocarcinoma of colon in this subject.

- Rectal cancer: A 49-year-old Asian male (mirikizumab induction nonresponder) experienced an SAE of "rectal cancer” of moderate severity that resulted in hospitalization. The SAE was reported 183 days after starting treatment with mirikizumab 300 mg IV Q4W (induction), 92 days after the first dose of mirikizumab 300 mg IV Q4W (OLEI), and 36 days after the last dose of mirikizumab 300 mg IV Q4W (OLEI). The subject reported no improvement in his condition at the time of the diagnosis. Given that rectal cancer was confirmed while receiving mirikizumab, the relationship between the event and mirikizumab could not be excluded. Patients with UC have higher risk for developing colorectal cancer and the risk increases with the duration of the disease. It is unlikely that a relatively short exposure to mirikizumab caused adenocarcinoma of colon/rectum.

- Hypersensitivity: A 29-year-old Asian male (mirikizumab induction nonresponder) experienced hypersensitivity reaction of mild severity that resulted discontinuation of

the study drug. Hypersensitivity reaction was reported on 127 days after starting treatment with mirikizumab 300 mg IV Q4W (induction) and 27 days after the first and the last dose of mirikizumab 300 mg IV Q4W (OLEI). The event reported as "related" to the study drug. Given that the hypersensitivity reaction occurred immediately after infusion, the event was likely related to the study drug.

Treatment Emergent Adverse Event

Overall, the proportion of subjects with at least one TEAE was reported by 38% of subjects in the mirikizumab induction nonresponders and 29% in placebo induction nonresponders. The majority of the TEAEs were mild or moderate in severity. The most common TEAEs were, arthralgia, UC and URI and were similar to study AMAN and AMBG.

Summary Open-label Extended Induction Period

Overall, the reported SAEs and TEAEs were similar to those reported during study AMAN. It appears that prolonged mirikizumab induction treatment may increase the risk of SAEs and AEs that led to study drug discontinuation. However, the comparison between AMAN and the OLEI is limited by the non-randomized and open-label nature of the OLEI.

8.2.6.3.2. *Open-label Maintenance Period*

Subjects who achieved clinical response following the OLEI were eligible to receive open-label 200 mg mirikizumab Q4W SC as part of the Open-label Maintenance (OLM) period for 28 weeks. The OLM period included 171 subjects who were mirikizumab induction nonresponders and 100 subjects who were placebo induction nonresponders. Safety information from the OLM period was reviewed as supportive safety information; however, the results are limited by the lack of a comparator arm, small sample size, and the open-label nature of the OLM period.

A summary of AEs reported during OLM period is provided in Table 61. Six subjects (3.5%) who received OLM in mirikizumab induction nonresponder group reported an SAE, whereas 2 subjects (2.0%) in placebo induction nonresponder group reported an SAE during OLM period.

AEs leading to study drug discontinuation was reported in 4 subjects (2.3 %) in mirikizumab induction nonresponder group and no subject in placebo induction nonresponders.

Table 61. Overview of Adverse Events: Open-label Maintenance Period (Safety Population)

Event Category	Placebo Induction Nonresponders to Mirikizumab 200 mg SC Q4W N=100 n (%)	Mirikizumab Induction Nonresponders to Mirikizumab 200 mg SC Q4W N=171 n (%)
SAE	2 (2.0)	6 (3.5)
SAEs with fatal outcome	0	0
AE leading to permanent discontinuation of study drug	0	4 (2.3)
TEAEs	56 (56.0)	99 (57.9)
Severe	1 (1.0)	4 (2.3)
Moderate	19 (19.0)	35 (20.5)
Mild	44 (44.0)	79 (46.2)

Source: adae.xpt and adsl.xpt; Software: JMP
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with at least one event; Q4W, once every 4 weeks; SAE, serious adverse event; SC, subcutaneous; TEAE, Treatment emergent adverse event

Deaths

The Applicant reported no deaths during the OLM period. One COVID-19 death occurred in a subject who withdrew informed consent and discontinued the OLM period after diagnosis of colonic Kaposi sarcoma. The death is described in detail below:

- COVID-19 death and Colonic Kaposi Sarcoma: A 68-year-old white male subject was hospitalized with a diagnosis of Kaposi's sarcoma of the colon and discontinued study drug and the study 190 days after starting treatment with mirikizumab 300 mg IV Q4W (induction), 98 days since the first dose of mirikizumab 300 mg IV Q4W (OLEI), and 14 days since the first dose of mirikizumab 200 mg SC Q4W (OLM). The subject was negative for Human Immunodeficiency Virus (HIV) and cutaneous lesions of Kaposi sarcoma. The subject withdrew informed consent during an early termination visit and denied providing further information regarding his clinical condition. For this reason, Week 4 follow-up visit following the early termination during the OLM period was not completed. On Study Day 173, 67 days after withdrawing consent and 97 days after his first and final dose of mirikizumab 200 mg SC, the study site was informed of a COVID-19 related death. Given that the subject died of COVID-19 infection 97 days since the last dose of mirikizumab 200 mg SC, it is unlikely that the cause of death was due to mirikizumab. However, patients with sarcoma/cancer may have immunosuppression and increased risk of infection. Because of limited clinical information, causality of Kaposi sarcoma to mirikizumab is not clear.

Serious Adverse Events

In subjects who were mirikizumab induction nonresponders and received OLM “colitis ulcerative” was reported in 2 subjects and the study drug was withdrawn due to lack of efficacy and worsening UC symptoms. The other 4 SAEs reported by 4 subjects were cellulitis, sepsis, Kaposi’s sarcoma (described above), and tooth extraction.

Study Discontinuation

Four (2%) subjects who were mirikizumab induction nonresponders and received OLM (3 subjects with UC exacerbation and 1 subject with Kaposi sarcoma) and no subjects who were placebo induction nonresponders and received OLM reported AEs leading to study drug discontinuation.

Adverse Events of Special Interest

There were 2 SAEs in 2 subjects who were mirikizumab induction nonresponders and received OLM that were considered AESIs. These were cardiovascular events (1 subject with acute coronary syndrome) and malignancy (1 subject with Kaposi sarcoma). Details regarding the Kaposi sarcoma SAE are described above. The SAE acute coronary syndrome is described in detail below:

- Acute coronary syndrome (ACS): A 65-year-old white male subject with a medical history of myocardial infarction (MI) in 2006 and 2011 and two internal thoracic artery bypasses with stent placement in 2011. The subject experienced an SAE of ACS of severe severity that resulted in hospitalization 340 days after starting treatment with mirikizumab 300 mg IV Q4W (AMAN), 249 days since the first dose of mirikizumab 300 mg IV Q4W (OLEI), 158 days since the first dose of mirikizumab 200 mg SC Q4W (OLM), and 25 days since the last dose of mirikizumab 200 mg SC Q4W (OLM). The subject experienced chest pain during a screening stress test and was admitted to the hospital with diagnosis of ACS. During hospitalization, coronary angiography showed 80% stenosis of proximal LAD, and 90% stenosis of the middle circumflex artery and posterolateral artery, and two drug eluting stents were placed. Approximately 5 days later the subject recovered from the event and was discharged from the hospital. The event was reported “related” to the study drug. The subjects continued the study drug. The event of ACS is likely not related to the study drug given long standing history of coronary artery disease, multiple prior MIs, and cardiac procedures.

Treatment Emergent Adverse Events

The most common TEAEs reported during the OLM were generally similar to the TEAEs reported during AMBG and included URI, arthralgia, UC, and headache.

Summary Open-label Maintenance Period

Overall, the safety findings during the OLM period were generally similar to the safety findings of the controlled trials AMAN and AMBG. Additionally, subjects who were mirikizumab induction nonresponders and received OLM reported more SAEs and AEs that led to discontinuation compared to subjects who were placebo induction nonresponders and received OLM. However, the interpretation of the safety results is limited by the non-randomized and open-label nature of the OLM period.

8.2.6.3.3. *Loss of Response Rescue Period*

During AMBG, subjects who experienced a loss of response[11] were eligible to receive "Loss of Response Rescue" (LORR) with open-label mirikizumab 300 mg Q4W IV for 12 weeks. Of note, placebo induction responders who continued on placebo during study AMBG and experienced loss of response received mirikizumab 300 mg IV Q4W for 12 weeks for the first time. During the LORR period, there were 29 placebo induction responders, 42 mirikizumab induction responders randomized to placebo, and 19 mirikizumab induction responders randomized to mirikizumab 200 mg SC during AMBG.

During the LORR period, no deaths were reported. Overall, the SAEs and TEAEs were similar to those observed in AMAN and AMBG, and there were no clear differences between the treatment groups. However, the safety information from the LORR period is limited by the lack of a comparator arm, small sample size, and the open-label nature of the LORR period.

8.2.6.4. *Safety in Integrated Summary of Safety*

The Applicant submitted an integrated summary of safety (ISS), which was an analysis that integrated all trials with UC subjects. The dataset included AMAN and AMBG as well as the phase 2 study AMAC and the open-label extension study AMAP (which enrolled subjects from AMAC, AMAN, and AMBG). Exposure-adjusted analyses are not included in this review, as the majority of subjects in the ISS were from AMAN and AMBG and are described in detail in their respective sections of the review. Additionally, as the safety data beyond 52 weeks were collected during AMAP, an open-label extension study, interpretation of the safety results is limited. Therefore, the review team focused the analysis of the results of the ISS analysis on rare safety events and safety events that might occur with prolonged drug exposure.

Deaths Reported in the UC Mirikizumab Clinical Program

The Applicant reported five deaths during AMAN and AMBG that were described in previous sections (AMAN, Section 8.2.4.1; AMBG, Section 8.2.5.1). The Applicant reported three deaths during AMAP. Two subjects had a pneumonia and one subject had thrombotic thrombocytopenic purpura (TTP).

> COVID-19 pneumonia: A 65-year-old male with medical history of HTN, experienced a SAE of COVID-19 pneumonia. The COVID-19 pneumonia was complicated by respiratory failure, renal failure, and arrhythmia. The subject was receiving mirikizumab 200 mg Q4W SC in AMAP at the time of his death, which occurred 460 days after the first dose

[11] The Applicant defined loss of response as ≥2-point increase from Study AMBG baseline in the combined SF + RB scores and combined SF + RB score of ≥4, on 2 consecutive visits [≥7 days apart, and with confirmation of negative C. difficile testing.

of mirikizumab and 27 days after the last dose of mirikizumab. The investigator considered the event "not related" to mirikizumab. Given that mirikizumab has immunosuppressive effects it may increase the risk of infection, the SAE of COVID-19 pneumonia may be related to mirikizumab.

Pneumonia and "multiple organ dysfunction syndrome": A 62-year-old female with medical history of NAFLD, obesity, and HTN, experienced a SAE of community-acquired pneumonia, which was considered a COVID-19 complication. Pneumonia was complicated by respiratory failure, sepsis, and multiple organ dysfunction. The subject was receiving mirikizumab 200 mg Q4W SC in AMAP at the time of her death, which occurred 892 days after the first dose of mirikizumab and 49 days after the last dose of mirikizumab. The investigator considered the event "not related" to mirikizumab. Given that mirikizumab has immunosuppressive effects it may increase the risk of infection, the SAEs of pneumonia may be related to mirikizumab.

Thrombotic thrombocytopenic purpura (TTP): A 51-year-old male with a 19-year history of TTP (since 2003), experienced a SAE of syncope and convulsions while on vacation in Suriname, and was subsequently hospitalized there for severe hematologic abnormalities. The subject was receiving mirikizumab 200 mg Q4W SC in AMAP at the time of his death, which occurred 834 days after the first dose of mirikizumab and 43 days after the last dose of mirikizumab. The event was reported as "not related" to the study drug by the investigator. This SAE is likely due to worsening underlying chronic disease of TTP; however, relationship between the event and mirikizumab could not be excluded.

Serious Adverse Events, Discontinuation due to Adverse Events and TEAEs in the UC Mirikizumab Clinical Program

The types of SAEs, AEs leading to study treatment discontinuation and TEAEs that were reported in all UC mirikizumab ISS were similar to events reported in the AMAN and AMBG. The most frequently reported SAE was "colitis ulcerative."

Summary Integrated Summary of Safety

Review of the ISS did not identify any clear safety signals distinct from those identified in the safety analyses of AMAN and AMBG.

8.2.6.5. *Safety in Subjects Who Received Mirikizumab for Other Indications*

The Applicant submitted an ISS that included subjects exposed to mirikizumab for other indications. These studies included subjects with moderate-to-severe Crohn's disease (CD) (AMAG, AMAX) and subjects with moderate-to-severe plaque psoriasis (AMBP, AMAF, AMAK, AMAJ, AMAH). The ISS for these indications was reviewed to facilitate identification of rare events or events with a delayed onset that might require further evaluation of mirikizumab

across indications (UC, CD, and psoriasis). Safety information from the ISS was reviewed as supportive safety information; however, the results are limited due to different dose, frequency of administration, duration, and treatment population.

Deaths in Other Indications

There were 12 deaths reported in subjects who received mirikizumab for indications other than UC. Eleven deaths were reported in subjects with psoriasis[12] (4 COVID-19, 3 malignancies [lung cancer, colon cancer, and lymphoma], 2 acute MI, 1 intracranial hemorrhage, and 1 unknown). Of note, all 4 of the COVID-19 related deaths were reported in subjects with multiple risk factors for severe COVID-19 disease (e.g., diabetes mellitus, obesity, smoking, and hypertension). Additionally, 1 death was reported in a subject with CD (sepsis)[13].

Serious Adverse Events, Discontinuation due to Adverse Events and TEAEs in Other Indications

The types of SAEs, AEs leading to study treatment discontinuation and TEAEs that were reported in other indications were generally similar to events reported in subjects with UC. Of note, two SAEs of anaphylactic reaction were reported in two subjects with CD. Both subjects received mirikizumab 1000 mg IV with the lyophilized formulation (not used in the UC clinical program). Both subjects discontinued study treatment. Following these events, mitigations were implemented by the Applicant including slowing of the rate of IV infusion and use of the shelf-stable solution formulation. No anaphylactic reactions were reported in the UC clinical program.

Summary of Safety in Subjects Who Received Mirikizumab for Other Indications

Review of the safety information for subjects who received mirikizumab for other indications did not identify any additional safety signals.

[12] The psoriasis development program has enrolled over 2200 subjects across four clinical trials (AMAJ, AMAK, AMAF, and AMBP).

[13] The Crohn's disease development program has enrolled 191 subjects across 1 clinical trial (AMAG).

8.2.7. Safety Analyses by Demographic Subgroups

Safety analyses were performed for the following demographic subgroups:

- Age (less than 65 years of age and at least 65 years of age)
- Sex (male and female)
- Race (White, Non-White)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)

8.2.7.1. *Safety Analyses by Demographic Subgroups During Induction (AMAN)*

Table 62 shows an overview of SAEs by demographic subgroup and Table 63 shows an overview of TEAEs by demographic subgroup for AMAN.

Table 62. Overview of Serious Adverse Events by Demographic Subgroup, AMAN –12 Week Induction Period (Safety Population)

Characteristic	Mirikizumab 300 mg IV Q4W N=958 n/Ns (%)	Placebo N=321 n/Ns (%)	Risk Difference (%)
Sex, n (%)			
Female	13/367 (3.5)	10/140 (7.1)	-3.6
Male	14/591 (2.4)	7/181 (3.9)	-1.5
Age group, years, n (%)			
<65	25/881 (2.8)	15/301 (5.0)	-2.1
≥65	2/77 (2.6)	2/20 (10.0)	-7.4
Age group ≥75, years, n (%)			
≥75	1/11 (9.1)	0/1 (0)	9.1
Race, n (%)			
American Indian or Alaska Native	1/10 (10.0)	0/2 (0)	10.0
Asian	7/223 (3.1)	4/68 (5.9)	-2.7
Black or African American	0/10 (0)	0/2 (0)	0
Multiple	0/1 (0)	0/2 (0)	0
Native Hawaiian or Other Pacific Islander	0/1 (0)	0/0 (NA)	NA
White	19/704 (2.7)	13/246 (5.3)	-2.6
Missing	0/9 (0)	0/1 (0)	0
Ethnicity, n (%)			
Hispanic or Latino	3/32 (9.4)	0/12 (0)	9.4
Not Hispanic or Latino	17/711 (2.4)	15/248 (6.0)	-3.7
Not Reported	7/215 (3.3)	2/61 (3.3)	0

Source: adae.xpt; Software: R
Risk difference (with 95% confidence interval) is shown between mirikizumab and placebo.
Abbreviations: CI, confidence interval; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; Ns, total number of subjects for each specific subgroup and were assigned to that specific arm; NA, not applicable; Q4W, once every 4 weeks

Table 63 Overview of TEAEs by Demographic Subgroup, AMAN – 12 Week Induction Period (Safety Population)

Characteristic	Mirikizumab 300 mg IV Q4W N=958 n/Ns (%)	Placebo N=321 n/Ns (%)	Risk Difference (%) (95% CI)
Sex, n (%)			
Female	182/367 (49.6)	66/140 (47.1)	2.4
Male	246/591 (41.6)	83/181 (45.9)	-4.2
Age group, years, n (%)			
<65	394/881 (44.7)	137/301 (45.5)	-0.8
≥65	34/77 (44.2)	12/20 (60.0)	-15.8
≥75	3/11 (27.3)	0/1 (0)	NA
Race, n (%)			
American Indian or Alaska Native	7/10 (70.0)	0/2 (0)	NA
Asian	96/223 (43.0)	36/68 (52.9)	-9.9
Black or African American	5/10 (50.0)	1/2 (50.0)	0
Multiple	1/1 (100)	2/2 (100)	0
Native Hawaiian or Other Pacific Islander	0/1 (0)	0/0 (NA)	NA
White	315/704 (44.7)	109/246 (44.3)	0.4
Missing	4/9 (44.4)	1/1 (100)	NA
Ethnicity, n (%)			
Hispanic or Latino	14/32 (43.8)	5/12 (41.7)	2.1
Not Hispanic or Latino	303/711 (42.6)	112/248 (45.2)	-2.5
Not Reported	111/215 (51.6)	32/61 (52.5)	-0.8

Source: adae.xpt; Software: R
Risk difference (with 95% confidence interval) is shown between mirikizumab and placebo.
Abbreviations: CI, confidence interval; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; Ns, total number of subjects for each specific subgroup and were assigned to that specific arm; NA, not applicable; Q4W, once every 4 weeks

Overall, there were no notable differences between the treatment groups within the demographic subgroups. Although no discernable differences were observed, the interpretability of subgroup analyses were limited due to the small number of non-White subjects, subjects aged 65 years of age or older, and Hispanic or Latino subjects.

8.2.7.2. *Safety Analyses by Demographic Subgroups During Maintenance (AMBG)*

Table 64 shows an overview of SAEs by demographic subgroup and Table 65 shows an overview of TEAEs by demographic subgroup for AMBG.

Table 64. Overview of Serious Adverse Events by Demographic Subgroup, AMBG – Maintenance Period (Safety Population)

Characteristic	Mirikizumab Responders to Mirikizumab 200 mg SC Q4W N=389 n/N_s (%)	Mirikizumab Responders to Placebo N=192 n/N_s (%)	Risk Difference (%) (95% CI)	Placebo Responders to Placebo N=135 n/N_s (%)
Sex, n (%)				
Female	6/160 (3.8)	7/78 (9.0)	-5.2	2/61 (3.3)
Male	7/229 (3.1)	8/114 (7.0)	-4.0	5/74 (6.8)
Age group, years, n (%)				
<65	10/357 (2.8)	15/181 (8.3)	-5.5	6/126 (4.8)
≥65	3/32 (9.4)	0/11 (0)	9.4	1/9 (11.1)
Age group ≥75, years, n (%)				
≥75	2/4 (50.0)	0/1 (0)	NA	0/0 (NA)
Race, n (%)				
American Indian or Alaska Native	0/3 (0)	0/1 (0)	0	0/2 (0)
Asian	3/93 (3.2)	3/51 (5.9)	-2.7	1/28 (3.6)
Black or African American	0/6 (0)	0/0 (NA)	NA	0/0 (NA)
Multiple	0/0 (NA)	0/0 (NA)	NA	1/2 (50.0)
White	10/285 (3.5)	12/138 (8.7)	-5.2	5/103 (4.9)
Missing	0/2 (0)	0/2 (0)	0	0/0 (NA)
Ethnicity, n (%)				
Hispanic or Latino	0/17 (0)	0/3 (0)	0	0/2 (0)
Not Hispanic or Latino	10/292 (3.4)	11/145 (7.6)	-4.2	6/115 (5.2)
Not Reported	3/80 (3.8)	4/44 (9.1)	-5.3	1/18 (5.6)

Source: adae.xpt; Software: R

Risk difference (with 95% confidence interval) is shown between mirikizumab responders to mirikizumab and mirikizumab responders to placebo.

Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; N_s, total number of subjects for each specific subgroup and were assigned to that specific arm; NA, not applicable; Q4W, once every 4 weeks; SC, subcutaneous

Table 65. Overview of Adverse Events by Demographic Subgroup, Study AMBG – Maintenance Period (Safety Population)

Characteristic	Mirikizumab Responders to Mirikizumab 200 mg SC Q4W N=389 n/N_s (%)	Mirikizumab Responders to Placebo N=192 n/N_s (%)	Risk Difference (%)	Placebo Responders to Placebo N=135 n/N_s (%)
Sex, n (%)				
Female	108/160 (67.5)	54/78 (69.2)	-1.7	30/61 (49.2)
Male	143/229 (62.4)	78/114 (68.4)	-6.0	52/74 (70.3)
Age group, years, n (%)				
<65	233/357 (65.3)	121/181 (66.9)	-1.6	78/126 (61.9)
≥65	18/32 (56.2)	11/11 (100)	-43.8	4/9 (44.4)
Age group ≥75, years, n (%)				
≥75	4/4 (100)	1/1 (100)	0	0/0 (NA)
Race, n (%)				
American Indian or Alaska Native	2/3 (66.7)	1/1 (100)	-33.3	1/2 (50.0)
Asian	65/93 (69.9)	37/51 (72.5)	-2.7	11/28 (39.3)
Black or African American	4/6 (66.7)	0/0 (NA)	NA	0/0 (NA)
Multiple	0/0 (NA)	0/0 (NA)	NA	2/2 (100)
White	180/285 (63.2)	93/138 (67.4)	-4.2	68/103 (66.0)
Missing	0/2 (0)	1/2 (50.0)	NA	0/0 (NA)
Ethnicity, n (%)				
Hispanic or Latino	7/17 (41.2)	3/3 (100)	NA	1/2 (50.0)
Not Hispanic or Latino	178/292 (61.0)	98/145 (67.6)	-6.6	70/115 (60.9)
Not Reported	66/80 (82.5)	31/44 (70.5)	12.0	11/18 (61.1)

Source: adae.xpt; Software: R
Risk difference (with 95% confidence interval) is shown between mirikizumab responders to mirikizumab and mirikizumab responders to placebo.
Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; N_s, total number of subjects for each specific subgroup and were assigned to that specific arm; NA, not applicable; Q4W, once every 4 weeks; SC, subcutaneous

Overall, there were no notable differences between the treatment groups within the demographic subgroups. Although no discernable differences were observed, the interpretability of subgroup analyses were limited due to the small number of non-White subjects, subjects aged 65 years of age or older, and Hispanic or Latino subjects.

8.2.8. Specific Safety Studies/Clinical Trials

No specific safety studies or clinical trials were performed.

8.2.9. Additional Safety Explorations

8.2.9.1. *120-Day Safety Update Report*

A 120-day safety update report (SUR) was provided by the Applicant that incorporated safety information and additional integrated cumulative clinical study safety data through March 22, 2022. The ongoing studies that were included in the SUR included open-label extension studies

AMAH (psoriasis), AMAP (ulcerative colitis), and AMAX (Crohn's disease). The review focused on the data available in subjects with UC to evaluate for rare events or events that may have a longer latency period.

Deaths

The Applicant reported one death in the SUR, which is described below.

- Worsening of coronary heart disease: A 63-year-old male with medical history of psoriasis, DM-2, CVA and CAD died of worsening of coronary heart disease on study day 1093. The participant was in study AMAH (an open-label extension study for subjects with moderate-to-severe plaque psoriasis) and receiving mirikizumab 250 mg SC Q8W.

Serious Adverse Events

Twenty additional subjects reported at least 1 SAE in the SUR. The most frequently reported SAEs were COVID-19 (3 subjects) and atrial fibrillation (4 subjects described in AESI section). No other SAEs were reported in more than a single subject.

Discontinuation due to Adverse Events

Eighteen additional subjects discontinued study treatment due to an AE in the SUR. The most frequently reported AE leading to study treatment discontinuation was "colitis ulcerative" and occurred in 11 subjects. The other AEs, each occurred in 1 subject were hematochezia, meningitis, psoriasis, multiple organ dysfunction due to pneumonia, TTP, and cerebellar stoke. AEs that led to discontinuation that were considered AESI (hematochezia, meningitis, and cerebellar stroke) are described below.

Adverse Events of Special Interest

Infections and Opportunistic infections

- Opportunistic infections: Four more subjects reported herpes zoster in the SUR. All were reported mild (3 subjects) and moderate (1 subject) in severity and single dermatomal and no subjects were discontinued from study treatment.
- Serious infections: Six more subjects reported at least 1 serious infection in the SUR. The most frequent serious infection was COVID-19 (4 subjects). All subjects with a serious infection of COVID-19 had at least 1 risk factor for adverse clinical outcomes, including age > 65 year, BMI>25, DM, or CVD. Previously unreported serious infection PTs include meningitis (1 subject), and sinusitis (1 subject).
- Meningitis: A 77-year-old Asian female was experienced SAE of "meningitis" that resulted in hospitalization, which was 439 days after starting treatment with mirikizumab 300 mg IV Q4W (induction), 348 days since the first dose of mirikizumab 200 mg SC Q4W (extension), and 17 days since the last dose of mirikizumab 200 mg SC

Q4W (extension). The subject experienced headache, nausea, loss of appetite and fever. Based on the result of cerebrospinal fluid, the subject was diagnosed with meningitis caused by sphenoid sinusitis. Emergency endoscopic sinus surgery was performed for sphenoid sinusitis and bacterial culture reported “staphylococcus aureus”. The subject was treated with intravenous antibiotic (meropenem hydrate) and recovered. The event was reported “related” to the study drug and the treatment discontinued.

These opportunistic and serious infections may possibly be related to the study treatment, given the study drug has immunosuppressive effects and may have the potential to increase risk for severe infection/opportunistic infections. This risk will be addressed in labeling with a Warnings and Precautions.

Cerebrovascular and cardiovascular events

- Cerebellar ischemic stroke: A 33-year-old white male with mildly elevated total cholesterol (222 mg/dl) experienced SAE of “right-sided cerebellar syndrome" that resulted in hospitalization, which was 594 days after starting treatment with mirikizumab 300 mg IV Q4W (induction), 451 days since the first dose of mirikizumab 200 mg SC Q4W (extension), and 21 days since the last dose of mirikizumab 200 mg SC Q4W (extension). No other relevant medical history, pre-existing condition, or family history of cerebro or cardiovascular disease were reported. The subject reported having dizziness, confused speech, paresis of the right hand at the time of diagnosis. Magnetic resonance imaging (MRI) showed “ischemic changes in the upper cerebellar lobe”. The subject was treated medically with atorvastatin, mesalazine and acetylsalicylic acid. Approximately 9 days later the subject recovered from the event. The event was reported “related” to the study drug and mirikizumab was discontinued. The causal role of mirikizumab cannot be excluded, and it may possibly be related to the study treatment. However, subjects with UC are at increased risk of cerebrovascular disease and this was the only cerebrovascular event reported in mirikizumab studies. Analysis of the AESI of data of the controlled studies did not show significant changes between treatment and placebo arm for the AESI of “cerebro-cardiovascular events.”
- Atrial fibrillation: Four subjects with history of atrial fibrillation reported SAE of “atrial fibrillation” All were reported as “not related” to the study drug. These events were likely not related to the study drug given that the subjects had known history of atrial fibrillation.

AESIs of malignant tumors, injection site reactions, depression, hypersensitivity reactions, including anaphylaxis, and hepatic reactions that were reported in SUR were similar to events reported in the AMAN and AMBG.

Treatment Emergent Adverse Events

Fifty-eight additional subjects (not previously described) reported at least 1 TEAE in the SUR. The most frequently reported PTs were nasopharyngitis, COVID-19, upper respiratory tract

infection, colitis ulcerative, arthralgia, and back pain. Most additional events were mild or moderate in severity. These TEAEs are generally similar to those reported during AMAN and AMBG.

Summary of the 120-Day Safety Update Report

Overall, the safety findings from the 120-day SUR were consistent with those from the initial UC BLA application and support the proposed labeling. There were no clinically meaningful changes in the types of AEs or other safety findings associated with longer durations of mirikizumab exposure, including AEs of special interest.

8.2.9.2. *Human Reproduction and Pregnancy*

Pregnancy

Pregnant women were excluded from clinical trials with mirikizumab during the clinical development program. At the time of the 120-day SUR, a total of 34 pregnancy exposure cases were reported with outcomes including: normal livebirth (7, 20.6%), preterm birth (1, 2.9%), ongoing (11, 32.4%), elective abortion (6, 17.6%), spontaneous abortion (5, 14.7%), and unknown (4, 11.8%). Overall, these limited available human data are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Animal reproduction studies do not indicate an increased risk for embryo-fetal toxicity. Therefore, subsection 8.1 of mirikizumab labeling will include a Risk Summary statement to summarize the limited available human pregnancy exposure data and the lack of reproductive toxicity findings in animal studies at exposures up to 60 times the maximum recommended human dose.

Considering mirikizumab is an IgG4 monoclonal antibody, subsection 8.1 will include language similar to the Agency's approach to PLLR labeling for other monoclonal antibodies. Pregnancy labeling will include information under Risk Summary and Clinical Considerations about the active transport of monoclonal antibodies across the placenta, the potential for immunosuppression in the in-utero exposed infant, and the risks and benefits that should be considered prior to administration of live vaccines. Live vaccines should be delayed for a minimum of 5 half-lives after birth in infants exposed to mirikizumab in utero.

Mirikizumab is indicated for a condition that would be expected to be seen in females of reproductive potential (including during pregnancy), and current data are insufficient to inform women regarding mirikizumab use during pregnancy. Therefore, postmarketing requirements will be issued for the Applicant to conduct a pregnancy exposure registry and a complimentary study of a different design (such as a claims database study). Language regarding the pregnancy exposure registry should be added to subsection 8.1 and section 17 of labeling once the study protocol has been finalized and registry contact information established.

Lactation

Lactating women were excluded from clinical trials with mirikizumab. At the time of the 120-day SUR, no lactation exposure cases were reported. There are no available data on the presence of mirikizumab in human milk, the effects on the breastfed infant, or the effects on milk production. The molecular weight for mirikizumab is 147,000 Daltons, and according to breastfeeding experts, the amount in human milk, if any, is expected to be low. Considering mirikizumab is an IgG4 monoclonal antibody, subsection 8.2 of mirikizumab labeling will include language similar to the Agency's approach to PLLR labeling for other monoclonal antibodies. Lactation labeling should include information under Risk Summary that "maternal IgG and monoclonal antibodies are known to be present in human milk" as well as the following risk/benefit statement: "the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for mirikizumab and any potential adverse effects on the breastfed infant from mirikizumab or from the underlying maternal condition."

Mirikizumab is indicated for a condition that would be expected to be seen in females of reproductive potential (including during lactation), and there are no current data available to inform women regarding mirikizumab use during lactation. Therefore, a PMR will be issued for the Applicant to conduct a clinical lactation study with mirikizumab to inform labeling.

Females and Males of Reproductive Potential

There are no available human data on the effects of mirikizumab on male or female fertility. Animal fertility studies do not indicate any adverse effects. In addition, animal reproduction studies do not indicate an increased risk for embryo-fetal toxicity. Therefore, subsection 8.3 will be omitted from labeling for mirikizumab.

8.2.9.3. *Pediatrics and Assessment of Effects on Growth*

No pediatric data was submitted as part of this BLA. At the time of this review, pediatric trials were ongoing. Refer to Section 13 Postmarketing Requirements and Commitments.

8.2.9.4. *Overdose, Drug Abuse Potential, Withdrawal, and Rebound*

There were no reports of overdose (accidental overdose or intentional overdose) in the submitted application. The potential for abuse, withdrawal, and rebound with mirikizumab have not been evaluated in clinical studies; however, risk is not suspected based on the mechanism of action. There were no reports of abuse in the clinical trial setting.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Mirikizumab is not currently approved in any country.

Expectations on Safety in the Postmarket Setting

Postmarket data will be collected to further evaluate the risk of drug-induced liver injury. Enhanced pharmacovigilance of liver injury and an observational study to assess the incidence of severe acute liver injury in patients with UC will be conducted. Additional data are also needed to characterize the safety of mirikizumab in special populations (such as pregnant and lactating women). Refer to Section 13 for details regarding postmarketing requirements and commitments agreed upon with the Applicant.

8.3. Conclusions and Recommendations

The safety profile of mirikizumab for the treatment of moderately to severely active UC was appropriately characterized within the UC development program and supports approval of this original BLA. The safety database and overall exposure to the drug in UC subjects was reasonable and comparable to what has been utilized to support the approval of other drugs for UC. Feasibility limits the size and scope of the safety database and therefore some residual uncertainty exists, particularly around potential AEs with long latency periods. During the induction period (AMAN), the most common adverse reactions included upper respiratory tract infection, and arthralgia. Additionally, hepatic enzyme elevation, opportunistic infections, and hypersensitivity reactions were reported more frequently in mirikizumab treatment group. During the maintenance period (AMBG), the most common adverse reactions included upper respiratory tract infection, injection site reactions, arthralgia, headache, and rash. Similar to AMAN, hepatic enzyme elevations and opportunistic infections were reported more frequently in mirikizumab treatment group. Signals of potential hepatotoxicity and a case of DILI were identified. The label contains information for providers to monitor patients' liver enzymes, and to discontinue use if clinically significant elevations occur, or if clinically apparent drug-induced hepatic injury occurs. Further evaluation of this safety signal will occur via a postmarketing requirement to be issued at the time of approval and enhanced pharmacovigilance. The available data are insufficient to inform mirikizumab-associated risk during pregnancy and lactation; therefore, postmarketing requirements related to pregnancy and lactation will be issued at the time of approval.

Mirikizumab demonstrated efficacy in inducing clinical remission after 12 weeks of treatment with 300 mg IV injection Q4W, and maintaining remission over 40 weeks (at the dosage of 200 mg SC injection Q4W). Efficacy was also demonstrated on multiple clinically relevant secondary endpoints at Week 12 and Week 52 (Week 40 of the maintenance study). Overall, the results from the analyses of the primary and multiple multiplicity-controlled secondary endpoints were statistically significant and provided substantial evidence of effectiveness for mirikizumab in treating adult patients with moderately to severely active UC.

Despite the demonstration of safety and effectiveness of mirikizumab, this BLA is not recommended for approval in its present form until the abovementioned facility deficiencies are satisfactorily resolved. Thus, a Complete Response (CR) action is recommended (refer to Section 4.2).

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9. Advisory Committee Meeting and Other External Consultations

An Advisory Committee meeting was not held to discuss this application.

10. Pediatrics

This program received Orphan Drug Designation for the treatment of ulcerative colitis in pediatric patients on June 15, 2017, and is therefore exempt from Pediatric Research Equity Act (PREA) requirements. Although the requirements for pediatric study under PREA do not apply, moderately to severely active UC occurs in pediatric patients and can lead to significant morbidity. Additionally, the Applicant has initiated trials in pediatric subjects, as described below. The Division recognizes the need for additional therapies to treat moderately to severely active UC in pediatric patients. The Applicant agreed to complete the following ongoing and planned trials in pediatric subjects with UC as post-marketing commitments (PMCs). Additional negotiations related to trial design will occur during the review of the protocols. Refer to Section 13 for the proposed PMCs.

- I6T-MC-AMBU (AMBU) – "A phase 2, multicenter, open-label PK study of mirikizumab in pediatric subjects 2 years to less than 18 years of age with moderately to severely active ulcerative colitis."
- I6T-MC-AMBA (AMBA) – "A phase 3, multicenter, open-label study to investigate the efficacy, PK, and safety of mirikizumab in subjects 2 years to less than 18 years of age with moderately to severely active ulcerative colitis."
- I6T-MC-AMAZ (AMAZ) – "A master protocol for a phase 3, multicenter, open-label, long-term extension study to evaluate the long-term efficacy and safety of mirikizumab in children and adolescents with moderate to severely active ulcerative colitis or Crohn's disease."

11. Labeling Recommendations

11.1. Prescription Drug Labeling

The following is a summary of the high-level changes to the US prescribing information that were negotiated during the review cycle. Labeling negotiations will be continued at the time of resubmission.

Section 1: Indications and Usage:

- Added indication of moderately to severely active UC in adults, as proposed by the Applicant.

Section 2: Dosage and Administration:

- Added recommendations to evaluate patients for tuberculosis prior to initiating treatment (See Warnings and Precautions below) and to obtain liver enzymes and bilirubin levels prior to initiating treatment with mirikizumab.
- The recommended dosage regimen for induction was limited to 8 weeks of treatment (i.e., 300 mg by intravenous infusion over at least 30 min at Weeks 0, 4, and 8). (b) (4)
- The recommended maintenance dosage regimen starts at Week 12 (200 mg administered by subcutaneous injection every 4 weeks). (b) (4)

Section 3: Dosage Forms and Strengths:

- (b) (4) Refer to the DMEPA review by Matthew Barlow and Jason Flint in DARRTS dated December 19, 2022.

Section 4: Contraindications:

- A contraindication in patients with a history of serious hypersensitivity reaction to mirikizumab or any of the excipients was added based upon two cases of anaphylaxis reported in the clinical trials for CD (Section 8.2.6.4). Although the two cases occurred in subjects with CD that received a higher dose of the lyophilized powder formulation of mirikizumab and not the to-be-marketed formulation, it is unclear that the risk to subjects with UC is less given that hypersensitivity reactions were observed more frequently in mirikizumab treatment groups compared to placebo during AMAN and AMBG.

Section 5: Warnings and Precautions:

- Added a subsection for tuberculosis (TB) to align with other interleukin-23 products. The W/P states to evaluate patients for TB infection prior to administering mirikizumab, to not administer mirikizumab to patients with active TB infection, to initiate treatment of latent TB prior to administering mirikizumab, and to monitor patients for signs and symptoms of active TB during and after treatment. A statement was added that subjects in the clinical trials were excluded if they had evidence of active TB, a past history of active TB, or were diagnosed with latent TB at screening.
- A subsection on "(b) (4) proposed by the Applicant was revised to "hepatotoxicity" and description of the case of drug-induced liver injury (Section 8.2.6.1) was added along with recommendations to evaluate liver enzymes and bilirubin at baseline and for at least 24 weeks of treatment, followed by monitoring according to routine patient management. For patients with evidence of liver cirrhosis, other treatment options should be considered.

Section 6.1: Adverse Reactions, Clinical Trials Experience

- The adverse reactions in the induction study UC-1 (AMAN) reported in at least 2% of subjects with mirikizumab and at a higher rate than placebo were included in a table of common adverse reactions for induction, and includes respiratory tract infections (URIs) and arthralgia. Additionally, a description of the infusion-related hypersensitivity reactions that occurred during UC-1 was added following the table.
- The adverse reactions in the maintenance study UC-2 (AMBG) reported in at least 2% of subjects with mirikizumab and at a higher rate than placebo were included in a table of common adverse reactions for maintenance, and includes URIs, injection site reactions, arthralgia, rash, headache, and herpes viral infections.
- Description of infections, including serious infections, and hepatic enzyme elevations observed during UC-1 and UC-2 were included in text following the tables as types of specific adverse reactions.

Section 7: Drug Interactions

- This section was not included because there are no clinically relevant drug interactions (observed or predicted) to describe.

Section 8: Use in Specific Populations

- In Section 8.1, Pregnancy, added a description of a pregnancy registry to monitor outcomes in women exposed to mirikizumab during pregnancy. Refer to the Maternal Health Review in DARRTS by Kristie Baisden dated December 19, 2022.
- Also added a subsection within Section 8.1 about clinical considerations (i.e., disease-associated maternal and embryo/fetal risk and fetal/neonatal adverse reactions).

- In Section 8.2, Lactation, added information that endogenous maternal IgG and monoclonal antibodies are transferred in human milk and the effects of local/systemic exposure in the breastfed infant are unknown.
- In Section 8.5 Geriatric Use, added information that the clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger adult subjects.

Section 10: Overdosage

- This section was not included because there are no findings of human toxicity in patients who experienced overdosage.

Section 12: Clinical Pharmacology

- Mechanism of Action: The mechanism of action of mirikizumab is described as selective binding to the p19 subunit of human IL-23 inhibiting its interaction with the receptor. (b) (4)
- Pharmacodynamics: Added a statement about the positive relationship between mirikizumab concentrations and rates of clinical remission/response based upon the E-R analyses from AMAN and AMBG.
- Pharmacokinetics:
    - A subsection describing the effects of body weight on mirikizumab concentrations was added. For subjects weighing 90 kg or greater, the average concentration of mirikizumab following induction dosing (300 mg IV) was 20% lower than subjects weighing less than 90kg. Similarly, the average concentration of mirikizumab following maintenance dosing (200 mg SC) was 38% lower in subjects weighing 90 kg or greater compared to subjects weighing less than 90 kg. However, the rate of clinical remission and clinical response did not differ significantly.
    - Results of population PK analysis and a clinical drug-drug interaction study were added (neither of which showed a clinically relevant effect on mirikizumab or the concomitant drugs).
- Immunogenicity: A description of the development of anti-mirikizumab antibodies was provided. There are insufficient data in subjects who developed anti-drug antibodies (ADA) to assess whether observed ADA-associated pharmacokinetic changes reduced effectiveness of mirikizumab (Section 6.3.1.4). No clinically significant effect of ADA on safety of mirikizumab was identified.

Section 14: Clinical Studies

- Baseline demographic information was added for UC-1 and UC-2.
- (b) (4) The review team

recommended labeling results from the FDA Preferred Analysis Population (i.e., subjects with an mMS of 5 to 9). Section 14 was updated to reflect the results in this population.

- (b) (4) The review team recommended labeling only "alternate clinical remission" but renaming it "clinical remission" because the definition for "alternate clinical remission" is consistent with FDA's preferred definition of "clinical remission."
- The following endpoints were included in the efficacy table for UC-1:
    - Clinical remission - based on mMS is defined as: stool frequency subscore = 0 or 1, rectal bleeding subscore = 0, and centrally read endoscopy subscore = 0 or 1 (excluding friability).
    - Clinical response - defined as a decrease in the mMS of ≥2 points with ≥30% decrease from baseline, and either a decrease of ≥1 point in the rectal bleeding subscore from baseline or a rectal bleeding subscore of 0 or 1.
    - Endoscopic improvement - defined as a centrally read endoscopy subscore of 0 or 1 (excluding friability).
    - Histologic-endoscopic mucosal improvement - defined as achieving both endoscopic improvement (centrally read endoscopy subscore of 0 or 1, excluding friability) and histologic improvement (neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue based on the Geboes scoring system).
- (b) (4) A description of bowel urgency based on achieving an Urgency NRS of 0 or 1 was added after the efficacy endpoint tables (refer below).
- (b) (4)
- The following endpoints were included in the efficacy table for UC-2:
    - Clinical remission - based on mMS is defined as: stool frequency subscore = 0 or 1, rectal bleeding subscore = 0, and centrally read endoscopy subscore = 0 or 1 (excluding friability).
    - Endoscopic improvement - defined as a centrally read endoscopy subscore of 0 or 1 (excluding friability).
    - Maintenance of clinical remission in patients who achieved clinical remission at Week 12 -

  - Corticosteroid-free clinical remission - defined as clinical remission at Week 40 and no corticosteroid use for ≥12 weeks prior to Week 40 assessment.
  - Histologic-endoscopic mucosal improvement - defined as achieving both endoscopic improvement (centrally read endoscopy subscore of 0 or 1, excluding friability) and histologic improvement (no neutrophils in crypts or lamina propria, no crypt destruction, and no erosions, ulcerations, or granulation tissue based on the Geboes scoring system).
- (b) (4) the endpoint (b) (4) "histologic-endoscopic mucosal improvement" (b) (4) Therefore, the same term was used in the table, but the definition of the two terms were distinguished with footnotes.
- Following the efficacy table for UC-2, the results of the Urgency NRS endpoint defined as the proportion of subjects with an Urgency NRS of 0 or 1 were added under a new subsection "Bowel Urgency." The proportion of patients with Urgency NRS of 0 or 1 was reported for UC-2, (b) (4) the endpoint was multiplicity-controlled for UC-2 only.
- (b) (4)

Section 17: Patient Counseling Information

- This section was updated to reflect information in the Full Prescribing Information. Specifically, subsections for tuberculosis and pregnancy (availability of a pregnancy exposure registry) were added.

11.2. Medication Guide

A Medication Guide was proposed by the Applicant and deemed necessary by the review team for mirikizumab to convey information necessary to inform patients of the risk of serious adverse reactions.

Updates were made to the proposed Medication Guide, and the Instructions for Use for the PFP, to be consistent with the prescribing information.

12. Risk Evaluation and Mitigation Strategies (REMS)

The risks of mirikizumab are adequately communicated in the prescribing information. A REMS is not considered necessary at this time.

13. Postmarketing Requirements and Commitments

The following postmarketing requirements and commitments were negotiated during the review cycle. Additional negotiations, including the timelines for final protocol submission, trial completion, and final report submission; will be continued at the time of resubmission.

4409-1

Perform a lactation trial (milk only) in lactating women who have received mirikizumab regardless of indication to assess concentrations of mirikizumab in breast milk using a validated assay and to assess the effects on the breastfed infant. A mother-infant pair study may be required in the future depending on the results of this milk-only study.

4409-2

Conduct a prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to mirikizumab-containing products regardless of indication during pregnancy to an unexposed control population. The registry should be designed to detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age births, preterm births, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, neonatal deaths, and infections, will be assessed through at least the first year of life.

4409-3

Conduct an additional pregnancy study that uses a different design from the prospective pregnancy registry established to fulfill postmarketing requirement 2 (for example a retrospective cohort study using claims or electronic medical record data with outcome validation or a case-control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm births in women exposed to mirikizumab-containing products regardless of indication during pregnancy compared to an unexposed control population.

4409-4

Conduct an observational study to assess the incidence of severe acute liver injury in adults with moderately to severely active ulcerative colitis who are exposed to

mirikizumab, relative to other therapies used to treat ulcerative colitis. Compare rates (per person-time) or risks (proportion of patients with a minimum amount of follow-up). Describe and justify the choice of appropriate comparator population(s). Specify concise case definition for severe liver injury and validation of algorithm(s) to identify severe liver injury in the proposed data source. For the mirikizumab exposed and comparator(s) cohorts, clearly define the study drug initiation period and any exclusion and inclusion criteria. Ensure that the data source allows for average follow-up for at least 1 year. Specify a minimum sample size and justify the precision of the estimate achievable with the proposed study.

4409-5

Complete the ongoing phase 2 study to evaluate the safety, pharmacokinetics (PK), pharmacodynamics (PD), and clinical response to mirikizumab in pediatric patients 2 to 17 years of age with moderately to severely active ulcerative colitis.

4409-6

Conduct a one-year, randomized trial to evaluate the safety, efficacy, and pharmacokinetics of mirikizumab in pediatric patients 2 to 17 years of age with moderately to severely active ulcerative colitis.

4409-7

Complete the ongoing open-label, long-term extension study to evaluate the safety and efficacy of mirikizumab in pediatric patients 2 to 17 years of age with moderately to severely active ulcerative colitis.

14. Division Director (Clinical) Comments

I concur with the recommendation of the review team to issue a Complete Response letter for BLA 761279 due to deficiencies identified during pre-license inspection of the drug product manufacturing facility listed in the application.

Mirikizumab-mrkz is a humanized immunoglobulin G4 (IgG4) monoclonal antibody that binds to the p19 subunit of interleukin 23 (IL-23), a cytokine that mediates intestinal mucosal inflammation and whose signaling has been implicated in the pathogenesis of inflammatory bowel diseases, including ulcerative colitis. The recommended induction dosage for the treatment of moderately to severely active ulcerative colitis in adults is 300 mg administered by intravenous infusion at Weeks 0, 4, and 8; the recommended maintenance dosage is 200 mg administered by subcutaneous injection (give as two consecutive injections of 100 mg each) at Week 12, and every 4 weeks thereafter.

As discussed in detail in this multi-disciplinary review, the benefits of mirikizumab outweigh the risks for the indication sought. The submission included one adequate and well-controlled 12-week induction trial (AMAN) that provided the scientific equivalent of two clinical investigations, and one adequate and well-controlled 40-week maintenance trial (AMBG), for a total treatment duration of 52 weeks; both trials achieved statistical significance. The primary endpoint was clinical remission, which was determined using the modified Mayo score (mMS), at the end of each trial. The results of secondary analyses support the primary efficacy results. The most common adverse reactions observed in clinical trials include upper respiratory tract infections, injection site reactions, arthralgia, rash, headache, and herpes viral infection, and are comparable to those associated with approved biologics, including other agents that target IL-23, for the treatment of inflammatory bowel diseases. Of note, there was one case of drug-induced liver injury that met Hy's Law criteria in a subject who received mirikizumab; thus, a subsection on hepatotoxicity will be added to the Warnings and Precautions section of the prescribing information, if approved.

Although the efficacy and safety data contained in this BLA support approval, the drug product manufacturing facility, Eli Lilly and Company, Indianapolis, Indiana, was determined to be unacceptable to support the approval of this BLA. The pre-license inspection identified several deficiencies that were conveyed to the representative of the facility. Because the data submitted in this application are not sufficient to support a conclusion that the manufacture of mirikizumab is well-controlled and will lead to a product that is pure and potent, OPQ recommends that a Complete Response letter be issued. Since the Applicant does not have an alternative drug product manufacturing facility for this BLA, an approval action of this application cannot be taken until the Applicant satisfactorily resolves the deficiencies observed during the inspection of the drug product manufacturing facility.

Labeling negotiation will be completed at the time of resubmission. As product labeling and Medication Guide will be sufficient to communicate the potential risks to healthcare providers and patients, respectively, a REMS will not be required, if approved.

Several post-marketing requirements will be issued at the time of approval, including (1) an observational study to assess liver injury in adults with moderately to severely active ulcerative colitis who are exposed to mirikizumab, relative to other therapies used to treat ulcerative colitis; (2) a lactation trial; and (3) a pregnancy registry to assess the maternal, fetal, and infant outcomes following exposure to mirikizumab-containing products during pregnancy. Additionally, enhanced pharmacovigilance will be requested to report cases of liver injury in an expedited manner.

Mirikizumab has an orphan drug designation and, therefore, the Applicant is exempt from Pediatric Research Equity Act requirements. However, the Applicant agreed to conduct pediatric studies as postmarketing commitments, which will be issued when the application may be approvable.

15. Office Director Comments

I concur with the recommendation of the Division of Gastroenterology to not approve original BLA 761279 for mirikizumab-mrkz for the treatment of moderately to severely active ulcerative colitis (UC) due to deficiencies observed at the Eli Lilly and Company, Indianapolis, Indiana (FEI 1819470), manufacturing facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

Mirikizumab is a novel humanized immunoglobulin 4 (IgG4) monoclonal antibody that binds to the p19 subunit of interleukin 23 (IL-23); IL-23 signaling has been implicated in the pathogenesis of inflammatory bowel diseases, including UC.

The efficacy of mirikizumab was demonstrated in two randomized controlled trials: 1) a 12-week induction trial comparing mirikizumab 300 mg IV every 4 weeks (Q4W) to placebo, and 2) a 40-week maintenance trial conducted in mirikizumab responders comparing mirikizumab 200 mg SC Q4W to placebo. In the induction trial, mirikizumab 300 mg IV Q4W was statistically significantly superior to placebo in achieving clinical remission in subjects at Week 12. In the maintenance trial conducted in mirikizumab responders, mirikizumab 200 mg SC Q4W was statistically significantly superior to placebo in achieving clinical remission at Week 40. In both trials, mirikizumab was also statistically significantly superior to placebo in achieving “alternate clinical remission”, the Division’s preferred clinical remission endpoint, and in achieving multiplicity-controlled secondary endpoints assessed at Weeks 12 and 40.

The safety profile of mirikizumab was comparable to that of other biologic products, including other agents that target IL-23 for the treatment of inflammatory bowel diseases. Hepatic enzyme elevations were observed in a few mirikizumab-treated subjects, including a case of drug-induced liver injury that met Hy’s Law criteria. If approved, the risk of hepatotoxicity will be mitigated by the recommendation of close monitoring of subjects in product labeling, and further assessed by a postmarketing observational study and enhanced pharmacovigilance.

If approved, mirikizumab-mrkz will represent a novel therapy for patients who have had an inadequate response, intolerance, or loss of response to available therapies for UC.

16. Appendices

16.1. References

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16.2. Financial Disclosure

The Applicant provided financial disclosures for the following covered clinical studies.

Covered Clinical Study

Study I6T-MC-AMAN: A phase 3, multicenter, randomized, double-blind, parallel group, placebo-controlled induction study. Study AMAN compared mirikizumab 300 mg IV every 4 weeks (Q4W) versus placebo for a treatment duration of 12 weeks.

Study I6T-MC-AMBG (AMBG) – A phase 3, multicenter, randomized, double-blind, parallel group, placebo-controlled maintenance study. Study AMBG compared mirikizumab 200 mg SC Q4W versus placebo for a treatment duration of 40 weeks.

Covered Clinical Study (Name and/or Number): I6T-MC-AMAN and I6T-MC-AMBG

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: AMAN: 2377 AMBG: 1958		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Study: 1 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) AMAN: 2 and AMBG: 4		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

16.3. OCP Appendices (Technical Documents Supporting OCP Recommendations)

16.3.1. Summary of Clinical Pharmacology Studies

The submission includes data from a total of ten clinical pharmacology studies. Data was provided from three phase 1 studies conducted in healthy subjects and subjects with psoriasis (AMAA, AMAD, AMBD), a drug-drug interaction (DDI) study conducted in subjects with psoriasis (AMBP), one phase 2 study for induction treatment (AMAC) in subjects with moderately to severely active UC, and one phase 3 induction study (AMAN) and one phase 3 maintenance study (AMBG) both conducted in subjects with moderately to severely active UC. The Applicant also conducted three relative bioavailability studies, including two studies to bridge the lyophilized formulation used in phase 1/2 with the solution formulation utilized in phase 3 and proposed for marketing (AMAE, AMAL), and one study to bridge the (b) (4) PFS and AI presentations (AMBW).

16.3.1.1. *Phase 1*

Study AMBW

Pivotal evidence to support use of the proposed to-be-marketed AI presented was derived from relative bioavailability study AMBW.

Study AMBW was an open-label, randomized, parallel-design, single-dose study to evaluate the PK of mirikizumab after SC administration of 200 mg doses administered via PFS (2 x 1 mL) or AI (2 x 1 mL) in healthy subjects (n = 240). Subjects were randomized to receive one of the two delivery devices with stratification by weight categories (< 70 kg, 70 to 80 kg, and > 80 kg). Within each delivery device group, subjects were randomized 1:1:1 to receive the dose at one of three injection sites (upper arm, thigh, or abdomen).

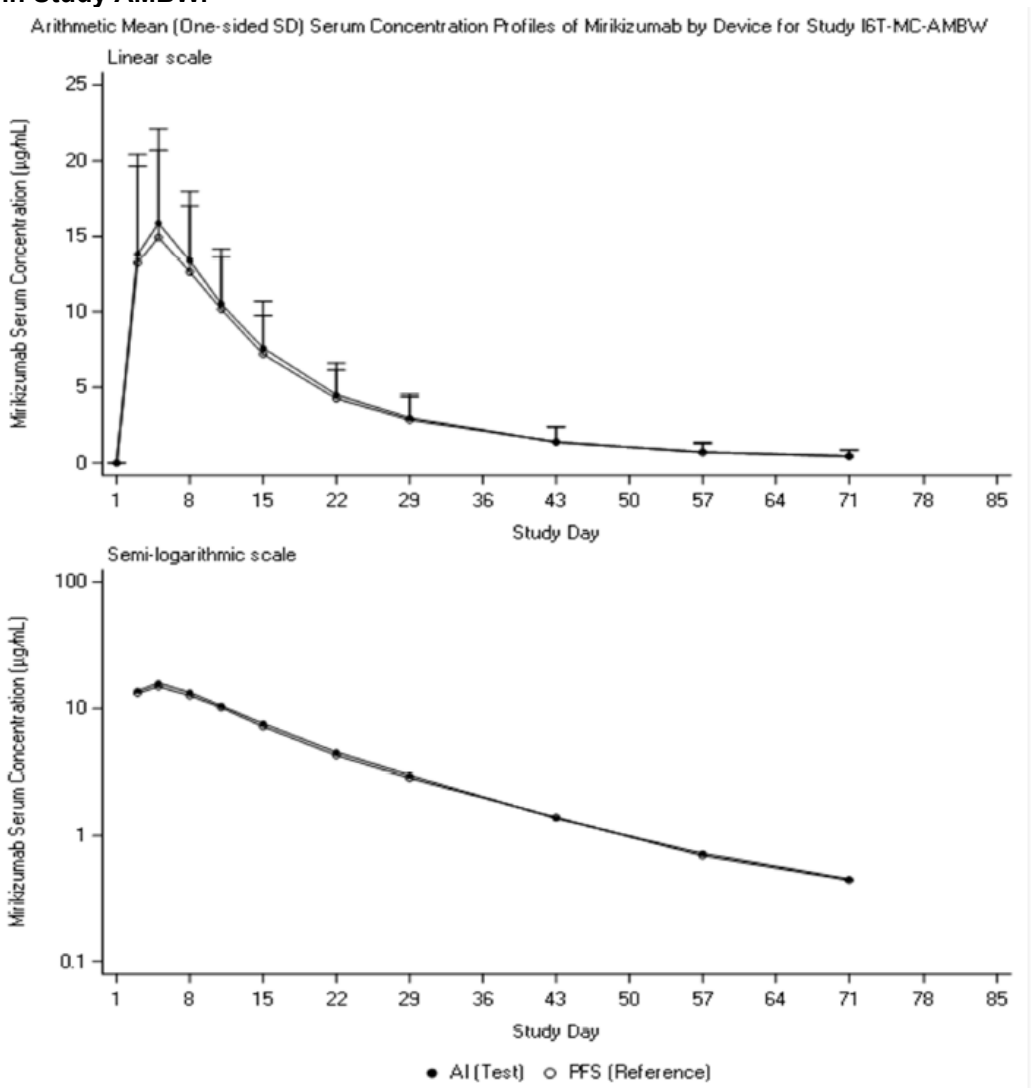
Subject demographics were balanced between delivery device groups as well as among injection site groups. Mean (range) body weight was similar between the treatment groups: 76.3 (50.9 to 112.0) kg and 76.2 (46.8 to 106.6) kg for the AI and PFS groups, respectively. Out of 240 subjects that were randomized and treated, 236 completed the study. All 240 subjects who enrolled in the study received at least one dose of mirikizumab and were included in the primary PK analysis, although 5 subjects with one or more missing samples at the end of the sampling schedule, including the 4 who discontinued from the study prematurely, did not have their AUC_{last} included in the analysis.

PK analysis was conducted using a linear fixed-effects model that adjusted for injection site (arm, abdomen, or thigh) and weight stratification (<70 kg, 70 to 80 kg, >80 kg). Mirikizumab exposure following administration of a single 200 mg dose via PFS (2 x 1 mL) was similar to that after administration via AI (2 x 1 mL) (Figure 19 and Table 66). The geometric mean ratios

(90% CI) for AUC_{last}, $AUC_{0\text{-}inf}$, and C_{max} were 1.05 (0.97, 1.14), 1.06 (0.98, 1.15), and 1.06 (0.98, 1.14), respectively. Meanwhile, no statistically significant difference in mirikizumab T_{max} was identified between the PFS and AI.

The review team analyzed the mirikizumab concentration data provided by the Applicant for study AMBW. The review team's analysis included use of non-compartmental analysis to estimate PK parameters followed by statistical analysis using a linear mixed-effects model with injection site and weight stratification as fixed effects, and subject as a random effect. The review team's analysis similarly concluded BE between the PFS and AI presentations for AUC_{last}, $AUC_{0\text{-}inf}$, and C_{max}.

Figure 19. Serum Mirikizumab Concentration Versus Time Profiles in the Arithmetic (Top) and Semi-Logarithmic (Bottom) Scales Following a Single 200 mg SC Dose Administered via PFS or AI in Study AMBW.



Note that error bars in the top panel represent standard deviation.
Source: Figure AMBW.5.1, Clinical Study Report for Study AMBW

Table 66. Summary of Mirikizumab PK Parameter Estimates Following a Single 200 mg SC Dose Administered via PFS or AI in Study AMBW

	Geometric mean (Geometric CV%) [n]	
Parameter	PFS (Reference) (N=120)	AI (Test) (N=120)
AUC(0-tlast) (ug.day/mL)	244 (44%) [116]	257 (39%) [119]
AUC(0-∞) (ug.day/mL)	246 (44%) [120]	262 (39%) [120]
%AUC(tlast-∞) (%)	1.43 (78%) [120]	1.44 (61%) [120]
Cmax (ug/mL)	14.3 (44%) [120]	15.2 (40%) [120]
tmax (day)#	4.00 (1.81-10.23) [120]	4.00 (1.83-7.05) [120]
t½ (day)*	10.9 (4.59-20.5) [120]	11.1 (6.09-21.3) [120]
CL/F (L/day)	0.813 (44%) [120]	0.764 (39%) [120]
Vz/F (L)	12.8 (37%) [120]	12.2 (35%) [120]
Vss/F (L)	13.6 (39%) [120]	12.9 (36%) [120]

Abbreviations: %AUC(tlast-∞) = percentage of AUC(0-∞) extrapolated; AI = 200 mg Mirikizumab 2 x 1-mL (100 mg/mL) autoinjector (Test); AUC(0-∞) = area under the concentration versus time curve from time zero to infinity; AUC(0-tlast) = area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration; CL/F = apparent total body clearance of drug calculated after extra-vascular administration; Cmax = maximum observed drug concentration; CV = coefficient of variation; N = number of participants; n = number of observations; PFS = prefilled syringe; t½ = half-life associated with the terminal rate constant in non-compartmental analysis; tmax = time of maximum observed drug concentration; Vss/F = apparent volume of distribution at steady state after extra-vascular administration; Vz/F = apparent volume of distribution during the terminal phase after extra-vascular administration

Median (minimum-maximum)

* Geometric mean (minimum-maximum)

Status of Program: Production
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Note the exclusion of 5 subjects from the overall summary of $AUC_{0\text{-tlast}}$ due to missing one or more samples at the end of the sampling schedule.
Source: Table AMBW.5.6, Clinical Study Report for Study AMBW

When exposure from the PFS versus AI were compared by injection site, exposure was found to be similar following administration in the abdomen and thigh, with geometric mean ratios and 90% CIs all completely contained between 0.8 and 1.25 (Table 67). Exposure following administration in the arm was 9 to 12% higher using the AI relative to the PFS, with geometric mean ratios (90% CI) for AUC_{last}, $AUC_{0\text{-inf}}$, and C_{max} of 1.09 (0.94, 1.28), 1.12 (0.97, 1.31), and 1.09 (0.93, 1.27), respectively. The Applicant indicates that study AMBW was not powered to assess PK of the PFS versus AI by injection site. In addition, the increase of 9 to 12% is smaller relative to the variability (CV%) observed for steady state C_{max} and AUC_{tau} at the recommended SC dosing regimen (52 to 58%), as determined via population PK analysis. Thus, the review team concluded that the PFS and AI presentations yielded similar mirikizumab exposures irrespective of injection site.

Table 67. Summary of Mirikizumab PK Parameter Estimates by Injection Site Following a Single 200 mg SC Dose Administered via PFS or AI in Study AMBW

Injection site	Parameter	Device	n	Geometric least squares mean	Ratio of geometric least squares mean (AI:PFS)	90% CI for the ratio (Lower, Upper)
Abdomen	AUC(0-tlast) (ug.day/mL)	PFS (Reference)	39	245		
		AI (Test)	39	244	0.996	(0.873, 1.14)
	AUC(0-∞) (ug.day/mL)	PFS (Reference)	40	248		
		AI (Test)	40	248	0.997	(0.878, 1.13)
	Cmax (ug/mL)	PFS (Reference)	40	15.0		
		AI (Test)	40	14.8	0.984	(0.853, 1.14)
Arm	AUC(0-tlast) (ug.day/mL)	PFS (Reference)	38	215		
		AI (Test)	39	236	1.09	(0.938, 1.28)
	AUC(0-∞) (ug.day/mL)	PFS (Reference)	41	213		
		AI (Test)	39	240	1.12	(0.966, 1.31)
	Cmax (ug/mL)	PFS (Reference)	41	12.3		
		AI (Test)	39	13.4	1.09	(0.928, 1.27)
Thigh	AUC(0-tlast) (ug.day/mL)	PFS (Reference)	39	279		
		AI (Test)	41	298	1.07	(0.931, 1.22)
	AUC(0-∞) (ug.day/mL)	PFS (Reference)	39	284		
		AI (Test)	41	303	1.07	(0.931, 1.22)
	Cmax (ug/mL)	PFS (Reference)	39	16.1		
		AI (Test)	41	17.8	1.10	(0.980, 1.24)

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

Source: Table AMBW.5.8, Clinical Study Report for Study AMBW

Differences in immunogenicity between the two presentations were also evaluated in study AMBW. All 240 subjects enrolled in the study were evaluable for TE ADAs. Overall, TE ADA and neutralizing antibody (NAb) incidence was similar regardless of the delivery device used for administration (Table 68).

Table 68. Summary of TE ADA and Neutralizing Antibody Incidence by Treatment Group in Study AMBW

	200 mg mirikizumab SC PFS (N=120)	200 mg mirikizumab SC AI (N=120)
TE-ADA evaluable,[a] n	120	120
TE-ADA positive,[b] n (%)	17 (14.2%)	16 (13.3%)
Treatment-induced ADA positive, n (%)	17 (14.2%)	15 (12.5%)
Treatment-boosted ADA positive, n (%)	0 (0%)	1 (0.8%)
NAb positive, n (%)	16 (13.3%)	15 (12.5)
Maximum TE-ADA titer		
Range	1:20 to 1:2560	1:20 to 1:2560
Median	1:160	1:40

Abbreviations: ADA = anti-drug antibody; AI = autoinjector; n = number of participants in category; N = number of participants studied; NAb = neutralizing antibodies; PFS = pre-filled syringe; SC = subcutaneous; TE = treatment emergent.

[a] An evaluable participant is defined as a subject with an evaluable baseline sample and at least 1 evaluable post-baseline sample.

[b] A participant is considered to be TE-ADA positive if the participant has at least 1 postbaseline titer that is 4-fold or greater increase in titer from baseline measurement (treatment boosted). If no ADA is present at baseline, then the participant is TE-ADA positive if there is at least 1 postbaseline ADA titer ≥1:20 (treatment induced).

Source: Table AMBW.5.9, Clinical Study Report for Study AMBW

Overall, the data support the comparability of the (b) (4) PFS and AI presentations for SC administration of mirikizumab.

An exploratory endpoint of study AMBW aimed to evaluate the impact of injection site location on the PK of mirikizumab. Table 69 and Table 70 below show statistical analysis of PK parameters AUC_{last}, AUC_{inf}, and C_{max} across injection sites for the PFS and AI presentations, respectively.

Table 69. Statistical Analysis of PK Parameters Across Injections Following a Single SC Dose of 200 mg Mirikizumab Administered via PFS in Study AMBW

Delivery device: PFS (Reference)

Parameter	Injection Location	n	Geometric least squares mean	Ratio of geometric least squares mean (Arm or Thigh versus Abdomen)	90% CI for the ratio (Lower, Upper)
AUC(0-tlast) (ug.day/mL)	Abdomen	39	244		
	Arm	38	215	0.883	(0.759, 1.03)
	Thigh	39	279	1.15	(0.986, 1.33)
AUC(0-∞) (ug.day/mL)	Abdomen	40	248		
	Arm	41	213	0.860	(0.743, 0.997)
	Thigh	39	284	1.15	(0.987, 1.33)
Cmax (ug/mL)	Abdomen	40	15.0		
	Arm	41	12.4	0.825	(0.711, 0.957)
	Thigh	39	16.1	1.08	(0.925, 1.25)

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

Source: Table AMBW.8.5, Clinical Study Report for Study AMBW, page 97, BLA 761279 SDN 1, submitted Mar. 30, 2022

Table 70. Statistical Analysis of PK Parameters Across Injections Following a Single SC Dose of 200 mg Mirikizumab Administered via AI in Study AMBW

Delivery device: AI (Test)

Parameter	Injection Location	n	Geometric least squares mean	Ratio of geometric least squares mean (Arm or Thigh versus Abdomen)	90% CI for the ratio (Lower, Upper)
AUC(0-tlast) (ug.day/mL)	Abdomen	39	243		
	Arm	39	235	0.966	(0.850, 1.10)
	Thigh	41	297	1.22	(1.08, 1.39)
AUC(0-∞) (ug.day/mL)	Abdomen	40	248		
	Arm	39	240	0.968	(0.853, 1.10)
	Thigh	41	303	1.22	(1.08, 1.39)
Cmax (ug/mL)	Abdomen	40	14.7		
	Arm	39	13.4	0.908	(0.798, 1.03)
	Thigh	41	17.7	1.20	(1.06, 1.37)

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

Source: Table AMBW.8.5, Clinical Study Report for Study AMBW, page 99, BLA 761279 SDN 1, submitted Mar. 30, 2022

Following administration with the PFS, C_{max} and AUC were approximately 12 to 17% lower after injection in the arm relative to the abdomen, while AUC was approximately 15% higher with no change in C_{max} after injection in the thigh relative to the abdomen. Following administration with the AI, C_{max} was approximately 9% lower with no change in AUC after injection in the arm relative to the abdomen, while C_{max} and AUC were approximately 20 to 22% higher after injection in the thigh relative to the abdomen. While evaluation of the impact of injection site on PK in study AMBW was considered an exploratory endpoint, results reveal little difference in mirikizumab exposure across injection sites. Changes in exposure up to 22% across injection sites and presentations are considered small relative to the variability (CV%) observed for steady state C_{max} and AUC_{tau} at the recommended SC dosing regimen (52 to 58%), as determined via population PK analysis (Section 16.3.3.5).

Study AMAA

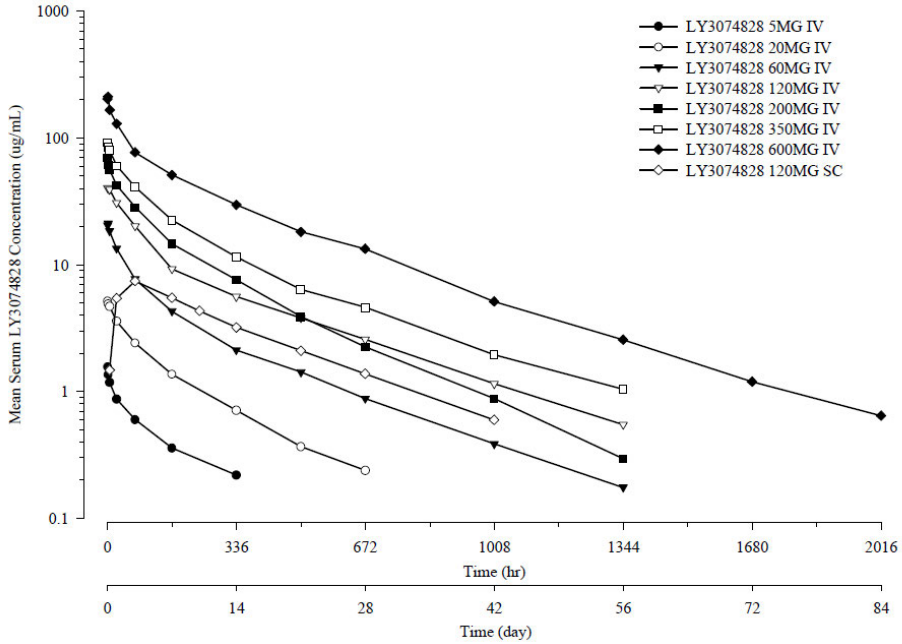
Study AMAA was a multicenter, single-ascending dose, parallel-group study conducted both in healthy adult subjects and in adult subjects with a confirmed diagnosis of chronic psoriasis for at least 6 months involving ≥ 2% body surface area (BSA). The primary and secondary objectives of the study were to characterize the tolerability, safety, and PK of mirikizumab after IV and SC administration.

The study enrolled a total of 45 subjects, including 40 subjects with psoriasis, and 5 healthy subjects. Seven IV dose levels were evaluated in subjects in psoriasis, including 5, 20, 60, 120, 200, 350, and 600 (n = 5/dose level, except for 5 mg for which n = 3). One SC dose level of 120 mg was evaluated in healthy subjects. (n = 5). IV doses were administered as an infusion over at least 30 minutes. Mirikizumab was supplied as a lyophilized powder requiring reconstitution prior to administration.

PK samples after IV dosing were collected on Day 1 pre-dose, at the end of IV infusion, and post-infusion start at hours 2, 6, and 24, and Days 4, 8, 15, 22, 29, 43, 57, 71, and 85.
PK samples after SC dosing were collected pre-dose on Day 1, and post-dose at hours 6 and 24, and Days 4, 8, 11, 15, 22, 29, 43, 57, 71, and 85. PK parameters were estimated using noncompartmental analysis.

The concentration-time profiles of mirikizumab are shown in Figure 20. PK parameters are shown in Table 71.

Figure 20. Study AMAA Mean Mirikizumab Plasma Concentration-Time Profiles After Single-Dose Administration of IV Doses in Subjects With Psoriasis and SC Doses in Healthy Subjects



IV = intravenous; LY3074828 = mir kizumab; SC = subcutaneous.
Source: Figure AMAA.7.1, Clinical Study Report for Study AMAA

Table 71. Study AMAA Plasma PK Parameters of Mirikizumab After Single-Dose Administration of IV Doses in Subjects With Psoriasis and SC Doses in Healthy Subjects

	LY3074828 Dose Cohort							
Treatment	LY3074828 5MG IV	LY3074828 20MG IV	LY3074828 60MG IV	LY3074828 120MG IV	LY3074828 120MG SC	LY3074828 200MG IV	LY3074828 350MG IV	LY3074828 600MG IV
N	3	5	5	5	5	5	5	5
C_{max}	1.60	5.34	20.6	41.1	7.28	68.8	91.8	220
(µg/mL)	22	6	29	15	23	19	6	24
t_{max}[a]	1.00	1.57	2.12	2.12	74.6	0.880	0.850	1.08
(hr)	(0.570 - 2.12)	(0.970 – 6.02)	(1.08 – 2.67)	(0.830 – 6.25)	(23.0 – 95.9)	(0.620 - 0.970)	(0.700 - 0.900)	(0.720 – 2.35)
$t_{1/2}$		9.59	10.7	12.8	9.97	9.65	9.63	13.0
(day)	(5.23, 10.5)[b]	18	26	27	23	18	30	18
AUC(0-t_{last})		31.6	114	283	112	364	552	1340
(µg•day/mL)	(5.70, 6.59)[b]	17	16	28	49	12	25	22
AUC(0-∞)		33.6	117	287	114	366	556	1360
(µg•day/mL)	(6.72, 8.40)[b]	17	15	29	49	12	25	23
CL		0.595	0.514	0.418	1.05[c]	0.547	0.629	0.440
(L/day)	(0.595, 0.744)[b]	17	15	29	49	12	25	23
V_z		8.23	7.92	7.71	15.1[c]	7.62	8.74	8.23
(L)	(5.61, 9.00)[b]	7	25	15	26	23	10	22
V_{ss}		6.84	6.24	5.75	15.7[c]	5.74	6.91	6.50
(L)	(5.40, 7.90)[b]	10	28	11	25	15	8	20

Note: Data are geometric mean (%CV) for PK parameters for serum LY3074828.
Abbreviations: AUC(0-t_{last}) = area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration, AUC(0-∞) = area under concentration versus time curve from zero to infinity, C_{max} = maximum observed drug concentration, CV = coefficient of variation, CL = total body clearance of drug calculated after intravenous administration, CL/F = apparent total body clearance of drug calculated after subcutaneous administration, IV = intravenous, SC = subcutaneous, tmax = time of maximum observed drug concentration, t1/2 = half-life associated with the terminal rate constant, Vss = volume of distribution at steady state after intravenous administration, Vss/F = apparent volume of distribution at steady state after subcutaneous administration, Vz = volume of distribution during the terminal phase after intravenous administration, Vz/F = apparent volume of distribution during the terminal phase after subcutaneous administration.
[a] Median (Min - Max)
[b] (Min, Max). N=2; Subject 9103 not included in calculation of summary statistics.
[c] As bioavailability was taken into consideration for SC administration, parameters from SC administration cohort would include a bioavailability term (F). For SC cohort, PK parameters determined were CL/F, Vz/F and Vss/F in place of CL, Vz, and Vss, respectively.
Source: Table AMAA.7.1, Clinical Study Report for Study AMAA

Mirikizumab serum concentrations followed a bi-exponential decline after administration. Clearance and volume of distribution appeared to be independent of dose, suggesting that the PK of mirikizumab was dose-proportional over the dose range of 5 to 600 mg IV. The overall mean half-life across all doses was approximately 10.5 days. The bioavailability following SC administration in healthy subjects was approximately 40%.

Study AMAD

Study AMAD was a single-site, subject- and investigator-blind, randomized, placebo-controlled, single-dose study to assess the safety, tolerability, and PK of mirikizumab in healthy Japanese and Caucasian subjects.

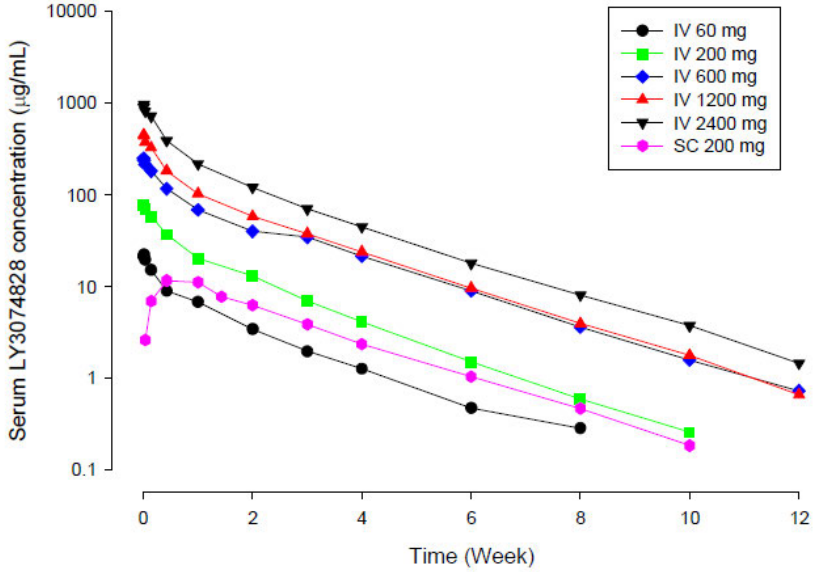
The study enrolled a total of 51 healthy subjects, including 26 Japanese subjects and 25 Caucasian subjects. It was noted that Japanese subjects had lower mean [SD] body weight relative to Caucasian subjects (65.2 [10.7] vs. 75.3 [13.0] kg, respectively).

Subjects were randomized to receive a single dose of either IV placebo; IV mirikizumab at doses of 60, 200, 600, 1200, or 2400 mg; SC placebo; or SC mirikizumab at a dose of 200 mg. IV doses were administered as an infusion over 30 minutes. The SC dose was administered as 2 injections into the abdominal wall. Mirikizumab was supplied as a lyophilized powder requiring reconstitution prior to administration.

PK samples after IV dosing were collected on Day 1 pre-dose, at the end of IV infusion, and post-infusion start at hours 2, 6, and 24, and Days 4, 8, 15, 22, 29, 43, 57, 71, and 85. PK samples after SC dosing were collected pre-dose on Day 1, and post-dose at hours 6 and 24, and Days 4, 8, 11, 15, 22, 29, 43, 57, 71, and 85. PK parameters were estimated using noncompartmental analysis.

The concentration-time profiles of mirikizumab are shown in Figure 21. PK parameters are shown in Table 72.

Figure 21. Mean Mirikizumab Serum Concentration-Time Profiles After Single-Dose Administration of IV and SC Doses in Healthy Japanese and Caucasian Subjects in Study AMAD



IV = intravenous; LY3074828 = mir kizumab; SC = subcutaneous; SD = standard deviation.
Source: Figure AMAD.7.1, Clinical Study Report for Study AMAD

Table 72. Plasma PK Parameters of Mirikizumab After Single-Dose Administration of IV and SC Doses in Healthy Japanese and Caucasian Subjects in Study AMAD

	LY3074828 Dose Cohort					
Treatment	60 mg IV	200 mg SC[a]	200 mg IV	600 mg IV	1200 mg IV	2400 mg IV
N	6	6	6	8	6	6
C_{max} (µg/mL)	23.1 (9)	11.8 (39)	78.8 (13)	250 (16)	454 (11)	985 (20)
t_{max}[b] (hr)	1.26 (0.50 - 6.00)	72.00 (72.00 - 168.00)	0.57 (0.52 - 2.00)	0.52 (0.50 - 2.07)	1.77 (1.50 - 2.10)	2.00 (1.48 - 2.00)
$t_{1/2}$ (day)	10.4 (27)	10.8 (13)	9.99 (17)	11.2 (17)	11.0 (15)	10.6 (16)
AUC(0-t_{last}) (µg•day/mL)	146 (30)	208 (30)	534 (11)	1960 (24)	2890 (14)	5970 (12)
AUC(0-∞) (µg•day/mL)	148 (29)	210 (29)	539 (12)	1970 (24)	2900 (14)	5990 (12)
CL (L/day)	0.404 (29)	0.951 (29)	0.371 (12)	0.305 (24)	0.414 (14)	0.401 (12)
V_z (L)	6.08 (29)	14.8 (28)	5.34 (18)	4.92 (28)	6.55 (14)	6.11 (14)
V_{ss} (L)	5.02 (25)	NC (NC)	4.35 (13)	4.47 (21)	5.22 (10)	4.90 (16)

Note: Data are geometric mean (%CV) for pharmacokinetic parameters for serum LY3074828.
Abbreviations: AUC(0-t_{last}) = area under the concentration versus time curve from time zero to the last time point with a measurable concentration; AUC(0-∞) = area under concentration versus time curve from zero to infinity; C_{max} = maximum observed drug concentration; CV = coefficient of variation; CL = total body clearance of drug calculated after intravenous administration; CL/F = apparent total body clearance of drug calculated after subcutaneous administration; IV = intravenous; N = number of subjects; NC = not calculated; SC = subcutaneous; t_{last} = last time point where the concentration is above the limit of quantification; t_{max} = time of maximum observed drug concentration; $t_{1/2}$ = half-life associated with the terminal rate constant; V_{ss} = volume of distribution at steady-state after intravenous administration; V_z = volume of distribution during the terminal phase after intravenous administration; V_z/F = apparent volume of distribution during the terminal phase after subcutaneous administration.

[a] As bioavailability was taken into consideration for SC administration, parameters from the SC administration cohort would include a bioavailability term (F). Thus, for the SC cohort, pharmacokinetic parameters determined were CL/F and V_z/F instead of CL and V_z, respectively.

[b] Median (Min - Max).

Source: Table AMAD.7.1, Clinical Study Report for Study AMAD

Mirikizumab serum concentrations followed a bi-exponential decline after IV administration. Clearance and volume of distribution appeared to be independent of dose, suggesting that the

PK of mirikizumab was dose-proportional over the dose range of 60 to 2400 mg IV. Dose-proportionality was concluded based on an exploratory power model analysis for C_{max} and AUC. The overall mean half-life across all doses was approximately 10.7 days. The bioavailability following SC administration in healthy subjects was approximately 40%.

When PK data was stratified between Japanese and Caucasian subjects, PK parameters were found to be comparable between the two populations (Table 73). It was concluded that the PK of mirikizumab was comparable between healthy Japanese and Caucasian subjects.

Table 73. Plasma PK Parameters of Mirikizumab Stratified by Japanese and Caucasian Subjects After Single-Dose Administration of IV and SC Doses in Study AMAD

	Serum LY3074828											
Race	Japanese						Caucasian					
Treatment	60 mg IV	200 mg SC[a]	200 mg IV	600 mg IV	1200 mg IV	2400 mg IV	60 mg IV	200 mg SC[a]	200 mg IV	600 mg IV	1200 mg IV	2400 mg IV
N	3	3	3	5	3	3	3	3	3	3	3	3
C_{max} (µg/mL)	23.1 (14)	11.3 (62)	79.3 (15)	248 (16)	475 (3)	996 (19)	23.1 (6)	12.2 (16)	78.4 (13)	253 (19)	434 (16)	975 (25)
t_{max}[b] (hr)	2.05 (0.50 - 6.00)	72.00 (72.00 - 168.00)	0.65 (0.52 - 2.00)	0.52 (0.50 - 2.00)	1.52 (1.50 - 1.53)	2.00 (1.48 - 2.00)	0.52 (0.50 - 2.00)	72.00 (72.00 - 120.02)	0.52 (0.52 - 0.62)	0.52 (0.52 - 2.07)	2.03 (2.00 - 2.10)	2.00 (1.62 - 2.00)
$t_{1/2}$ (day)	11.0 (36)	10.2 (8)	9.03 (9)	11.1 (20)	11.9 (11)	10.9 (12)	9.92 (22)	11.5 (16)	11.0 (19)	11.4 (13)	10.1 (14)	10.3 (21)
AUC(0-t_{last}) (µg•day/mL)	144 (33)	215 (47)	535 (12)	2060 (14)	3070 (6)	6040 (13)	148 (34)	202 (6)	534 (13)	1800 (40)	2720 (18)	5900 (14)
AUC(0-∞) (µg•day/mL)	147 (32)	217 (47)	542 (13)	2070 (14)	3080 (6)	6060 (13)	150 (34)	204 (5)	536 (13)	1810 (40)	2730 (18)	5920 (14)
CL (L/day)	0.409 (32)	0.922 (47)	0.369 (13)	0.290 (14)	0.389 (6)	0.396 (13)	0.400 (34)	0.980 (5)	0.373 (13)	0.332 (40)	0.440 (18)	0.405 (14)
V_z (L)	6.47 (43)	13.6 (38)	4.80 (19)	4.63 (25)	6.67 (12)	6.21 (21)	5.72 (13)	16.2 (16)	5.94 (10)	5.47 (36)	6.42 (19)	6.02 (7)
V_{ss} (L)	5.18 (34)	NC (NC)	4.09 (10)	4.36 (17)	5.14 (7)	4.96 (21)	4.87 (19)	NC (NC)	4.63 (14)	4.64 (30)	5.30 (14)	4.84 (15)

Note: Data are geometric mean (%CV) for pharmacokinetic parameters for serum LY3074828.

Abbreviations: AUC(0-t_{last}) = area under the concentration versus time curve from time zero to the last time point with a measurable concentration; AUC(0-∞) = area under concentration versus time curve from zero to infinity; C_{max} = maximum observed drug concentration; CV = coefficient of variation; CL = total body clearance of drug calculated after intravenous administration; CL/F = apparent total body clearance of drug calculated after subcutaneous administration; IV = intravenous; N = number of subjects; NC = not calculated; SC = subcutaneous; t_{last} = last time point where the concentration is above the limit of quantification; t_{max} = time of maximum observed drug concentration; $t_{1/2}$ = half-life associated with the terminal rate constant; V_{ss} = volume of distribution at steady-state after intravenous administration; V_z = volume of distribution during the terminal phase after intravenous administration; V_z/F = apparent volume of distribution during the terminal phase after subcutaneous administration.

[a] As bioavailability was taken into consideration for SC administration, parameters from the SC administration cohort would include a bioavailability term (F). Thus, for the SC cohort, pharmacokinetic parameters determined were CL/F and V_z/F instead of CL and V_z, respectively.

[b] Median (Min - Max).

Source: Table AMAD.7.4, Clinical Study Report for Study AMAD

Study AMBD

Study AMBD was a subject- and investigator-blind, randomized, placebo-controlled, parallel-group, single-dose study to assess the safety, tolerability, and PK of mirikizumab in healthy Chinese subjects. The study enrolled a total of 60 healthy Chinese subjects.

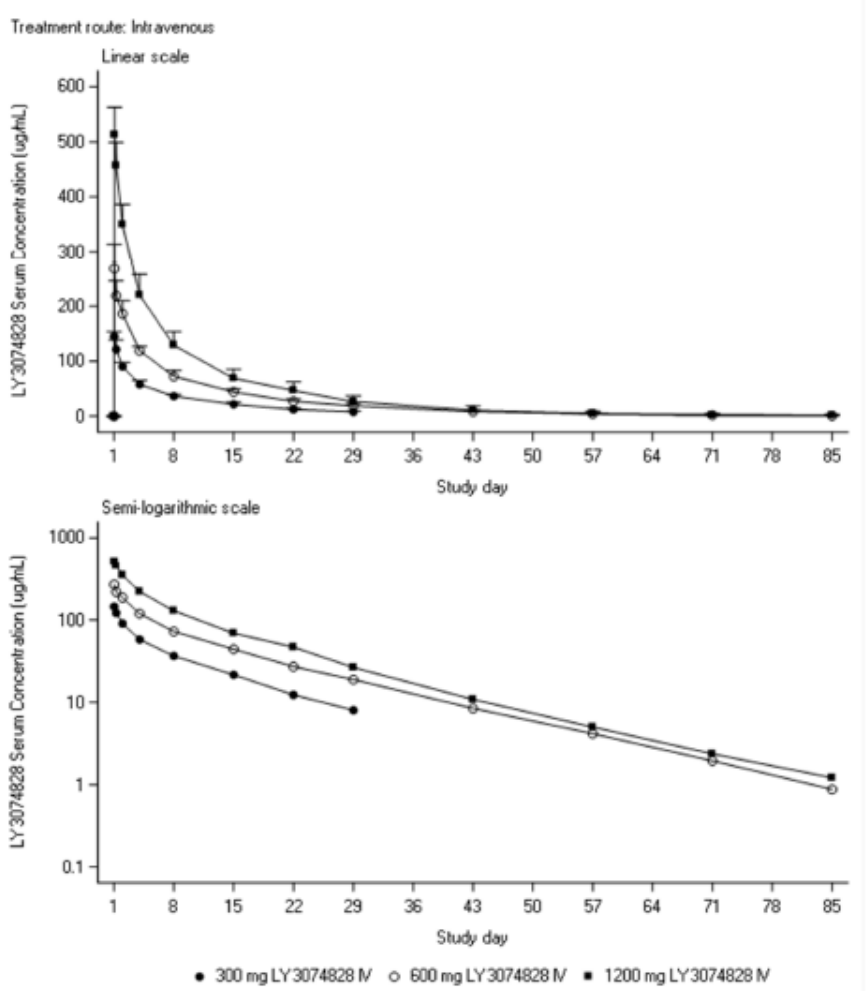
The study consisted of five dose cohorts, including three IV dose levels of 300, 600, and 1200 mg; and two SC dose levels of 200 and 400 mg. Within each cohort, subjects were randomized to receive either mirikizumab or placebo (n = 12/cohort; 10 mirikizumab, 2 placebo). IV doses were infused at a rate of at most 10 mg/min (i.e., 300 mg over at least 30 minutes; 600 mg over at least 60 minutes; 1200 mg over at least 120 minutes). SC doses were administered as either two (200 mg) or four (400 mg) injections into the abdominal wall.

Note that in study AMBD, the solution formulation of mirikizumab was used. This is the same formulation that was used in the phase 3 program and proposed for marketing.

PK samples after IV dosing were collected on Day 1 pre-dose, at the end of IV infusion, and post-infusion start at hours 6 and 24, and Days 4, 8, 15, 22, 29, 43, 57, 71, and 85. PK samples after SC dosing were collected pre-dose on Day 1, and post-dose at hours 6 and 24, and Days 4, 8, 11, 15, 22, 29, 43, 57, 71, and 85. PK parameters were estimated using noncompartmental analysis.

The concentration-time profiles of mirikizumab are shown in Figure 22 and Figure 23 for IV and SC dosing, respectively. PK parameters are shown in Table 74 and Table 75 for IV and SC dosing, respectively.

Figure 22. Mean Mirikizumab Serum Concentration-Time Profiles After Single-Dose Administration of IV Doses in Healthy Chinese Subjects in Study AMBD



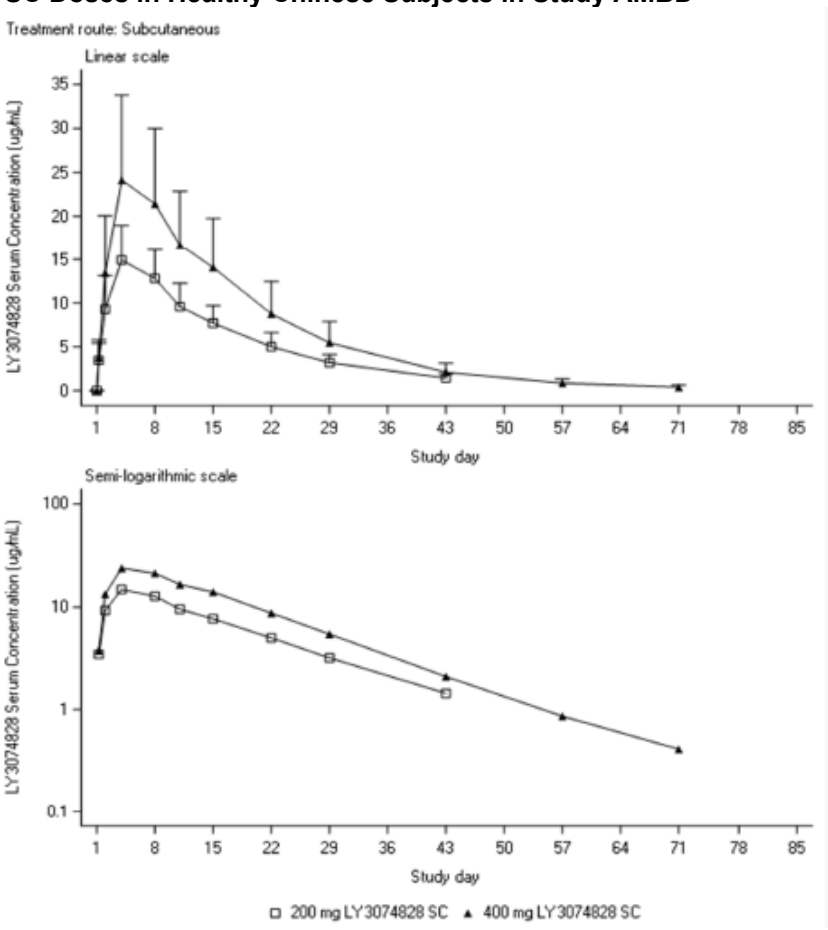
IV = intravenous; LY3074828 = mirikizumab.
Source: Figure AMBD.5.2, Clinical Study Report for Study AMBD

Table 74. Plasma PK Parameters of Mirikizumab After Single-Dose Administration of IV Doses in Healthy Chinese Subjects in Study AMBD

Parameter	300 mg IV (n=10)	600 mg IV (n=10)	1200 mg IV (n=10)
$AUC_{0\text{-tlast}}$ (µg*day/mL)	964 (15%)	2010 (12%)	3300 (24%)
$AUC_{0\text{-inf}}$ (µg*day/mL)	936 (12%)	2030 (12%)	3320 (23%)
$\%AUC_{ext}$	2.02 (553%)	0.547 (133%)	0.422 (299%)
C_{max} (µg/mL)	145 (6%)	266 (16%)	511 (10%)
T_{max} (day)	0.03 (0.03, 0.25)	0.05 (0.05, 0.06)	0.10 (0.09, 0.10)
$t_{1/2}$ (day)	9.53 (7.73, 11.7)	11.9 (9.26, 15.0)	10.4 (8.18, 15.9)
CL (L/day)	0.321 (12%)	0.296 (12%)	0.361 (23%)
V_z (L)	4.41 (14%)	5.07 (17%)	5.41 (13%)
V_{ss} (L)	3.98 (12%)	4.38 (14%)	4.43 (13%)

Note that all values are reported as geometric mean (geometric CV%) except for T_{max}, which is reported as median (minimum, maximum), and $t_{1/2}$, which is reported as geometric mean (minimum, maximum).
Abbreviations: $\%AUC_{ext}$ = percent of $AUC_{0\text{-inf}}$ extrapolated; $AUC_{0\text{-inf}}$ = area under the concentration-time curve from time zero to infinity; $AUC_{0\text{-tlast}}$ = area under the concentration time curve from time zero to the last time point with measurable concentration; CL = total body clearance of drug calculated after IV administration; C_{max} = maximum observed drug concentration; CV = coefficient of variation; $t_{1/2}$ = half-life associated with the terminal rate constant in noncompartmental analysis; IV = intravenous; T_{max} = time of maximum observed concentration; V_{ss} = volume of distribution at steady state after IV administration; V_z = volume of distribution during the terminal phase after IV administration.
Source: Adapted from Table AMBD.5.4, Clinical Study Report for Study AMBD

Figure 23. Mean Mirikizumab Serum Concentration-Time Profiles After Single-Dose Administration of SC Doses in Healthy Chinese Subjects in Study AMBD



LY3074828 = mirikizumab; SC = subcutaneous.
Source: Figure AMBD.5.3, Clinical Study Report for Study AMBD

Table 75. Plasma PK Parameters of Mirikizumab After Single-Dose Administration of SC Doses in Healthy Chinese Subjects in Study AMBD

Parameter	200 mg (n = 10)	400 mg (n = 10)
$AUC_{0\text{-tlast}}$ (µg*day/mL)	248 (34%)	417 (46%)
$AUC_{0\text{-inf}}$ (µg*day/mL)	263 (29%)	421 (46%)
$\%AUC_{ext}$	1.93 (139%)	0.779 (52%)
C_{max} (µg/mL)	14.9 (28%)	23.1 (44%)
T_{max} (day)	2.98 (2.97, 6.95)	2.98 (2.97, 7.04)
$t_{1/2}$ (day)	10.6 (9.16, 12.0)	10.4 (8.44, 11.9)
CL/F (L/day)	0.759 (29%)	0.951 (46%)
V_z/F (L)	11.6 (25%)	14.2 (39%)
V_{ss}/F (L)	301 (27%)	377 (42%)
F(%)	42.8	34.2

Note that all values are reported as geometric mean (geometric CV%) except for T_{max}, which is reported as median (minimum, maximum), and $t_{1/2}$, which is reported as geometric mean (minimum, maximum).
Abbreviations: $\%AUC_{ext}$ = percent of $AUC_{0\text{-inf}}$ extrapolated; $AUC_{0\text{-inf}}$ = area under the concentration-time curve from time zero to infinity; $AUC_{0\text{-tlast}}$ = area under the concentration time curve from time zero to the last time point with measurable concentration; CL/F = total body clearance of drug calculated after extravascular administration; C_{max} = maximum observed drug concentration; CV = coefficient of variation; F = absolute bioavailability; SC = subcutaneous $t_{1/2}$ = half-life associated with the terminal rate constant in noncompartmental analysis; T_{max} = time of maximum observed concentration; V_{ss}/F = volume of distr bution at steady state after extravascular administration; V_z/F = volume of distribution during the terminal phase after extravascular administration.
Source: Table AMBD.5.4, Clinical Study Report for Study AMBD

Geometric mean $AUC_{0\text{-inf}}$ and C_{max} increased approximately linearly over the dose range of 300 to 1200 mg IV and 200 to 400 mg SC. After IV administration, the geometric mean half-life ranged from 9.5 to 11.9 days. Following SC dosing, the median T_{max} was approximately 3 days for both the 200 and 400 mg doses. The geometric mean half-life after SC administration was similar to that after IV administration, with geometric mean values of 10.6 and 10.4 days for the 200 and 400 mg doses, respectively. A comparison of exposure based on pooled SC dose data with pooled IV dose data indicated an absolute bioavailability of 38.2%.

Drug-Drug Interactions

Study AMBP

Study AMBP was a clinical drug-drug interaction study conducted in subjects with moderate-to-severe psoriasis. Study AMBP was designed as a phase 1, two-period, fixed-sequence, open-label study aimed at evaluating the impact of mirikizumab treatment, administered as 250 mg SC Q4W, on the PK of a cocktail of CYP substrates, including caffeine (CYP1A2), warfarin (CYP2C9), omeprazole (CYP2C19), dextromethorphan (CYP2D6), and midazolam (CYP3A4).

Of note, the dosage regimen evaluated of 250 mg SC Q4W is greater than the dosage regimen proposed for maintenance treatment (200 mg SC Q4W) but is expected to provide lower exposure relative to the dosage regimen proposed for induction (300 mg IV Q4W for three doses). Mirikizumab was administered using the to-be-marketed PFS presentation containing a 125 mg/mL strength of the solution formulation with identical composition to the 100 mg/mL strength proposed for marketing. Mirikizumab was administered as 2 x 1 mL injections.

In Period 1 of the study, the PK of CYP450 substrates in the cocktail was assessed after administration on Day 1. In Period 2 of the study, the same cocktail of CYP substrates was

administered on Day 116 for PK assessment following SC administration of 250 mg mirikizumab Q4W on Days 1, 29, 57, 85, and 113. A total of 29 subjects with plaque psoriasis were enrolled in the study. All subjects completed Period 1, while 26 subjects completed Period 2.

In both periods, PK samples were collected up to 96 hours post-dose to evaluate all drugs in the cocktail as follows:

- Midazolam and 1'-hydroxymidazolam: predose, and post-dose at hours 0.5, 1, 2, 3, 4, 6, 8, 12, and 24
- S-warfarin: predose, and post-dose at hours 1, 2, 4, 6, 8, 10, 24, 48, 72, and 96
- Dextromethorphan and dextrorphan: predose, and post-dose at hours 1, 2, 4, 6, 8, 10, 24, 48, and 72
- Omeprazole and 5-hydroxyomeprazole: predose, and post-dose at hours 0.5, 1, 2, 3, 4, 6, 8, 12, 24, and 48
- Caffeine and paraxanthine: predose, and post-dose at hours 0.5, 1, 2, 3, 4, 6, 8, 12, 24, and 48

PK was analyzed using a linear mixed-effect model using treatment as a fixed effect and subject as a random effect. Differences in drug exposure across periods were evaluated based on the geometric mean ratios and associated 90% confidence intervals for C_{max}, $AUC_{0\text{-}tlast}$, and $AUC_{0\text{-}inf}$.

Table 76 shows PK results from study AMBP. Data indicates that the geometric mean ratios and 90% CIs for C_{max}, AUC_{inf}, and $AUC_{0\text{-}t}$ for all probe substrates were mostly contained within the no-effect boundaries of 0.8 to 1.25. The exception is omeprazole (CYP2C19) in which the upper bound of the 90% CI for C_{max} and $AUC_{0\text{-}t}$ reached a value of 1.26. Overall, the data suggests low potential for clinically relevant drug interactions with drugs metabolized by all the CYPs evaluated (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) in patients with moderate-to-severe psoriasis.

Table 76. Statistical Analysis of Plasma C_{max}, AUC_{inf}, and $AUC_{0\text{-}t}$ After Oral Administration of a Cocktail of CYP Substrates in the Absence of Mirikizumab (Period 1) and After SC Administration of 250 mg Mirikizumab Q4W (Period 2)

Probe Substrate	C_{max} (Period 2/Period 1)		AUC_{inf} (Period 2/Period 1)		$AUC_{0\text{-}t}$ (Period 2/Period 1)	
	GMR	90% CI	GMR	90% CI	GMR	90% CI
Caffeine	0.965	[0.872, 1.07]	1.04	[0.967, 1.12]	1.04	[0.964, 1.11]
Warfarin	0.937	[0.893, 0.983]	0.958	[0.916, 1.00]	0.976	[0.934, 1.02]
Omeprazole	1.03	[0.844, 1.26]	1.06	[0.958, 1.18]	1.05	[0.874, 1.26]
Dextromethorphan	1.03	[0.872, 1.22]	0.971	[0.817, 1.15]	0.981	[0.820, 1.17]
Midazolam	1.09	[1.01, 1.18]	1.15	[1.06, 1.25]	1.14	[1.05, 1.23]

AUC_{inf} = area under the concentration-versus-time curve from time of administration to infinity following a single dose; $AUC_{0\text{-}t}$ = area under the concentration-versus-time curve from time of administration to the time of last quantifiable concentration; CI = confidence interval; C_{max} = maximum concentration; CYP = cytochrome P450; GMR = geometric mean ratio; Q4W = every 4 weeks; SC = subcutaneous.
Source: Reviewer-generated table adapted from Tables AMBP.7.3, AMBP.7.5, AMBP.7.7, AMBP.7.9, AMBP.7.11, Clinical Study Report for Study AMBP

Given possible differences in inflammatory burden across disease states, it is not clear that data generated in subjects with moderate-to-severe psoriasis would apply to patients with UC. In study AMBP, exploratory biomarkers including IL-19 and high sensitivity C-reactive protein (hsCRP) were evaluated throughout period 2, during which mirikizumab was administered. Mean biomarker concentrations over time are shown in Table 77. Modest decreases in hsCRP were observed. Decreases in IL-19 were observed, although there was large inter-patient variability in IL-19 concentrations.

Table 77. Mean Concentrations of IL-19 and hsCRP Over Time in Subjects With Moderate-to-Severe Psoriasis in Period 2 of DDI Study AMBP

	Sample Timepoint in Period 2		
Parameter	Day 1 predose N=29	Day 29 predose N=29	Day 113 predose N=27
hsCRP (mg/L)	4.840 (4.528)	3.066 (2.340) [-1.774]	3.654 (3.287) [-0.628]
IL-19 (pg/mL)	241.315 (352.554)*	54.022 (71.553) [-185.621]	24.863 (25.968) [-230.167]

Abbreviations: hsCRP = high-sensitivity C-reactive protein; IL = interleukin; N = number of patients; Q4W = once every 4 weeks; SD = standard deviation.
Results are presented as: mean (SD) [change from Period 2 Day 1 predose].
* N = 28.
Source: Table AMBP.7.13, Clinical Study Report for Study AMBP

IL-19 concentrations were not measured in phase 2 study AMAC and phase 3 studies AMAN/AMBG, all of which enrolled subjects with moderate-to-severe UC. However, hsCRP concentrations were measured and reported in studies AMAC and AMAN/AMBG. Table 78 below shows mean hsCRP concentrations at Baseline across studies.

Table 78. Mean (SD) and Median (IQR) hsCRP Concentrations and Number of Subjects With hsCRP <10 mg/L at Baseline in Subjects With Moderate-to-Severe Psoriasis (Study AMBP) and Subjects With Moderate-to-Severe UC (Studies AMAC and AMAN)

	Baseline hsCRP (mg/L)		Subjects with hsCRP <10 mg/L n (%)
	Mean (SD)	Median (IQR)	
AMBP (psoriasis) (N=29)	4.8 (4.5)	3.2 (1.9, 6.5)	27 (93%)
AMAC (UC) (N=239)	10.7 (17.3)	4.7 (1.5, 12.8)	166 (69%)
AMAN (UC) (N=1218)	9.7 (15.4)	4.3 (1.6, 9.9)	920 (76%)

Abbreviations: hsCRP = high-sensitivity C-reactive protein; IQR = interquartile range; SD = standard deviation; UC = ulcerative colitis.
Note that the number of subjects represented includes all enrolled subjects with non-missing baseline hsCRP measurements.
Source: Reviewer-generated table using data adapted from clinical laboratory datasets [ad b] for studies AMBP, AMAC, and AMAN.

Baseline mean hsCRP values in subjects with UC from studies AMAC and AMAN appear elevated relative to baseline mean hsCRP values in subjects with psoriasis from study AMBP. Median values in subjects with UC appear modestly elevated relative to that in subjects with psoriasis. The discrepancy between mean and median values among subjects with UC indicates high variability in hsCRP across subjects, with mean values likely skewed by subjects with greatly elevated hsCRP.

Based on clinical interpretation, CRP values < 3 mg/L are typically considered within normal range, while values between 3 and 10 mg/L are associated with normal or minor elevations in

inflammation (e.g., obesity, pregnancy) (Black et al. 2004; Nehring et al. 2022). Data shown in Table 78 indicates that the proportion of subjects with hsCRP values <10 mg/L was greater in study AMBP (subjects with psoriasis) relative to studies AMAC and AMAN (subjects with UC). Despite this, at least 69% of subjects across all studies had hsCRP values that could be classified as normal or associated with normal or minor elevations.

Relative Bioavailability Studies

Study AMAE

Study AMAE was a single-center, open-label, randomized, parallel-group study designed to evaluate the relative bioavailability of a lyophilized formulation of mirikizumab (used in phase 1 and phase 2) with a solution formulation administered via PFS in healthy subjects. Subjects were randomized to one of three treatment arms:

- 250 mg mirikizumab administered as 2 x 1 mL and 1 x 1.5 mL SC injections of a 72 mg/mL reconstituted lyophilized formulation (total dose of 252 mg).
- 250 mg mirikizumab administered as 2 x 1 mL SC injections of a 125 mg/mL solution formulation in a PFS presentation
- 500 mg mirikizumab administered as 4 x 1 mL SC injections of a 125 mg/mL solution formulation in a PFS presentation

Study AMAE was conducted using a 125 mg/mL solution formulation with identical composition to the to-be-marketed 100 mg/mL formulation. The solution formulation was supplied in the same PFS presentation used in the phase 3 studies. Dose proportionality has been established for SC doses between 200 and 400 mg. Therefore, PK is presumed to be linear following a SC 200 mg dose (100 mg/mL, 2 x 1 mL injections) and a SC 250 mg dose (125 mg/mL, 2 x 1 mL injections). All doses were administered in the abdominal region.

A total of 54 healthy subjects were enrolled. Subject demographics were balanced across groups. Mean (range) body weight was similar between the treatment groups:
72.1 (57.5, 96.6) kg, 82.5 (57.8, 112) kg, and 77.8 (41.9, 109) kg for the groups receiving the lyophilized formulation, 250 mg of the solution formulation, and 500 mg of the solution formulation, respectively. Out of 54 subjects enrolled, 53 completed the study. All 53 subjects who completed the study were included in the PK analysis.

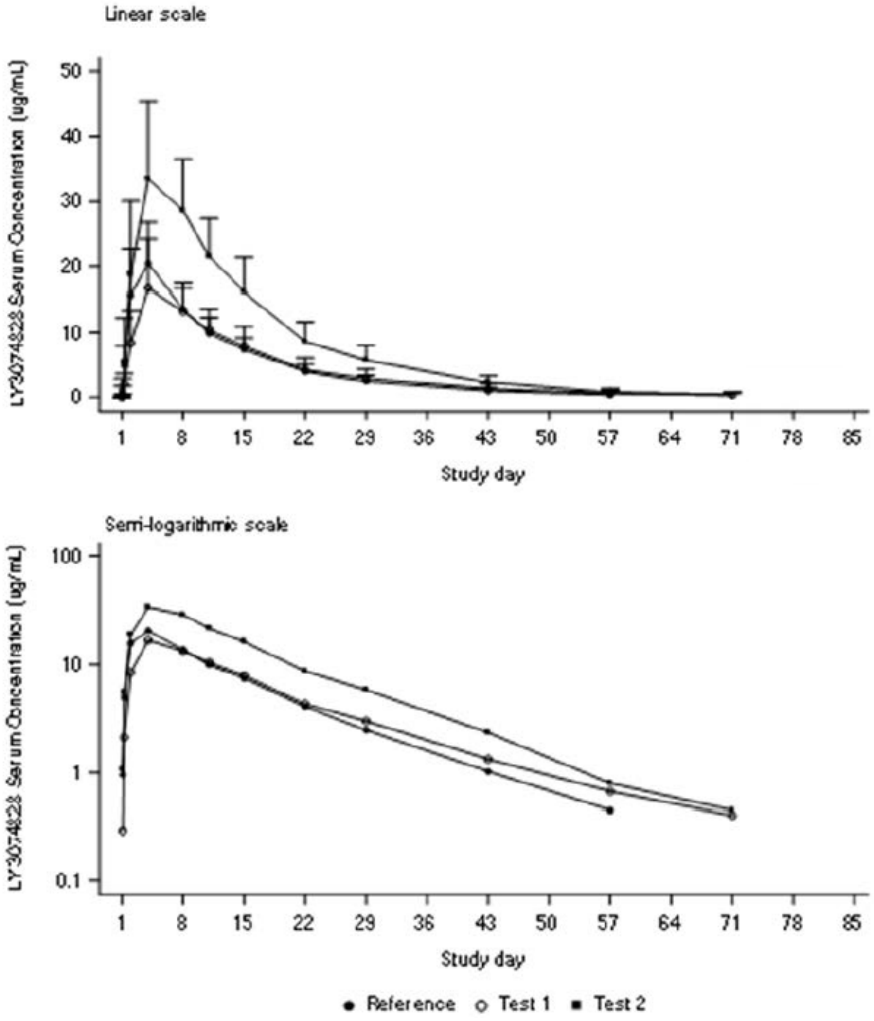
Injection site leakage occurred in approximately 74% (40/54) of subjects across all treatment groups. The amount of leakage based on filter paper blotting was ≤2.2 mg in all groups. All subjects were included in the descriptive statistics and statistical analysis. Whether or not injection site leakage occurred was included as a covariate in the linear fixed-effects model used to compare PK across treatment groups.

PK samples were collected pre-dose and post-dose at hours 2 and 6, and days 2, 4, 8, 11, 15, 22, 29, 43, 57, 71, and 85. PK parameters were estimated using noncompartmental analysis. PK analysis was conducted using a linear fixed-effects model with formulation as a fixed effect.

Injection site leakage was also included as a covariate in the model. Geometric mean ratios and associated 90% confidence intervals for dose-normalized C_{max}, $AUC_{0\text{-tlast}}$, and $AUC_{0\text{-inf}}$ were used to assess the comparability of the formulations.

The concentration-time profiles across treatment groups and estimated PK parameters are shown in Figure 24 and Table 79, respectively.

Figure 24. Serum Mirikizumab Concentration Versus Time Profiles in the Arithmetic (Top) and Semi-Logarithmic (Bottom) Scales Following a Single 250 mg SC Dose Administered as a Lyophilized Formulation (Reference), or as Two Injections of a Solution Formulation in a PFS (Test 1), or a Single 500 mg SC Dose Administered as Four Injections of a Solution Formulation in a PFS (Test 2) in Study AMAE



Source: Figure AMAE.7.1, Clinical Study Report for Study AMAE

Table 79. Plasma PK Parameters Single-Dose Administration of SC Doses of Mirikizumab as a Lyophilized Formulation or Solution Formulation in Healthy Subjects in Study AMAE

	Geometric mean (Geometric CV%)		
Parameter	250 mg LY3074828 lyophilized formulation (N=18)	250 mg LY3074828 PFS solution formulation (N=17)	500 mg LY3074828 PFS solution formulation (N=18)
AUC(0-tlast) (ug.day/mL)	267 (27%)	257 (40%)	522 (32%)
DN-AUC(0-tlast) (ug.day/mL/mg)	1.06 (27%)	1.03 (40%)	1.04 (32%)
AUC(0-∞) (ug.day/mL)	270 (27%)	261 (40%)	526 (32%)
DN-AUC(0-∞) (ug.day/mL/mg)	1.07 (27%)	1.05 (40%)	1.05 (32%)
%AUC(tlast-∞) (%)	0.952 (39%)	1.31 (72%)	0.619 (58%)
Cmax (ug/mL)	19.0 (37%)	15.6 (46%)	33.4 (34%)
DN-Cmax (ug/mL/mg)	0.0754 (37%)	0.0623 (46%)	0.0667 (34%)
tmax (day)#	2.90 (1.01-6.89)	2.92 (2.89-7.00)	2.90 (1.01-6.96)
t½ (day)~	10.6 (6.68-15.2)	11.6 (5.45-20.4)	10.6 (6.08-15.4)
CL/F (L/day)	0.934 (27%)	0.956 (40%)	0.951 (32%)
Vz/F (L)	14.3 (33%)	16.0 (36%)	14.5 (34%)
Vss/F (L)	13.4 (34%)	15.9 (40%)	14.5 (32%)

Abbreviations: %AUC(tlast-∞) = percentage of AUC(0-∞) extrapolated; AUC(0-∞) = area under the concentration versus time curve from time zero to infinity; AUC(0-tlast) = area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration; CL/F = apparent total body clearance calculated after extravascular administration; Cmax = maximum observed concentration; CV = coefficient of variation; DN = dose normalized; N = number of subjects; t1/2 = half-life associated with the terminal rate constant in non-compartmental analysis; tmax = time of maximum observed concentration; Vss/F = apparent volume of distribution at steady state after extravascular administration; Vz/F = apparent volume of distribution during the terminal phase after extravascular administration

Median (minimum-maximum)
~ Geometric mean (minimum-maximum)

Source: Table AMAE.7.1, Clinical Study Report for Study AMAE

Statistical analysis comparing dose-normalized PK parameters across treatment groups is shown in Table 80. The geometric mean ratios and 90% confidence intervals for dose-normalized $AUC_{0\text{-tlast}}$ and $AUC_{0\text{-inf}}$ all fell within the no-effect boundaries of 80-125%, suggesting no difference between the lyophilized and solution formulations. With respect to dose normalized C_{max}, although all point estimates fell within the 80-125% range, the 90% confidence intervals fell outside of that range. As compared with the lyophilized formulation, the solution formulation resulted in approximately 12 to 18% lower C_{max}. Administration of a 500 mg dose as four SC injections yielded a 7% higher C_{max} relative to administration of a 250 mg dose as two SC injections.

Table 80. Statistical Analysis of Dose-Normalized PK Parameter Estimates Following SC Doses of 250 or 500 mg Mirikizumab as a Lyophilized or Solution Formulation in Study AMAE

Parameter	Treatment	N	Geometric least squares mean	Comparison	Ratio of geometric least squares means	90% CI for the ratio (Lower, Upper)
DN-AUC(0-tlast) (ug.day/mL/mg)	Reference	18	1.06	Test 1 versus Reference	0.971	(0.805, 1.17)
	Test 1	17	1.03	Test 2 versus Test 1	1.01	(0.841, 1.22)
	Test 2	18	1.05	Test 2 versus Reference	0.985	(0.819, 1.18)
DN-AUC(0-∞) (ug.day/mL/mg)	Reference	18	1.08	Test 1 versus Reference	0.978	(0.811, 1.18)
	Test 1	17	1.05	Test 2 versus Test 1	1.00	(0.833, 1.21)
	Test 2	18	1.06	Test 2 versus Reference	0.982	(0.817, 1.18)
DN-Cmax (ug/mL/mg)	Reference	18	0.0737	Test 1 versus Reference	0.823	(0.664, 1.02)
	Test 1	17	0.0607	Test 2 versus Test 1	1.07	(0.867, 1.33)
	Test 2	18	0.0652	Test 2 versus Reference	0.885	(0.716, 1.09)

Abbreviations: AUC(0-tlast) = area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration; AUC(0-∞) = area under the concentration versus time curve from time zero to infinity; CI = confidence interval; Cmax = maximum observed concentration; DN = dose normalized; N = number of subjects; Reference = 250 mg LY3074828 lyophilized formulation; Test 1 = 250 mg LY3074828 PFS solution formulation; Test 2 = 500 mg LY3074828 PFS solution formulation Model: Log(PK) = Formulation + Injection Site Leakage + Random Error

Source: Table AMAE.7.2, Clinical Study Report for Study AMAE

Median T_{max} was also found to be similar across all treatment groups. Statistical analysis suggested a statistically significant median difference in T_{max} of 0.03 days between the 250 mg solution formulation relative to the 250 mg lyophilized formulation. However, this difference is not considered to be clinically relevant.

Taken together, data from study AMAE support the comparability of the lyophilized formulation used in phase 1 and 2, and the solution formulation administered using the PFS presentation used in phase 3.

Study AMAL

The Applicant's proposal for maintenance dosing specifies administration of mirikizumab as "two consecutive subcutaneous injections of 100 mg each" (i.e., 2 x 1 mL). The Applicant evaluated the PK comparability of administering mirikizumab as two injections (2 x 1 mL) versus as a single injection (1 x 2 mL) in relative bioavailability study AMAL.

Study AMAL was an open-label, randomized, parallel-design, single-dose study designed to evaluate the relative bioavailability of a lyophilized formulation of mirikizumab that was used in the phase 1 and 2 studies with that of a solution formulation. A secondary objective was to determine the relative bioavailability of the solution formulation when the same volume is administered through a single SC injection (1 x 2 mL) and as two SC injections (2 x 1 mL). Study AMAL was conducted using a 125 mg/mL solution formulation with identical composition to the to-be-marketed 100 mg/mL formulation. The formulation was supplied frozen and prepared extemporaneously at the CRU pharmacy, distinguishing it from the solution formulation supplied in the PFS presentation used in phase 3 (b) (4)

As dose proportionality has been established for SC doses between 200 and 400 mg, PK is presumed to be linear following a SC 200 mg dose (100 mg/mL, 2 x 1 mL injections) and a SC 250 mg dose (125 mg/mL, 2 x 1 mL injections). Of note, the lyophilized formulation was administered as three injections as the maximum achievable concentration of this formulation is 72 ng/mL making it impossible to administer 250 mg with a total injection volume of 2 mL. The total injection volume was therefore increased to 3.5 mL, administered as 2 x 1 mL and 1 x 1.5 mL.

Healthy subjects (n = 67) were enrolled. Subject demographics were balanced across groups. Mean (range) body weight was similar between the treatment groups: 77.8 (53.0 to 92.9) kg, 75.5 (54.7, 100.0) kg, and 72.3 (57.6 to 91.7) kg for the groups receiving the lyophilized formulation, the solution formulation as 2 x 1 mL, and the solution formulation as 1 x 2 mL, respectively. Out of 67 subjects that were enrolled, 66 completed the study. All 67 subjects who enrolled in the study received at least one dose of mirikizumab and were included in the primary PK analysis. Of note, injection site leakage was reported for 21 subjects following SC administration, including 11 subjects who received the solution formulation as 1 x 2 mL and 10 subjects who received the solution formulation as 2 x 1 mL. Based on filter paper blotting, the amount of leakage was ≤ 8.7 mg. All subjects, regardless of whether injection site leakage was observed, were included in the descriptive statistics and statistical analysis.

PK data were analyzed using a linear fixed-effect model with a fixed effect for formulation. Whether injection site leakage occurred was included in the model as a covariate as a binary variable (yes/no). If found to be significant, the amount of leakage would be added to the

model. The final model used for statistical analysis of PK parameters did not include a term for injection site leakage, suggesting that it was not found to be significant.

To determine whether injection site leakage had any impacts to PK, the review team summarized C_{max}, AUC_{last} and $AUC_{0\text{-}inf}$ by whether injection site leakage occurred within each cohort administered the solution formulation (Table 81). Accounting for measures of variability, the evaluated PK parameters were comparable regardless of whether injection site leakage had occurred. For subjects who received 2 injections of the solution formulation, C_{max}, AUC_{inf}, and AUC_{last} were numerically greater in subjects for whom injection site leakage was noted. This suggests that leakage did not impact PK and yield reduced exposure to mirikizumab.

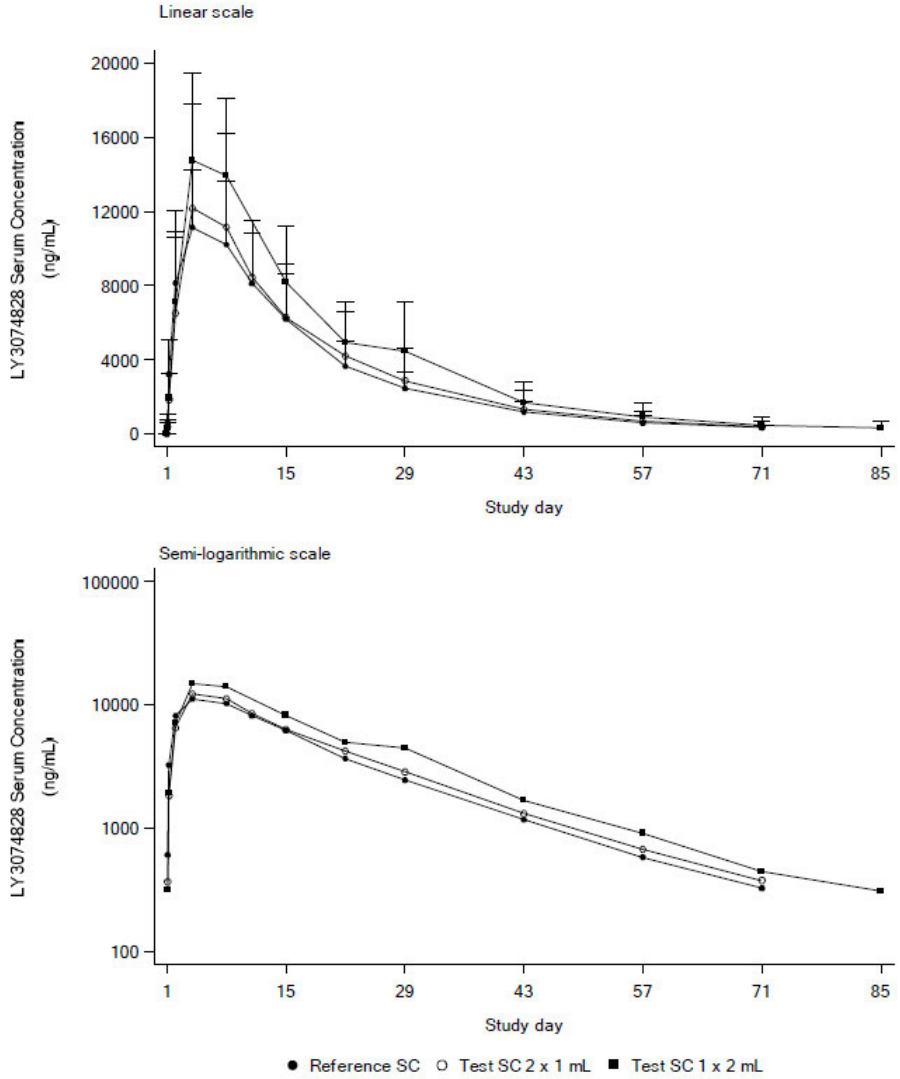
Table 81. Mirikizumab PK Parameters Following 2 x 1 mL or 1 x 2 mL Administration of the Solution Formulation by Whether Injection Site Leakage Occurred

	2 x 1 mL Administration		1 x 2 mL Administration	
	Injection Leakage Geometric mean (CV%) (n=10)	No Leakage Geometric mean (CV%) (n=6)	Injection Leakage Geometric mean (CV%) (n=11)	No Leakage Geometric mean (CV%) (n=6)
C_{max} (µg/mL)	12.3 (36%)	9.62 (60%)	15.4 (26%)	14.0 (41%)
AUC_{inf} (µg·day/mL)	236 (46%)	181 (56%)	294 (25%)	291 (58%)
AUC_{last} (µg·day/mL)	232 (46%)	178 (56%)	291 (25%)	285 (56%)

AUC_{inf} = Area under the concentration-versus-time curve from time of administration to infinity following a single dose; AUC_{last} = area under the concentration-versus-time curve from time of administration to the time of the last measurable concentration; C_{max} = maximum concentration; CV = geometric coefficient of variation.
Source: Reviewer's analysis

Mirikizumab exposure following administration of the solution formulation as two injections (2 x 1 mL) was found to be similar to that after administration of the lyophilized formulation as three injections (2 x 1 mL and 1 x 1.5 mL, 3.5 mL total injection volume). The geometric mean ratios (90% CI) for AUC_{last}, $AUC_{0\text{-}inf}$, and C_{max} were 1.00 (0.81, 1.23), 1.00 (0.81, 1.23), and 0.99 (0.81, 1.20), respectively. Meanwhile, exposure following administration of mirikizumab as two injections (2 x 1 mL) was found to be lower relative to that after administration as a single injection (1 x 2 mL). The geometric mean ratios (90% CI) for AUC_{last}, $AUC_{0\text{-}inf}$, and C_{max} were 0.73 (0.59, 0.90), 0.73 (0.59, 0.90), and 0.75 (0.62, 0.92), respectively. Figure 25 shows the concentration versus time profiles across the treatment groups.

Figure 25. Serum Mirikizumab Concentration Versus Time Profiles in the Arithmetic (Top) and Semi-Logarithmic (Bottom) Scales Following a Single 250 mg SC Dose Administered as a Lyophilized Formulation (Reference), or as a Solution Formulation (Test) as a Single Injection (1 x 2 ml) or as Two Injections (2 x 1 ml) in Study AMAL



Reference SC = 250 mg LY3074828 reference SC (2 x 1 mL, 1 x 1.5 mL);
Test SC 2 x 1 mL = 250 mg LY3074828 test SC (2 x 1 mL);
Test SC 1 x 2 mL = 250 mg LY3074828 test SC (1 x 2 mL)

Source: Figure AMAL.7.1, Clinical Study Report for Study AMAL

Results from study AMAL indicated similarity in exposure following administration of the lyophilized formulation (2 x 1 mL and 1 x 1.5 mL) and the solution formulation administered as 2 x 1 mL, while exposure differed between 2 x 1 mL and 1 x 2 mL administration. As a result, the solution formulation administered SC as 2 x 1 mL was carried forward into phase 3. Overall, the data from study AMAL support the SC administration of mirikizumab as two injections.

16.3.1.2. *Phase 2*

Study AMAC

Study AMAC was designed as a phase 2, multicenter, randomized, double-blind, parallel-group, placebo-controlled study in subjects with moderate to severe UC (n = 249). Subjects were required to have had a diagnosis of UC for at least 3 months before baseline, and to have moderately-to-severely active UC, as defined by an mMS score of 6 to 12 with an endoscopic subscore ≥2 within 14 days before the first dose of study drug. Subjects either received treatment with one or more biologic agents with or without documented history of failure or were naïve to biologic therapy with inadequate response or failure to tolerate current treatment with corticosteroids or immunomodulators.

For all doses administered, mirikizumab was supplied as a lyophilized formulation. Subjects were randomized to receive IV placebo, or mirikizumab induction at Weeks 0, 4, and 8 at starting doses of 50, 200, or 600 mg IV. Subjects in the 50 and 200 mg dose groups could have their doses increased at the Week 4 and Week 8 visits if the projected mirikizumab C_{trough} fell below prespecified thresholds. The concentration thresholds for the 50 and 200 mg dose groups were 0.5 and 2.0 µg/mL, respectively. These thresholds were equal to the 40^{th} percentiles of C_{trough} following 50 mg IV Q4W and 200 mg IV Q4W predicted from earlier clinical studies. The thresholds were selected such that approximately 40% of subjects would have their doses increased. The maximum dose administered did not exceed 600 mg during the induction period. Table 82 summarizes the exposure-based dose adjustments in study AMAC.

Table 82. Summary of Dosing Information in the 50-mg and 200-mg Mirikizumab Cohorts as a Result of Exposure-Based Dose Adjustments in Study AMAC

Induction Cohort	Percentage of Patients Dose-Adjusted	Average Dose at Week 4 (mg)	Patients at 600 mg at Week 4 n/N (%)	Average Dose at Week 8 (mg)	Patients at 600 mg at Week 8 n/N (%)	Overall Average Dose for Induction (mg)
50 mg	73	120	1/63 (2%)	140	3/63 (5%)	100
200 mg	44	280	6/62 (10%)	290	7/62 (11%)	250

N = number of patients in the analysis population; n = number of patients in the specified category.
Source: Table AMAC.11.37, Clinical Study Report for Study AMAC

Subjects who achieved clinical response at Week 12 of mirikizumab induction treatment entered the maintenance period and were re-randomized to receive mirikizumab 200 mg SC at a frequency of Q4W or Q12W. Subjects who received placebo in the induction period continued to receive placebo SC Q4W.

Subjects who did not achieve clinical response at Week 12 had the option to enter an unblinded 92-week extension period that included additional evaluations of induction and maintenance dosing. In the induction phase of the extension period, all subjects received IV mirikizumab at a dose of either 600 or 1000 mg at Weeks 0, 4, and 8. The 600 mg dose was given until implementation of a protocol amendment on Oct. 2016, after which only the 1000 mg dose was administered in the induction phase. Subjects achieving clinical response at Week 12 were

moved into the maintenance phase of the extension period, where they received mirikizumab 200 mg SC Q4W. Subjects who did not achieve clinical response after induction were discontinued from the study.

A total of 249 subjects entered the induction period and 238 completed the induction period. A total of 106 subjects were eligible for and entered the maintenance period, while 132 subjects did not achieve clinical response at Week 12 and were eligible for the extension period. Among the eligible subjects, 128 entered the extension period.

Samples for assessment of mirikizumab PK were collected on Days 1, 15, 29, 43, 57, 78, 85, 92, 113, 141, 169, 225, 281, 337, and 393. On days of IV dosing (Days 1, 29, and 57), samples were collected pre-dose and at the end of IV infusion. On days of SC dosing, samples were collected pre-dose. After dosing on Day 85, an additional PK sample was collected 2-10 days post-dose.

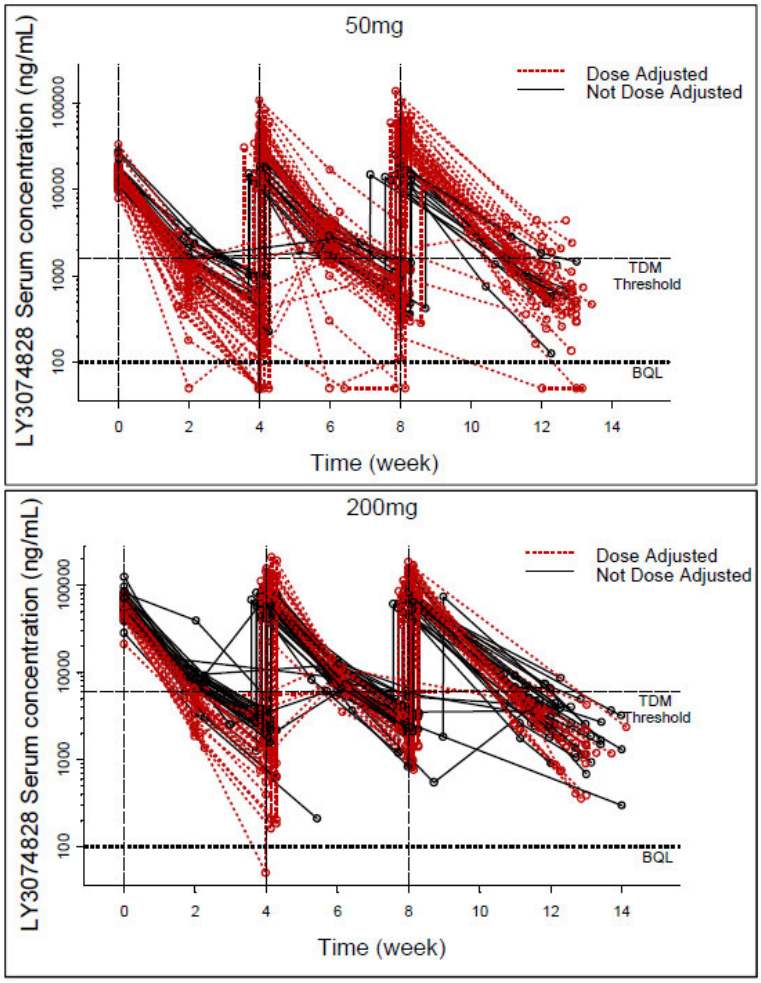
All subjects who received at least one dose of study drug and had sufficient blood sampling to allow for PK evaluation were included in the PK-evaluable population. Data was analyzed using a nonlinear mixed-effect modeling approach. Population PK was also used to characterize the PK of mirikizumab after IV and SC dosing.

Pharmacokinetics

Based on population PK analysis, the estimated systemic clearance (95% CI) of mirikizumab in subjects with UC was 0.023 (0.022, 0.026) L/h. When compared to values from phase 1 studies in healthy subjects (0.013 to 0.017 L/h in study AMAD and 0.012 to 0.015 L/h in study AMBD), mirikizumab clearance appears to be higher in subjects with UC. The estimated SC bioavailability (95% CI) in subjects with UC was 42 (39, 49)%. This is similar to the SC bioavailability observed in healthy subjects, which ranged from 34 to 43% across studies AMAD and AMBD.

Individual mirikizumab concentration-time profiles during the induction period are shown in Figure 26 and highlight the impact of dose adjustment in the 50-mg and 200-mg cohorts. As expected, dose-adjustments led to increases in maximum concentrations and average concentrations during the dosing interval.

Figure 26. Observed Mirikizumab Concentration-Time Profiles and Impact of Dose Adjustment During Induction Treatment at Doses of 50 mg (Top) and 200 mg (Bottom) in Subjects With UC in Phase 2 Study AMAC

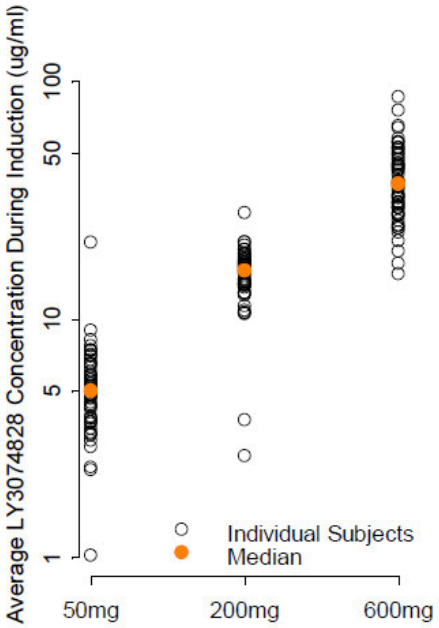


Abbreviations: BQL = lower limit of quantitation of the LY3074828 (mirikizumab) bioanalytical assay; TDM Threshold = therapeutic drug monitoring concentration threshold at Week 2 and Week 6 used to determine if a patient had their dose increased at Week 4 and Week 8.
Note: The overall average doses in the 50-mg and 200-mg cohorts during induction were 100 mg and 250 mg, respectively.

Source: Figure AMAC.11.1, Clinical Study Report for Study AMAC

Figure 27 shows the individual time-averaged serum concentrations across all three induction dosing cohorts estimated using population PK.

Figure 27. Population PK Estimated Time-Averaged Serum Mirikizumab Concentrations Across Dose Cohorts in Subjects With UC During the Induction Period in Phase 2 Study AMAC

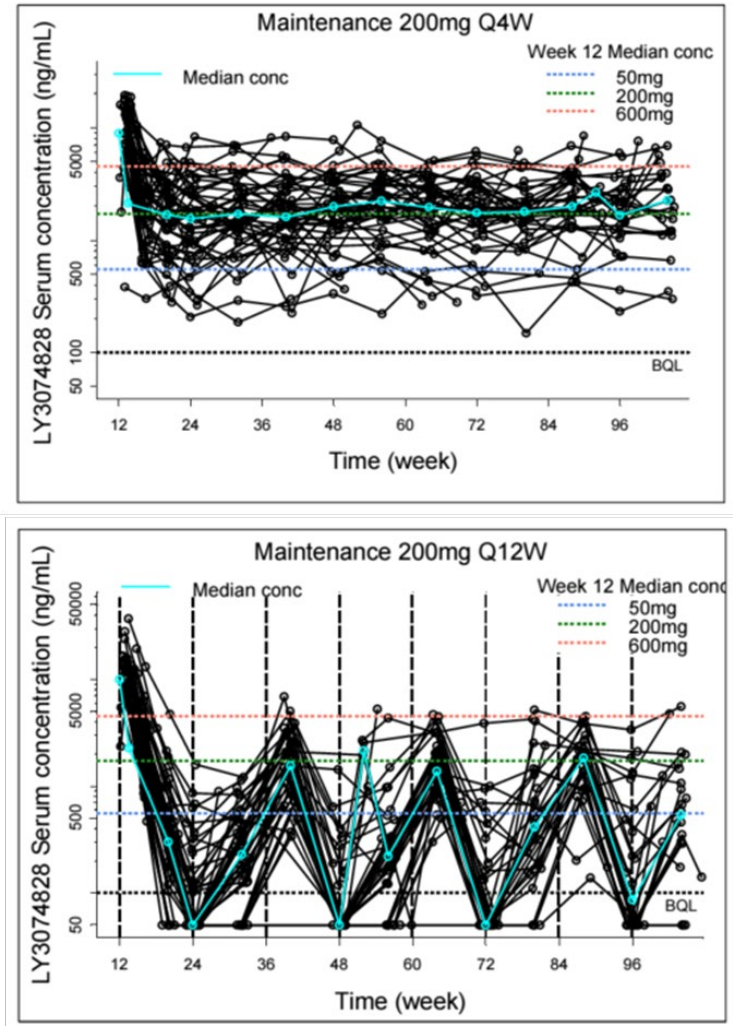


Note: The overall average doses in the 50-mg and 200-mg cohorts during induction were 100 mg and 250 mg, respectively.

Source: Figure AMAC.11.3, Clinical Study Report for Study AMAC

The observed concentration versus time profiles for the Q4W and Q12W SC dosing regimens during the maintenance period are shown in Figure 28. Data from the Q4W regimen represent trough concentrations, while data from the Q12W regimen represent samples collected throughout the dosing interval. Compared to the Q4W regimen, the Q12W regimen showed greater differences between peak and trough concentrations with most trough concentrations falling below the limit of quantitation (BLQ) due to the longer dosing interval. Patients who received the Q4W maintenance regimen also had 2.9-fold higher C_{avg} during maintenance treatment compared to those who received the Q12W maintenance regimen (geometric mean [CV%] = 5.5 ug/mL [41%] versus 1.9 ug/mL [42%]).

Figure 28. Observed Serum Mirikizumab Concentration Versus Time Profiles in Subjects Receiving SC Maintenance Regimens of 200 mg Q4W (Top) and Q12W (Bottom) in Phase 2 Study AMAC.



Note that samples identified as below the quantitation limit (BQL) were plotted at a concentration of 50 ng/mL (i.e., 50% of the lower limit of quantification) to allow visualization on the plot. The Week 12 median concentrations are the median induction concentrations in the induction cohorts of 50, 200, and 600 mg (average induction doses of 100, 250, and 600 mg due to exposure-based dose adjustment, respectively).
Conc = concentration; Q4W = every 4 weeks; Q12W = every 12 weeks.
Source: Figure AMAC.11.2, Clinical Study Report for Study AMAC, pages 142-143, BLA 761279 SDN 1, submitted Mar. 30, 2022

Efficacy and PK during Induction Treatment

The proportions of subjects achieving clinical efficacy endpoints at Week 12 were higher in the 200 mg cohort compared to placebo, the 50 mg cohort, or the 600 mg cohort. The observed efficacy appeared similar or worse in the 600 mg cohort compared to the 200 mg cohort, even though the 600 mg cohort had higher median C_{avg} during induction treatment. It was noted that median CRP at baseline was higher in the 600 mg dose cohort than other treatments and it may suggest that the disease severity may be greater in the 600 mg dose cohort (Table 83). Figure 7

shows the median C_{avg} per cohort during induction treatment and the percent of subjects achieving efficacy endpoints at Week 12 in each induction dosing cohort.

Table 83. Study AMAC Baseline Serum High-Sensitivity C-Reactive Protein Concentration by Cohort

Covariate	Statistic	Placebo induction cohort	50 mg starting dose induction cohort	200 mg starting dose induction cohort	600 mg induction cohort
Baseline High-Sensitivity C-Reactive Protein (mg/L)	N	59	61	61	58
	Mean (SD)	9.3 (13.6)	9.4 (12.9)	9.3 (12.9)	15.1 (26.2)
	Median	4.9	4.9	3.7	6.6
	Min - Max	0.4 - 85.6	0.3 - 67.4	0.4 - 79.1	0.2 - 164

Subjects in the 50 mg starting dose and 200 mg starting dose cohorts received exposure-based mirikizumab dose adjustment at Week 4 and Week 8 up to a maximum of 600 mg per dose.
SD=standard deviation.
Source: Reviewer Analysis of Applicant's Study AMAC Exposure-Response Efficacy Dataset submitted in response to 18May2022 Information Request.

The induction treatment dose for Phase 3 was selected based on comparison of efficacy in each cohort. An induction dosage of 300 mg IV Q4W was selected to closely match the average Week 8 dose in the cohort with the highest rates of efficacy (i.e., 290 mg at Week 8 in the 200 mg cohort following exposure-based dose adjustment).

Efficacy and PK during Maintenance Treatment

A summary of maintenance treatment efficacy outcomes in study AMAC is shown in Table 84. Although no statistical comparisons were made between mirikizumab maintenance treatment groups and placebo, numerically higher proportions of subjects randomized to mirikizumab treatment (200 mg SC Q4W or Q12W) achieved endpoints of clinical remission, clinical response, and endoscopic remission. When comparing the Q4W and Q12W mirikizumab regimens, no statistically significant differences were observed for any efficacy outcomes with the exception of histologic remission in which a lower proportion of subjects achieved histologic remission with the Q12W regimen (2.2% versus 17.0%). A numerically larger proportion of subjects receiving the Q4W regimen achieved endpoints of clinical remission (46.8% versus 37.0%) and clinical response (83.0% versus 76.1%), while a numerically larger proportion of subjects receiving the Q12W regimen achieved endoscopic remission (28.3% versus 14.9%).

Table 84. Summary of Efficacy Outcome Measures at Week 52 for Subjects Who Received Placebo or Mirikizumab Maintenance Treatment in Study AMAC

	Placebo[a] SC Q4W (N = 13)	Miri 200 mg SC Q4W (N = 47)	Miri 200 mg SC Q12W (N = 46)
Secondary Endpoints			
Clinical Remission (%)	7.7%	46.8%	37.0%
Durability of Clinical Remission (%)[b]	0	61.1%	38.5%
Clinical Response (%)	53.8%	83.0%	76.1%
Durability of Clinical Response (%)[c]	53.8%	83.0%	75.0%
Endoscopic Remission (%)	7.7%	14.9%	28.3%
IBDQ Total Score (LS Mean)	64.7	58.3	51.2
IBDQ MCID (%)	76.9%	85.1%	80.4%
IBDQ Remission (%)	53.9%	68.1%	67.4%
SF-36 PCS Score (LS Mean)	10.1	10.1	9.5
SF-36 PCS MCID ≥2.5 points from baseline (%)	61.5%	85.1%	65.2%
SF-36 PCS MCID ≥5 points from baseline (%)	53.9%	74.5%	54.4%
SF-36 MCS Score (LS Mean)	11.7	8.5	7.8
SF-36 MCS MCID ≥2.5 points from baseline (%)	69.2%	70.2%	58.7%
SF-36 MCS MCID ≥5 points from baseline (%)	69.2%	72.3%	63.0%
Exploratory Endpoints			
Partial Mayo (LS Mean)	1.85	1.62	1.98
UCEIS (LS Mean)	-1.31	-2.58	-2.33
Histologic Remission (%)	0	17.0%	2.2%[d]

Abbreviations: EB = exposure-based dosing; IBDQ = Inflammatory Bowel Disease Questionnaire; ITT = intent-to-treat; LS Mean = least squares mean; MCID = minimum clinically important difference; MCS = mental component summary; Miri = mirikizumab;; N = number of patients in the ITT Population; PCS = physical component summary; Q4W = every 4 weeks; Q12W = every 12 weeks; SC = subcutaneous; SF-36 = Medical Outcomes Study 36-Item Short-Form Health Survey; UCEIS = Ulcerative Colitis Endoscopic Index; vs. = versus.

a Although a placebo treatment group in included in this table, there were no statistical comparisons between either of the mirikizumab treatment groups and the placebo group; statistical comparisons were performed between each of the mirikizumab treatment groups. The inclusion of the placebo group helped to maintain the blind during the Maintenance Period of the study

b Durability of clinical remission at Week 52 was assessed in the ITT Population who achieved clinical remission at Week 12 (N=18, Miri SC Q4W; N=31, Miri SC Q12W).

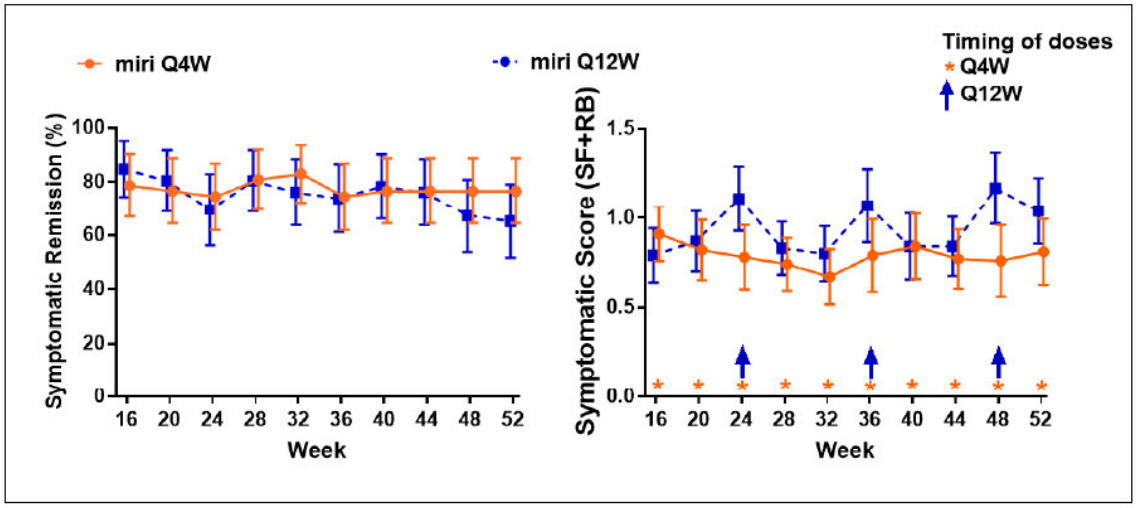
c Durability of clinical response at Week 52 was assessed in the ITT Population who achieved clinical response at Week 12 (N=47, Miri SC Q4W; N=44, Miri SC Q12W).

d p<.05 vs. Miri 200 mg SC Q4W (unadjusted nominal p-value).

Source: Table AMAC.11.40, Clinical Study Report for Study AMAC, pages 159-160, BLA 761279 SDN 1, submitted Mar. 30, 2022

Although the proportions of subjects with symptomatic remission (defined as achieving a rectal bleeding [RB] Mayo subscore of 0, and a stool frequency [SF] Mayo subscore of 0 or 1) did not differ significantly in the Q4W regimen compared to Q12W, the symptomatic score (defined as the sum of the RB and SF Mayo subscores) tended to increase (i.e., worsen) at the end of each dosing interval in subjects receiving the Q12W regimen (Figure 29).

Figure 29. Summary of Symptomatic Remission (Left) and Mayo Symptomatic Score (Right) Over Time Among Subjects Receiving Mirikizumab Maintenance Treatment 200 mg SC Q4W or Q12W in Study AMAC



Abbreviations: miri = mirikizumab; Q4W = every 4 weeks; Q12W = every 12 weeks.
RB = rectal bleeding; SF = stool frequency.

Source: Figure 2.7.2.18, Summary of Clinical Pharmacology, page 64, BLA 761279 SDN 1, submitted Mar. 30, 2022

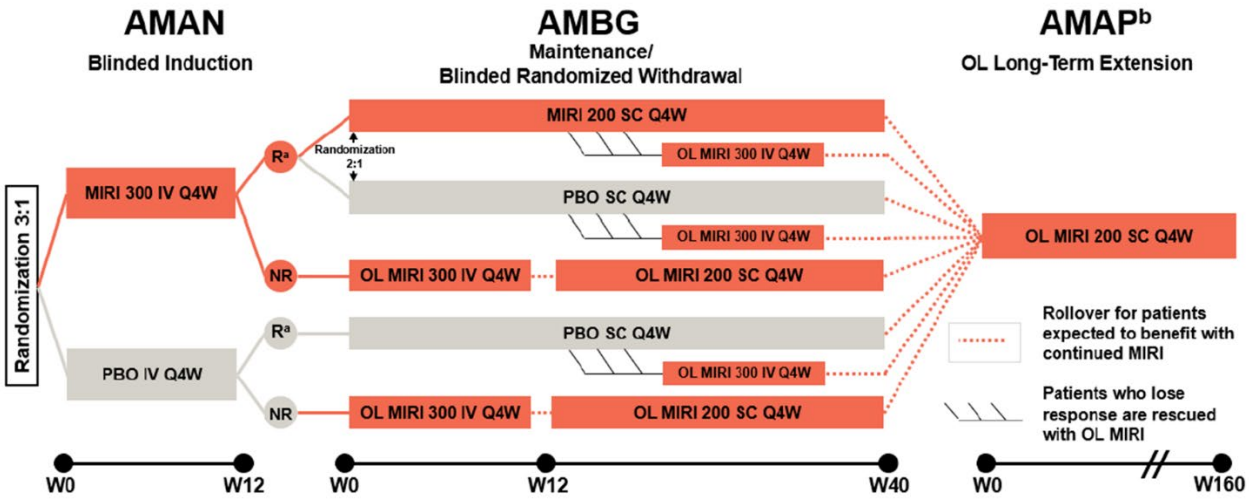
Overall, the results from study AMAC suggest that the higher C_{avg}, C_{trough}, or both, associated with the Q4W regimen results in better average symptomatic scores compared to the Q12W regimen. Based on data presented above, the 200 mg SC Q4W maintenance regimen was selected for evaluation in phase 3.

16.3.1.3. *Phase 3*

Study AMAN and Study AMBG

The phase 3 program was comprised of AMAN and AMBG, sequentially conducted studies enrolling a single cohort of subjects with UC. The studies were designed as multicenter, randomized, double-blind, parallel-arm, and placebo-controlled. The aim of the studies was to evaluate the safety and efficacy of mirikizumab as compared with placebo. AMAN evaluated induction dosing, while AMBG evaluated maintenance dosing. The phase 3 development program is shown in Figure 30. Refer to Section 8.1 for more details.

Figure 30. Phase 3 Development Program for Mirikizumab for the Treatment of UC



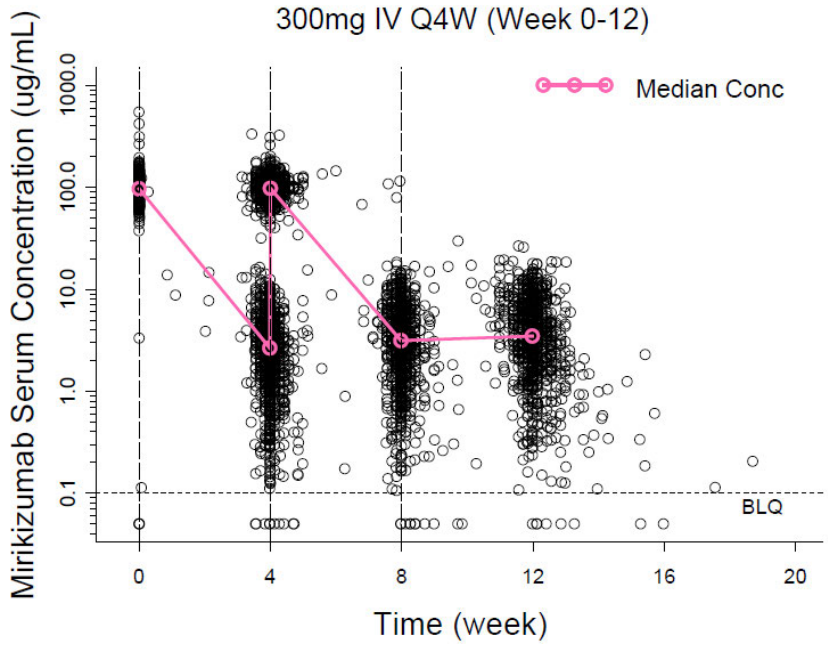
Source: Figure 2.5.1.1, Clinical Overview

Pharmacokinetics

In AMAN, pre-dose PK samples were collected at Weeks 0, 4, and 8. Post-dose samples were collected at Weeks 0 and 4 up to 2 hours after dosing. Another sample was collected at Week 12, which served as the Week 0 value for AMBG. In AMBG, pre-dose samples were collected at Weeks 4, 12, 24, and 40. Additional samples could be collected at Weeks 16, 20, 28, 32, and 36 in subjects with confirmed loss of response prior to open-label mirikizumab IV rescue induction.

Observed mirikizumab concentrations in AMAN following 300 mg IV Q4W induction dosing are shown in Figure 31 and observed trough concentrations are summarized in Table 85. Data indicate similar mirikizumab trough concentrations at Weeks 4, 8, and 12, with limited accumulation after repeat dosing.

Figure 31. Observed Mirikizumab Concentrations After Induction Dosing With 300 mg IV Q4W in Study AMAN



Note that the vertical dashed lines represent scheduled mirikizumab dose administration. The horizontal dashed line represents the assay LLOQ of 0.1 mcg/mL (100 ng/mL). BLQ concentrations are represented as LLOQ/2.
BLQ = below the limit of quantification; conc = mir kizumab concentration; IV = intravenous; LLOQ = lower limit of quantification; Q4W = every 4 weeks.
Source: Figure AMAN.5.6, Clinical Study Report for Study AMAN

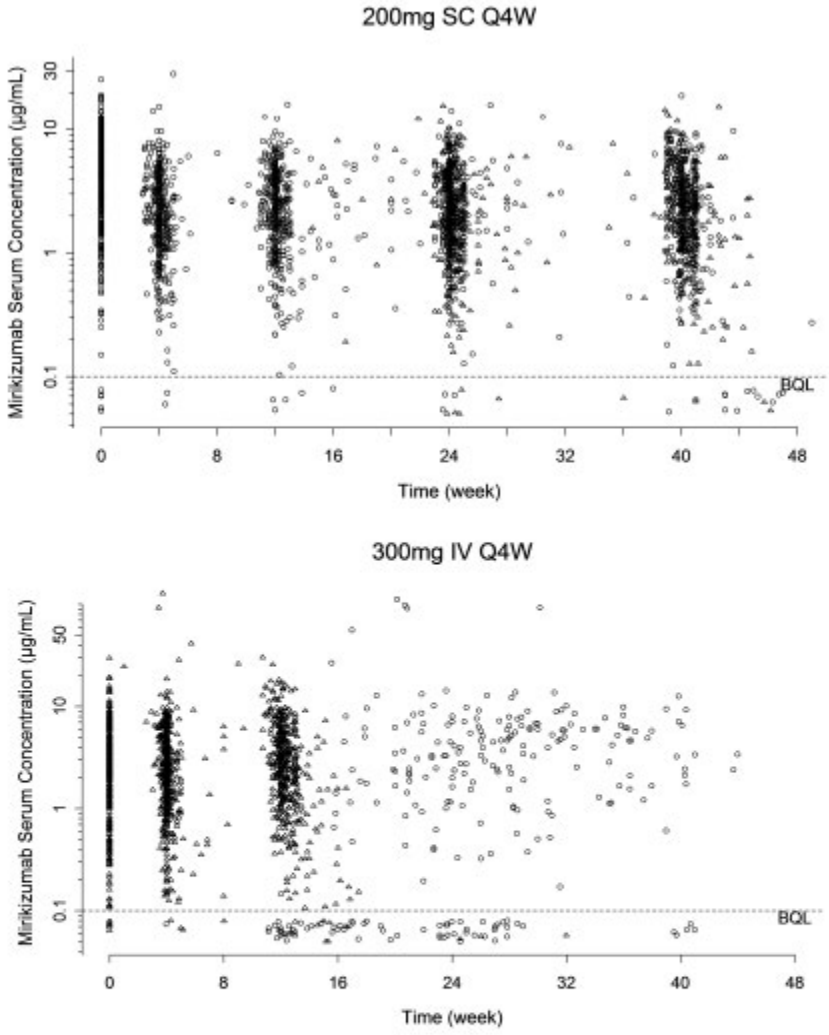
Table 85. Summary of Mirikizumab Trough Concentrations During Induction Period Following Mirikizumab 300 mg IV Q4W in Study AMAN.

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

Abbreviations: BLQ = below limit of quantitation; CV = coefficient of variation; IV = intravenous; LLOQ = lower limit of quantitation; n = number of samples; Q4W = every 4 weeks.
Note: Trough is defined as being collected between 21 and 35 days from the last dose for Q4W dosing regimen.
BLQ concentrations were represented as 0.05 µg/mL, which is half of the assay LLOQ.
Source: Table 2.7.2.5 in Applicant's Summary of Clinical Pharmacology

Observed mirikizumab concentrations in AMAN responders and nonresponders in AMBG following 200 mg SC Q4W maintenance dosing, 300 mg IV Q4W extended induction dosing, or 300 mg IV Q4W rescue induction dosing are shown in Figure 32. Trough concentrations following 200 mg SC Q4W maintenance dosing in AMAN responders and 300 mg IV Q4W extended induction dosing in AMAN nonresponders are tabulated in Table 86.

Figure 32. Observed Mirikizumab Concentrations in AMAN Responders and Nonresponders After Mirikizumab Maintenance Dosing With 200 mg SC Q4W (Top) or Extended/Rescue Induction Dosing With 300 mg IV Q4W (Bottom) in Study AMBG



Abbreviations: BQL = lower limit of quantitation of the LY3074828 (mirikizumab) bioanalytical assay; IV = intravenous; Q4W = every 4 weeks; SC = subcutaneous.

Note: Results from Visit 5 (Week 12) of Study AMAN were included as Week 0 for patients who started on either 200 mg SC Q4W or 300 mg IV Q4W in Study AMBG.

Top plot: Circles represent AMAN responders receiving 200mg SC Q4W and the triangles represent AMAN nonresponders who became responders at Week 12 in Study AMBG and received 200mg SC Q4W in the Open-label Maintenance Period.

Bottom plot: Triangles represent AMAN nonresponders receiving 300mg IV Q4W in the Open-label Extended Induction Period and circles represent AMAN responders who lost response after Week 12 in Study AMBG and received 300mg IV Q4W.

Source: Figure AMBG.5.10, Clinical Study Report for Study AMBG

Table 86. Observed Mirikizumab Trough Concentrations in AMAN Responders and Nonresponders After Mirikizumab Maintenance Dosing With 200 mg SC Q4W or Extended Induction Dosing With 300 mg IV Q4W, Respectively, in Study AMBG

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

Abbreviations: BLQ = below limit of quantitation; CV = coefficient of variation; IV = intravenous; LLOQ = lower limit of quantitation; n = number of samples; NC = not calculated; Q4W = every 4 weeks; SC = subcutaneous.
Note: Results from V5 (Week 12) of Study AMAN were included as Week 0 for patients who started on either 300 mg Q4W IV or 200 mg Q4W SC in this study. Responders in Study AMAN who received rescue therapy of 300 mg Q4W IV were not included in this summary. Trough is defined as being collected between 21-35 days from last dose for Q4W regimen. BLQ concentrations were represented as 0.05 ug/mL, which is half of the assay LLOQ.
Source: Table AMBG.5.53, Clinical Study Report for Study AMBG

AMAN responders who were randomized to 200 mg SC Q4W maintenance treatment showed reductions in the median trough concentration after the first maintenance dose (i.e., at Week 4), as compared with the median trough concentration following the third 300 mg IV induction dose (i.e., at Week 0, Week 12 of AMAN). Median trough concentrations remained similar with repeat maintenance dosing at Weeks 12, 24, and 40, with limited accumulation after repeat dosing. Mirikizumab trough concentrations in AMAN nonresponders who continued on open-label 300 mg IV Q4W extended induction were consistent with values observed after induction dosing in AMAN as well as with values observed in AMAN responders receiving SC maintenance treatment.

Population PK was also used to analyze serum concentration-time data in AMAN/AMBG. Refer to Section 16.3.3 for the detailed population PK analysis.

Pharmacodynamics

PD biomarkers were measured during phase 3, including high-sensitivity C-reactive protein (hsCRP) and fecal calprotectin, markers of inflammation. During induction treatment in phase 3 (AMAN), subjects randomized to receive mirikizumab showed significant reductions from baseline in mean hsCRP and fecal calprotectin at Week 12 (Table 87).

Table 87. Changes in Mean and Median High-Sensitivity C-Reactive Protein and Fecal Calprotectin From Baseline to Week 12 in Phase 3 Study AMAN After Induction Dosing With Placebo or Mirikizumab in Subjects With UC

	High-Sensitivity C-Reactive Protein		Fecal Calprotectin	
	Placebo IV Q4W (n=294)	Mirikizumab 300 mg IV Q4W (n=868)	Placebo IV Q4W (n=294)	Mirikizumab 300 mg IV Q4W (n=868)
Baseline				
N	279	837	243	722
LS mean (SE), mg/L	9.44 (0.91)	9.25 (0.53)	2970 (304)	3121 (176)
Median, mg/L	4.25	4.04	1465	1556
Week 12				
N	279	837	243	722
LS mean (SE), mg/L	8.42 (0.57)	4.68 (0.35)	2386 (207)	1222 (130)
Median, mg/L	3.13	1.70	1040	398

Note that sample sizes remained the same at Baseline and Week 12 as a modified baseline observation carried forward approach was used to handle missing data.
Source: Reviewer-generated table adapted from Tables 2.7.2.11 and 2.7.2.13, Summary of Clinical Pharmacology, pages 52 and 54, BLA 761279 SDN 1, submitted Mar. 30, 2022

Among subjects who were considered mirikizumab induction responders after induction dosing in AMAN and continued to receive 200 mg SC Q4W maintenance treatment in AMBG, mean hsCRP and fecal calprotectin remained low (Table 88). While hsCRP concentrations were sustained over 40 weeks of maintenance treatment, mean fecal calprotectin appeared to reduce further relative to observations at the end of AMAN. Mirikizumab induction responders who were randomized to receive placebo maintenance treatment in AMBG showed increases in mean hsCRP and fecal calprotectin relative to observations at the end of AMAN.

Results in Table 88 should be interpreted with caution given the differences in sample size between observations at baseline (Week 12 of AMAN) and those at Week 40 of AMBG, with more dropouts in subjects re-randomized to placebo compared to those randomized to receive mirikizumab maintenance treatment.

Table 88. Changes in Mean and Median High-Sensitivity C-Reactive Protein and Fecal Calprotectin From Baseline (Week 12 of Study AMAN) to Week 40 in Phase 3 Study AMBG (Week 52 Overall) After Maintenance Dosing With Placebo or Mirikizumab in Subjects With UC Who Responded to Mirikizumab Induction

	High-Sensitivity C-Reactive Protein		Fecal Calprotectin	
	Placebo SC Q4W (n = 179)	Mirikizumab 200 mg SC Q4W (n = 365)	Placebo SC Q4W (n = 179)	Mirikizumab 200 mg SC Q4W (n = 365)
Baseline				
N	177	357	169	332
Mean (SD), mg/L	2.91 (5.68)	3.33 (6.93)	612 (1051)	749 (2042)
Median, mg/L	1.02	1.17	151	211
Week 40				
N	105	319	89	283
Mean (SD), mg/L	4.07 (9.20)	3.23 (5.18)	833 (1374)	398 (830
Median, mg/L	1.01	1.36	283	124

Note that Baseline values are derived from measurements taken at Week 12 of study AMAN (prior to mirikizumab maintenance)
Source: Reviewer-generated table adapted from Tables APP.2.7.3.6.85 and APP.2.7.3.6.87, Summary of Clinical Efficacy Appendix, pages 831 and 837, BLA 761279 SDN 1, submitted Mar. 30, 2022

Overall, the observed PD changes support the purported mechanism of action of mirikizumab, including blocking binding of IL-23 with subsequent reductions in inflammatory markers. However, the relationship between these PD effects and the mechanisms through which mirikizumab exerts its clinical effects is not known.

Immunogenicity

In AMAN, samples to assess immunogenicity were collected at Baseline, pre-dose at Weeks 4 and 8, and at Week 12. Induction responders entering AMBG for maintenance treatment had immunogenicity samples collected pre-dose at Weeks 0, 4, 12, 16, 20, 24, 28, 32, 36, and 40. Subjects who did not respond to induction in AMAN and entering AMBG for extended induction dosing had immunogenicity samples collect pre-dose at Weeks 0, 4, 8. Additional pre-dose samples were collected at Weeks 24 and 40, after subjects transitioned to open-label 200 mg SC Q4W maintenance treatment.

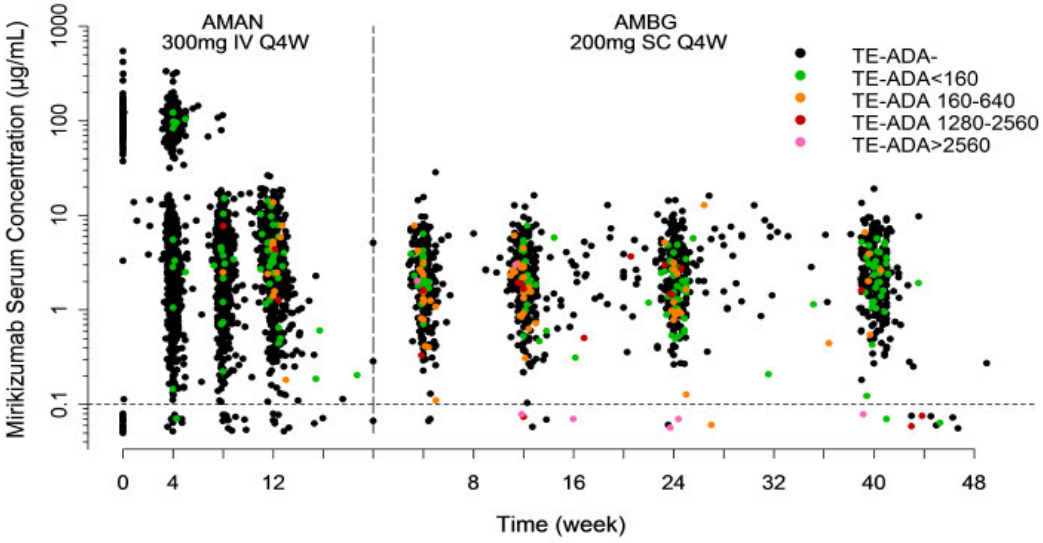
Although the primary immunogenicity assessment was based on subjects that were randomized to receive the proposed dosing regimen for treatment of UC (see Section 6.3.1.4), additional immunogenicity analysis was carried out using a population consisting of patients treated at any time with mirikizumab (all dosing regimens) in AMAN, AMBG, and the long-term extension study AMAP. Out of 1159 evaluable subjects in this population, 210 (18%) developed TE-ADAs. Out of 210 TE-ADA positive subjects, 96 (46%) had titers ≥160. When considering all subjects receiving any mirikizumab dosing regimen, the incidence of immunogenicity is consistent with analyses of subjects receiving the proposed dosing regimen for treatment of UC.

Impact of Immunogenicity on PK

Across studies AMAN and AMBG, TE ADA positive subjects generally had mirikizumab exposures similar to that in subjects who were negative for TE ADAs. Population PK analysis determined that neither TE ADA status nor TE ADA titer had a statistically significant impact on individual predicted clearance. See Figure 6 for a summary of model-estimated individual mirikizumab CL by TE ADA titer. However, the lack of an observed effect may be due to the low numbers of subjects with TE ADA titers ≥1280.

Although population PK analysis did not identify any differences in PK or exposure according to TE ADA titer, patients with TE ADA titers ≥1280 may have lower PK concentrations than patients without TE ADA and patients with lower TE ADA titers.

Figure 33. Observed Mirikizumab Serum Concentrations by TE ADA Titer Categories Following Administration of Mirikizumab 300 mg IV Q4W in Study AMAN and 200 mg SC Q4W in Study AMBG.



Abbreviations: IV = intravenous; LLOQ = lower limit of quantitation of the LY3074828 (mirikizumab) bioanalytical assay; Q4W = every 4 weeks; SC = subcutaneous; TE ADA = treatment-emergent anti-drug antibody.

Note: Individual dots represent individual PK samples. The week 4 visit in study AMAN included samples taken both before and after the mirikizumab infusion. The horizontal dashed line represents the LLOQ value (0.1µg/mL) reported from bioanalytical results.

(Source: Figure ISI.8.1, Integrated Summary of Immunogenicity, page 66, BLA 761279 SDN 1, submitted Mar. 30, 2022)

See Figure 33 for observed PK concentrations over time according to TE ADA titer.

Out of 32 subjects with TE ADA titers ≥160, 10 (31%) were identified as having reduced mirikizumab exposures. Based on the Applicant's definition, to be classified as having reduced exposures due to TE ADAs, changes in mirikizumab concentrations needed to occur after the emergence of TE ADAs, and concentrations were required to drop below a cutoff of 0.511 µg/mL during maintenance treatment. This cutoff is the 5th percentile of trough concentrations associated with ADA negative samples among subjects randomized to receive mirikizumab 200 mg SC Q4W in study AMBG.

Due to the low occurrence of relatively high TE ADA titers (≥ 160), the effect of high TE ADA titers on the pharmacokinetics of mirikizumab is unknown.

Impact of Immunogenicity on Efficacy

The impact of immunogenicity on efficacy in phase 3 was also evaluated among subjects who received the proposed induction and maintenance dosage for UC. The impacts of both TE ADA presence and titer on clinical outcomes were assessed at Week 40 of maintenance study AMBG (52 weeks of treatment including the induction study AMAN), including clinical remission, endoscopic improvement, and clinical response.

Baseline characteristics of subjects by ADA status and titer categories are shown below in Table 89. Baseline disease characteristics and current or prior therapy for UC appeared generally similar between subjects that were TE ADA negative and TE ADA positive, although with a couple differences. For example, a greater proportion of TE ADA negative subjects had failed previous biologic or tofacitinib therapy at baseline (38% versus 28%) and TE ADA negative subjects had longer mean duration of UC (7.1 vs. 5.9 years). Meanwhile, a greater proportion of TE ADA positive subjects had pancolitis (i.e., inflammation affecting the entire colon) (43% versus 32%). Further imbalances were observed between ADA titer groups, likely due to the small sample sizes of subjects with higher ADA titers. For example, greater proportions of subjects in higher ADA titer groups had baseline severe Modified Mayo Score (mMS), presented with pancolitis, and were taking baseline corticosteroids.

Table 89. Baseline Characteristics by ADA Status Categories for Subjects Treated With Mirikizumab 300 mg IV Q4W Induction Followed by 200 mg SC Q4W Maintenance Over 52 Weeks in Studies AMAN and AMBG

Baseline Characteristics by ADA Status Categories

UC Treatment Regimen Immunogenicity and Efficacy Analysis Set, Excluding Patients in China (Studies: AMAN/AMBG)

ADA Status Category	n (%)	BL MMS	BL MMS Severe	BL Mayo Endo	BL Mayo Endo Severe	BL Corticosteroids	BL Immunomodulators	Failed Biologic/Tofa	Pancolitis	Duration of UC (y)
All Subjects	356 (100.0)	6.51 (1.33)	50.8% (181/356)	2.64 (0.48)	64.3% (229/356)	37.4% (133/356)	21.3% (76/356)	35.4% (126/356)	34.3% (122/356)	6.85 (7.16)
TE ADA-	269 (75.6)	6.50 (1.36)	50.6% (136/269)	2.64 (0.48)	64.3% (173/269)	37.2% (100/269)	21.6% (58/269)	37.9% (102/269)	31.6% (85/269)	7.14 (7.57)
TE ADA+	87 (24.4)	6.55 (1.23)	51.7% (45/87)	2.64 (0.48)	64.4% (56/87)	37.9% (33/87)	20.7% (18/87)	27.6% (24/87)	42.5% (37/87)	5.94 (5.65)
TE ADA-, or TE ADA+ with Max Titer < 1:80	307 (86.2)	6.50 (1.35)	50.2% (154/307)	2.64 (0.48)	64.2% (197/307)	36.5% (112/307)	21.5% (66/307)	36.8% (113/307)	32.6% (100/307)	6.90 (7.33)
TE ADA+ with Max Titer >= 1:80	49 (13.8)	6.59 (1.21)	55.1% (27/49)	2.65 (0.48)	65.3% (32/49)	42.9% (21/49)	20.4% (10/49)	26.5% (13/49)	44.9% (22/49)	6.53 (5.99)
TE ADA-, or TE ADA+ with Max Titer < 1:160	324 (91.0)	6.52 (1.35)	50.6% (164/324)	2.65 (0.48)	64.5% (209/324)	36.7% (119/324)	21.3% (69/324)	37.0% (120/324)	33.3% (108/324)	6.96 (7.31)
TE ADA+ with Max Titer >= 1:160	32 (9.0)	6.50 (1.19)	53.1% (17/32)	2.62 (0.49)	62.5% (20/32)	43.8% (14/32)	21.9% (7/32)	18.8% (6/32)	43.8% (14/32)	5.74 (5.27)
TE ADA-, or TE ADA+ with Max Titer < 1:320	338 (94.9)	6.51 (1.33)	50.6% (171/338)	2.64 (0.48)	64.5% (218/338)	37.0% (125/338)	21.6% (73/338)	36.4% (123/338)	33.4% (113/338)	6.86 (7.23)
TE ADA+ with Max Titer >= 1:320	18 (5.1)	6.50 (1.34)	55.6% (10/18)	2.61 (0.50)	61.1% (11/18)	44.4% (8/18)	16.7% (3/18)	16.7% (3/18)	50.0% (9/18)	6.63 (5.89)
TE ADA-, or TE ADA+ with Max Titer < 1:640	344 (96.6)	6.51 (1.34)	50.3% (173/344)	2.64 (0.48)	64.2% (221/344)	37.2% (128/344)	21.5% (74/344)	36.0% (124/344)	33.7% (116/344)	6.85 (7.20)
TE ADA+ with Max Titer >= 1:640	12 (3.4)	6.67 (1.23)	66.7% (8/12)	2.67 (0.49)	66.7% (8/12)	41.7% (5/12)	16.7% (2/12)	16.7% (2/12)	50.0% (6/12)	6.74 (5.95)
TE ADA-, or TE ADA+ with Max Titer < 1:1280	349 (98.0)	6.51 (1.33)	50.4% (176/349)	2.64 (0.48)	64.2% (224/349)	37.0% (129/349)	21.5% (75/349)	35.8% (125/349)	34.1% (119/349)	6.87 (7.19)
TE ADA+ with Max Titer >= 1:1280	7 (2.0)	6.71 (1.38)	71.4% (5/7)	2.71 (0.49)	71.4% (5/7)	57.1% (4/7)	14.3% (1/7)	14.3% (1/7)	42.9% (3/7)	5.78 (5.36)

Program Location: /lillyce/prd/ly3074828/regulatory/subm_uc/programs/non_sas/primary/isi/miri_uc_efficacy_versus_ada_displays.R
Dataset Location: /lillyce/prd/ly3074828/regulatory/subm_uc/output/shared/non_sas/isi/baseline_characteristics_by_ada_status_categories.rds
Output Location: /lillyce/prd/ly3074828/regulatory/subm_uc/output/shared/non_sas/isi/baseline_characteristics_by_ada_status_categories.png

Source: Table App.2.16, Integrated Summary of Immunogenicity Appendix, page 59, BLA 761279 SDN 1, submitted Mar. 30, 2022

The proportions of subjects achieving clinical outcomes at Week 40 of study AMBG (Week 52 of treatment overall) by ADA status and titer categories are shown in Table 90. The proportion of TE ADA positive subjects (n = 87) that achieved outcomes of clinical remission and endoscopic improvement was not lower relative to TE ADA negative subjects (n = 269) (58% versus 48%, respectively for clinical remission; and 66% versus 57%, respectively for endoscopic improvement). A similar proportion of patients also achieved clinical response at Week 40 regardless of TE ADA status (83% versus 80%). Among ADA titer groups, a lower proportion of TE ADA positive subjects with titers ≥160 (n = 32) achieved clinical remission (38% versus 51%), endoscopic improvement (50% versus 60%), and clinical response (72% versus 81%).

Overall, TE ADA status (positive versus negative) was not associated with lower efficacy at Week 52 following the proposed induction and maintenance dosage. TE ADA titers ≥160 may be associated with lower efficacy at Week 52, but the presence and magnitude of this effect is uncertain due to the limited number of patients with titers ≥160.

Table 90. Clinical Outcomes at Week 40 of Study AMBG by ADA Status Categories for Subjects Treated With Mirikizumab 300 mg IV Q4W Induction Followed by 200 mg SC Q4W Maintenance Over 52 Weeks

Key Outcomes at AMBG Week 40 by ADA Status Categories

UC Treatment Regimen Immunogenicity and Efficacy Analysis Set, Excluding Patients in China (Studies: AMAN/AMBG)

ADA Status Category	n (%)	Clinical Remission	Endoscopic Improvement	Clinical Response
All Subjects	356 (100.0)	50.0% (178/356)	58.7% (209/356)	80.3% (286/356)
TE ADA-	269 (75.6)	47.6% (128/269)	56.5% (152/269)	79.6% (214/269)
TE ADA+	87 (24.4)	57.5% (50/87)	65.5% (57/87)	82.8% (72/87)
TE ADA-, or TE ADA+ with Max Titer < 1:80	307 (86.2)	49.5% (152/307)	58.3% (179/307)	80.5% (247/307)
TE ADA+ with Max Titer >= 1:80	49 (13.8)	53.1% (26/49)	61.2% (30/49)	79.6% (39/49)
TE ADA-, or TE ADA+ with Max Titer < 1:160	324 (91.0)	51.2% (166/324)	59.6% (193/324)	81.2% (263/324)
TE ADA+ with Max Titer >= 1:160	32 (9.0)	37.5% (12/32)	50.0% (16/32)	71.9% (23/32)
TE ADA-, or TE ADA+ with Max Titer < 1:320	338 (94.9)	51.5% (174/338)	59.5% (201/338)	81.1% (274/338)
TE ADA+ with Max Titer >= 1:320	18 (5.1)	22.2% (4/18)	44.4% (8/18)	66.7% (12/18)
TE ADA-, or TE ADA+ with Max Titer < 1:640	344 (96.6)	50.6% (174/344)	59.0% (203/344)	81.1% (279/344)
TE ADA+ with Max Titer >= 1:640	12 (3.4)	33.3% (4/12)	50.0% (6/12)	58.3% (7/12)
TE ADA-, or TE ADA+ with Max Titer < 1:1280	349 (98.0)	50.4% (176/349)	59.0% (206/349)	80.8% (282/349)
TE ADA+ with Max Titer >= 1:1280	7 (2.0)	28.6% (2/7)	42.9% (3/7)	57.1% (4/7)

NOTE: Efficacy data from AMBG Week 40 in AMAN Miri Responders after 52 weeks of treatment.
Program Location: /lillyce/prd/ly3074828/regulatory/subm_uc/programs/non_sas/primary/isi/miri_uc_efficacy_versus_ada_displays.R
Dataset Location: /lillyce/prd/ly3074828/regulatory/subm_uc/output/shared/non_sas/isi/miri_uc_efficacy_results_by_ada_status_categories.rds
Output Location: /lillyce/prd/ly3074828/regulatory/subm_uc/output/shared/non_sas/isi/key_outcomes_by_ada_status_categories.png

Source: Figure ISI.8.4, Integrated Summary of Immunogenicity, page 71, BLA 761279 SDN 1, submitted Mar. 30, 2022

Impact of Immunogenicity on PK and Efficacy

Additional analysis was conducted to determine whether a reduction in exposure to mirikizumab due to TE ADAs was associated with loss of response in phase 3. Subjects were classified as having lost response if they achieved either clinical remission or clinical response at the end of induction in AMAN (Week 12), but no longer met that same endpoint after maintenance treatment at the end of AMBG (either at Week 52, or at the second of two Loss of Response visits). Table 91 below describes how subjects were categorized as demonstrating a loss of response during study AMBG.

Table 91. Categorization for Identifying Subjects Who Lost Response at the End of Study AMBG (Week 52) Based on Response Achieved at the End of Study AMAN (Week 12)

Study AMAN		Study AMBG		Classified as Loss of Efficacy
Clinical Remission	Clinical Response	Clinical Remission	Clinical Response	
X	X	-	-	Yes
	X	-	-	Yes
X	X	-	X	Yes
	X	-	X	No
X	X	X	X	No
	X	X	X	No

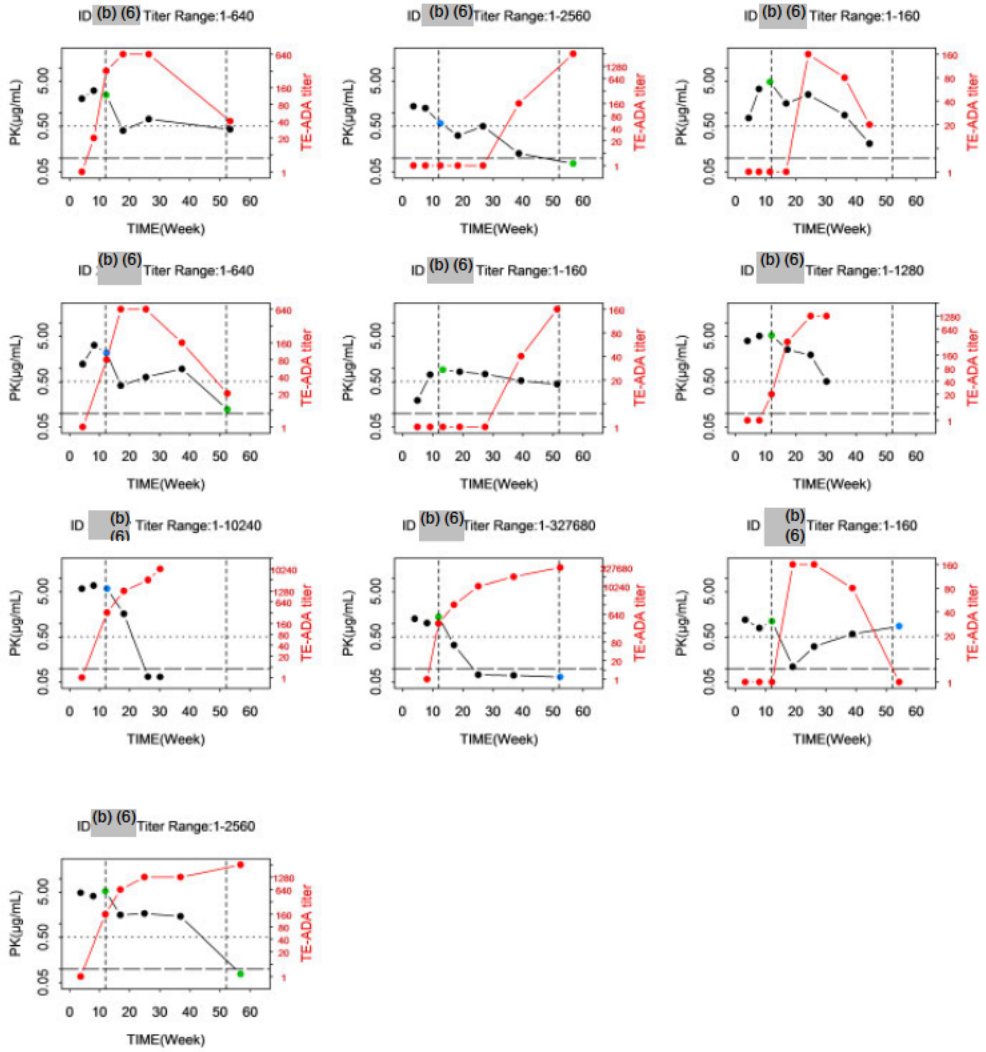
Note: Based on how these endpoints are evaluated, any patient achieving Clinical Remission will also have achieved Clinical Response. Clinical evaluations were made at Week 12 of the Study AMAN (end of study) and Week 40 of the Study AMBG (end of the study; Week 52 overall).

Source: Figure ISI.8.5, Integrated Summary of Immunogenicity, page 72, BLA 761279 SDN 1, submitted Mar. 30, 2022

All 10 patients with reduced mirikizumab exposures due to the presence of TE ADA achieved clinical response (n = 7) or clinical remission (n = 3) by the end of study AMAN (Week 12). Loss of efficacy at the end of study AMBG (Week 40) was observed in 7 of these 10 subjects (70%), including 5 subjects who did not achieve clinical response (Figure 34). One subject classified as having loss of response (ID (b) (6) in Figure 34) received rescue induction and was transitioned to open-label mirikizumab 300 mg IV Q4W. This subject was discontinued from the study due to lack of efficacy after receiving three doses of rescue induction therapy. Although loss of efficacy in 7 subjects was associated with reduced mirikizumab exposure due to the presence of TE ADA, it is noteworthy that two subjects (IDs (b) (6) and (b) (6) in Figure 34) did not demonstrate a loss of response and still achieved either clinical remission or clinical response at Week 52 despite having mirikizumab concentrations below the limit of quantitation.

Overall, higher TE ADA titers that were associated with reductions in mirikizumab PK and loss of efficacy were observed in approximately 2% (7/356) of ADA evaluable patients treated with mirikizumab induction (300 mg IV Q4W) followed by mirikizumab maintenance (200 mg SC Q4W) in phase 3 studies AMAN and AMBG.

Figure 34. Individual PK and TE ADA Titer Profiles for Subjects Receiving 200 mg SC Q4W Mirikizumab in Study AMBG and Identified as Having Reduced Exposure to Mirikizumab Due to TE ADA



Note that subject IDs denoted with an asterisk (*) are those identified as having a loss of efficacy corresponding to reduced PK and TE ADA. Black circles represent PK concentrations. Green and blue circles represent achieving clinical response or clinical remission, respectively, based on modified Mayo score at Weeks 12 and 52. Red circles represent TE ADA titers over time.
The horizontal dotted line is set to a value of 0.511 µg/mL, the 5th percentile of trough concentrations at Weeks 4, 12, 20, and 40 in all ADA negative samples from patients who received 200 mg SC Q4W in study AMBG.
The horizontal dashed line is set to a value of 0.1 µg/mL, the lower limit of quantitation derived from the bioanalytical method
The vertical dashed lines indicate time at Weeks 12 and 52.
Source: Figure APP.2.3, Integrated Summary of Immunogenicity Appendix, pages 24-25, BLA 761279 SDN 1, submitted Mar. 30, 2022

16.3.2. Bioanalytical Method Validation

Throughout the program, mirikizumab in serum was measured by the same bioanalytical method (Method Validation Report 179714) at the same bioanalytical site (b) (4) except for study AMBD for which the bioanalytical assay was done at (b) (4)).

The cross-validation performed for the assay performance between two laboratories was acceptable. It was noted that the validated concentration range was up to 10000 ng/ml while the majority of samples had concentrations higher than 10000 ng/ml concentrations. The dilution linearity was established for dilutions ranging from 1:62.5 to 1:2,500.

Review of bioanalytical reports indicated that the bioanalytical method for measurement of mirikizumab concentrations performed acceptably in each study. This includes relative bioavailability study AMBW, which provides pivotal evidence to support use of the AI presentation.

Assay Method Validation Report 179714 – Determination of LY3074828 [mirikizumab] in Human Serum by ELISA ((b) (4))

The assay method is based on binding of mirikizumab to IL-23 that has been immobilized onto a microtiter plate. After blocking un-adsorbed sites, analyte in the samples, including standards, quality control samples (QCs), and trial samples, are dispensed onto the plate and incubated. A mouse anti-human IgG4 horseradish peroxidase (HRP) conjugate is added. The reaction is initiated via the addition of tetramethylbenzidine, which leads to the development of color proportional to the amount of mirikizumab present. Runs are read on a plate reader at 450 nm (detection) and 620 nm (background), and concentrations are determined on a standard curve.

Table 92. Method Validation Report 179714

Bioanalytical method review summary	Method validation adequate to support results in studies AMAA, AMAD, AMBP, AMAC, AMAN, AMBG, AMAE, AMAL, and AMBW.	
Materials used for calibration curve, QCs & concentration	LY3074828 [mirikizumab] (anti-IL-23) reference standard, Lot #RS0868, 5.7 mg/mL, supplied by Lilly Research Laboratories	
Validated assay range	100 ng/mL (LLOQ) to 10,000 ng/mL (ULOQ) in human serum	
Minimum required dilutions (MRDs)	1:100	
Source & lot of reagents (LBA)	LSN2821342 (IL-23), Lot #RS1136, 0.08 mg/mL, Lilly Mouse anti-human IgG4 HRP-conjugate, Cat. #9200-05, Lot #G4818-VF28F, 1 mg/mL, (b) (4)	
Regression model & weighting	4-parameter logistic fit with $1/Y^2$ weighting	
Validation parameters	**Method validation summary**	**Acceptability**

Calibration curve performance during accuracy & precision	No of standard calibrators from LLOQ to ULOQ	7	Yes
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-5.2 to 2.8%	Yes
	Cumulative precision (%CV) from LLOQ to ULOQ	≤3.3%	Yes
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 5 QCs	-9.1 to 2.3%	Yes
	Inter-batch %CV	≤6.6%	Yes
	Percent total error (TE)	≤12%	Yes
Selectivity & matrix effect	30 lots of normal human serum were evaluated. 80% (24/30) met acceptance criteria. 10 lots of human serum from ulcerative colitis patients were evaluated. 90% (9/10) met acceptance criteria.		Yes
Hemolysis effect	No observed effect in 1 lot of pooled human serum supplemented with 5% hemolysate		Yes
Lipemic effect	No observed effect in 1 lot of pooled human serum supplemented with 300 mg/dL intralipid		Yes
Dilution linearity & hook effect	Acceptance criteria met for dilutions ranging from 1:62.5 to 1:2,500. No hook effect was observed for samples at concentrations up to 500,000 ng/mL		Yes
Bench-top/process stability	Stable in human serum at room temperature for 25 hours, and at 2 to 8 °C for 26 hours		Yes
Freeze-Thaw stability	Established for up to 5 freeze-thaw cycles		Yes

Long-term storage	Established stability in human serum at -20 °C for 444 days and at -70 °C for 1018 days	Yes
Parallelism	6 human serum test samples were evaluated at dilutions up to 1:200. All had %CV ≤ 5.2% at each dilution and %CV of back-calculated mean concentrations ≤ 4.7%	Yes

For phase 1 study AMBD conducted in healthy Chinese subjects, serum mirikizumab concentrations were determined using the same method described above in validation report 179714, but transferred to [redacted] (b) (4)). Under [redacted] (b) (4), the method was validated, and cross-validation experiments were performed (described in validation report 400008-191684-PMV). The table below describes modification and cross-validation performance.

Method Validation Report 400008-191684-PMV: Quantification of LY3074828 [mirikizumab] in Human Serum by an ELISA Method ([redacted] (b) (4)

Table 93. Method Validation Report 400008-191684

Cross-validation review summary	Method validation and cross-validation adequate to support results in study AMBD.		
Changes in method	No method changes. Method was transferred to another laboratory and re-validated. Cross-validation experiments were also performed.		
New validated assay range if any	N/A		
Validation parameters	**Assay performance**		**Acceptability**
Calibration curve performance during accuracy & precision	Cumulative accuracy (%bias) in standard calibrators from LLOQ to ULOQ	-4.1 to 11.8%	Yes
	Cumulative precision (%CV) from LLOQ to ULOQ	≤6.4%	Yes
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 5 QCs	-11.6 to -1.0%	Yes
	Inter-batch %CV	≤11.6%	Yes

	Percent total error (TE)	≤18.7%	Yes
Cross-validation	15 spiked QC samples (four concentrations plus a blank, all run-in triplicate) and 16 incurred human serum samples were evaluated. 100% (31/31) of samples fell within the pre-specified acceptance range of ± 30%. The concordance correlation coefficient (95% CI) was 0.99 (0.99, 1.00).		Yes

Phase 1 DDI study AMBP evaluated the effect of mirikizumab on the PK of a cocktail of CYP substrates including caffeine, dextromethorphan, midazolam, omeprazole, and warfarin. The Applicant developed a bioanalytical method to support the quantitation of each analyte. The method validation reports are as follows:

- Caffeine: 8386664 (b) (4)
- Dextromethorphan: 2100-949 (b) (4)
- Midazolam: 080459VRLC_EII_R4 ((b) (4)
- Omeprazole: 150531VRM_QIN_R1 (b) (4)
- Warfarin: 8331439 (b) (4)

All analytes were measured using a validated bioanalytical method. Bioanalytical reports indicated that for each analyte, the method performance was acceptable.

16.3.3. Population PK Analysis

16.3.3.1. *Executive Summary*

The population PK (PPK) model is generally acceptable for characterization of PK and prediction of exposure following the proposed 300 mg IV Q4W induction dosage and 200 mg SC Q4W maintenance dosage in patients with UC.

Following the proposed induction and maintenance dosage, higher body weight was associated with lower exposure. However, the exposure difference according to body weight did not have a statistically significant impact on clinical efficacy or safety. No alternative dosage is recommended for any intrinsic or extrinsic patient characteristics in induction or maintenance treatment of UC.

16.3.3.2. *Objectives*

The objectives of the population pharmacokinetic/pharmacodynamic (PK/PD) analysis were:

- To characterize the PK of mirikizumab in patients with ulcerative colitis;
- To identify demographic factors, laboratory parameters, immunogenicity, prior and concomitant therapies, and disease characteristics that may influence mirikizumab disposition in this patient population;

- To estimate mirikizumab systemic exposure in Study AMAN and Study AMBG subjects with ulcerative colitis for exposure-response analyses.

16.3.3.3. *Population PK Data*

The final population PK model was developed using data from patients with ulcerative colitis who received mirikizumab 300 mg IV Q4W induction treatment in Study AMAN and patients with ulcerative colitis who received mirikizumab 200 mg SC Q4W maintenance treatment in Study AMBG.

Out of 1129 total subjects in the PPK model input, 952 subjects had at least one PK concentration for induction treatment and 914 subjects had at least one PK concentration for maintenance treatment. The PPK model input contained 4058 PK concentrations for induction treatment plus 3070 PK concentrations for maintenance treatment. Table 94 summarizes the characteristics of patients with PPK data in Study AMAN and Study AMBG.

Table 94. Summary of Patient Characteristics in PK Analyses Datasets

Covariate	Statistic or Category	Study AMAN n=952	Study AMBG n=914	OVERALL n=1129
Baseline Age (years)	Mean (CV%)	42.8 (32.2%)	42.8 (32.2%)	42.6 (32.4%)
	Median	41	41	41
	Min - Max	18 - 79	18 - 79	18 - 79
Sex	Female [n (%)]	363 (38.1%)	357 (39.1%)	442 (39.1%)
	Male [n (%)]	589 (61.9%)	557 (60.9%)	687 (60.9%)
Baseline Body Weight (kg)	Mean (CV%)	72.8 (23.6%)	72.8 (23.6%)	72.6 (23.6%)
	Median	70.7	71	70.8
	Min - Max	34 - 151.5	34 - 151.5	34 - 151.5
Baseline BMI	Mean (CV%)	24.9 (21.3%)	25 (21.2%)	24.9 (21.3%)
	Median	24.1	24.2	24.1
	Min - Max	13.8 - 53.5	14.6 - 53.5	13.8 - 53.5
Race Category	American Indian or Alaska Native [n (%)]	10 (1.1%)	8 (0.9%)	11 (1%)
	Asian [n (%)]	219 (23%)	192 (21%)	251 (22.2%)
	Black or African American [n (%)]	9 (0.9%)	12 (1.3%)	12 (1.1%)
	Native Hawaiian or Pacific Islander [n (%)]	1 (0.1%)	1 (0.1%)	1 (0.1%)
	White [n (%)]	703 (73.8%)	694 (75.9%)	843 (74.7%)
	Multiple [n (%)]	1 (0.1%)	1 (0.1%)	1 (0.1%)
	Not reported [n (%)]	9 (0.9%)	6 (0.7%)	10 (0.9%)
Baseline Creatinine Clearance (mL/min)	Mean (CV%)	113.7 (28.4%)	109.9 (27.6%)	113.2 (28.4%)
	Median	108.6	106.2	108.4
	Min - Max	43.5 - 267.6	36.2 - 277.1	43.5 - 267.6
Baseline Creatinine Clearance Category	Mild renal impairment (60 to <90 mL/min) [n (%)]	192 (20.2%)	215 (23.5%)	242 (21.4%)
	Moderate renal impairment (30 to <60 mL/min) [n (%)]	19 (2%)	25 (2.7%)	23 (2%)
	Normal renal function (90 mL/min or greater) [n (%)]	741 (77.8%)	674 (73.7%)	864 (76.5%)

Covariate	Statistic or Category	Study AMAN n=952	Study AMBG n=914	OVERALL n=1129
Baseline Albumin (g/L)	Mean (CV%)	42.8 (9.8%)	42.8 (9.6%)	42.8 (9.8%)
	Median	43	43	43
	Min - Max	21 - 54	23 - 54	21 - 54
Albumin at Week 12 (g/L)	Mean (CV%)	N/A	44.4 (7.7%)	N/A
	Median	N/A	44	N/A
	Min - Max	N/A	27 - 57	N/A
Baseline Bilirubin (umol/L)	Mean (CV%)	7 (61.4%)	6.9 (62.3%)	6.9 (62.3%)
	Median	6	6	6
	Min - Max	1.5 - 29	1.5 - 29	1.5 - 29
Baseline Modified Mayo Score	3 [n (%)]	1 (0.1%)	1 (0.1%)	1 (0.1%)
	4 [n (%)]	71 (8.2%)	77 (9.3%)	89 (8.7%)
	5 [n (%)]	133 (15.4%)	121 (14.6%)	154 (15.1%)
	6 [n (%)]	198 (22.9%)	187 (22.6%)	233 (22.8%)
	7 [n (%)]	232 (26.8%)	221 (26.7%)	281 (27.5%)
	8 [n (%)]	201 (23.2%)	194 (23.4%)	231 (22.6%)
	9 [n (%)]	30 (3.5%)	27 (3.3%)	34 (3.3%)
Duration of UC from Diagnosis (years)	Mean (CV%)	7.2 (93.1%)	7.2 (95.8%)	7.2 (94.4%)
	Median	5	4.8	4.9
	Min - Max	0.2 - 44.3	0.2 - 47.6	0.2 - 47.6
Clinical Remission Status at Week 12	No [n (%)]	743 (78%)	751 (82.2%)	911 (80.7%)
	Yes [n (%)]	209 (22%)	163 (17.8%)	218 (19.3%)

Includes patients with at least one mirikizumab pharmacokinetic sample. Baseline refers to Week 0 of Study AMAN before first mirikizumab dose. Week 12 refers to Week 12 of Study AMAN.
CV = coefficient of variation. N/A = not applicable; UC = ulcerative colitis.
Source: Reviewer analysis of Applicant's PPK dataset

16.3.3.4. *Population PK Model Development*

The population PK model is acceptable for characterizing and predicting PK in patients with UC following the proposed induction dosing and following the proposed maintenance dosing.

Population PK analysis evaluated the impact of intrinsic and extrinsic patient factors on the PK of mirikizumab. Intrinsic factors evaluated included age, sex, race, baseline body weight, baseline body mass index (BMI), Cockcroft-Gault creatinine clearance, baseline bilirubin, baseline and time-varying albumin, baseline, and time-varying C-reactive protein, baseline fecal calprotectin, duration of disease, prior biologic therapy, baseline mMS (and related subscores), and ADA status. Extrinsic factors included SC injection site, smoking status, baseline corticosteroid or immunomodulator use, baseline aspirin use, and baseline use of aminosalicylic acid.

The final mirikizumab PPK model is a 2-compartment model with estimated absolute bioavailability and first-order absorption rate constant (Ka) terms for SC administration. Increased albumin at a given time point was associated with lower CL at that time point. Increased body weight was associated with increased systemic clearance (CL), intercompartmental clearance (Q), central volume of distribution (V2), and peripheral volume of distribution (V3). Increased BMI was associated with lower bioavailability following SC administration. The final PPK model parameters are summarized in Table 95.

Table 95. Parameter Estimates for the Final Population PK Model

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

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

a The CI was estimated using bootstrap.

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

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

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

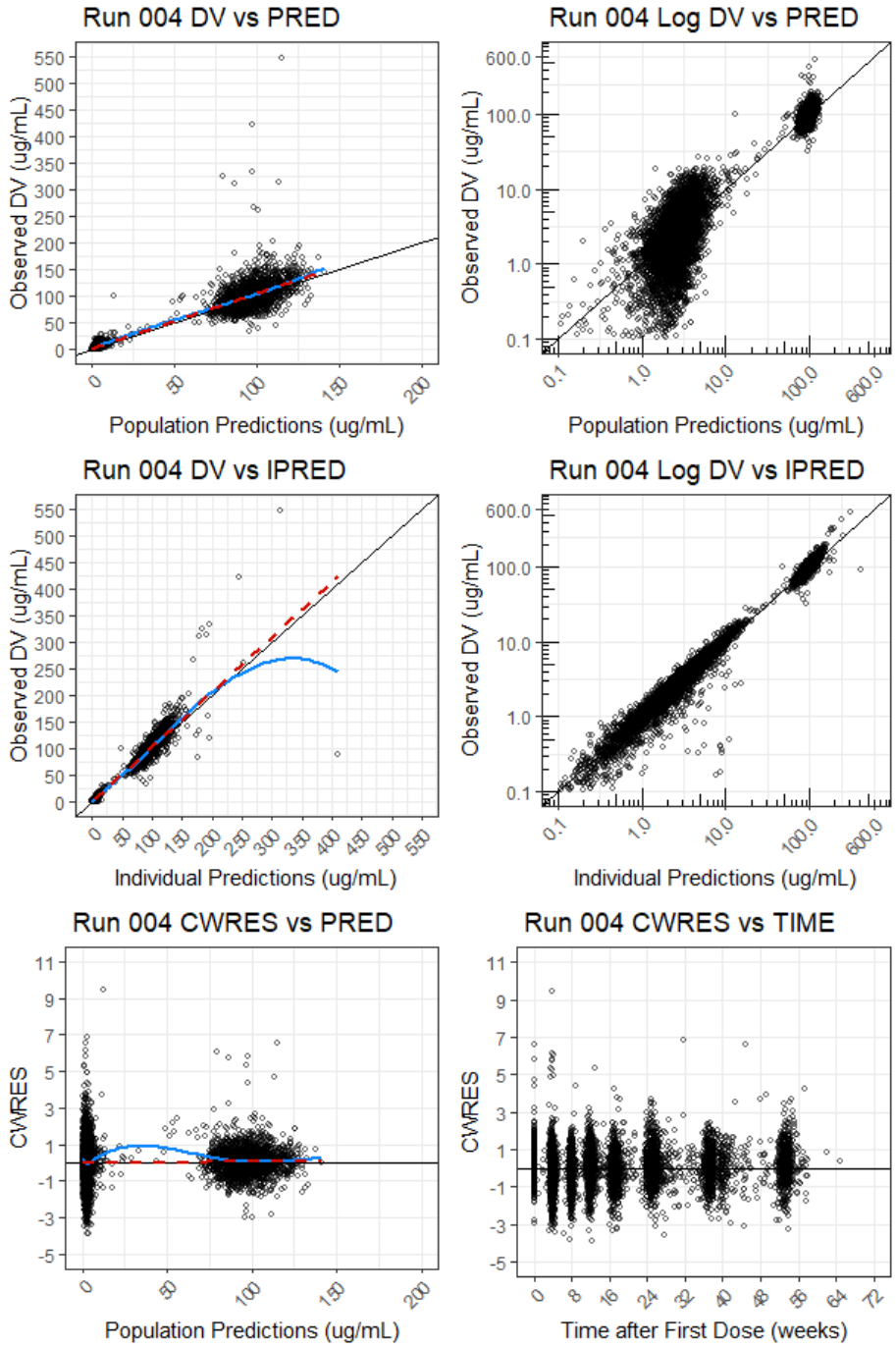
e Estimate is on the logit parameter for bioavailability. This translates to bioavailability of 55% and 40% for patients with baseline BMI of 20 kg/m^2 (10th percentile of analysis population) and 32 kg/m^2 (90th percentile of the analysis population).

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

Source: Table 9.2, Phase 3 Population PK Report, page 37, BLA 761279 SDN 1, submitted Mar. 30, 2022

Goodness-of-fit plots are displayed in Figure 35 and indicate adequate model fit. Additionally, the fit of the data did not appear to differ significantly according to study (Study AMAN versus Study AMBG) or route of administration (IV versus SC). The PPK model adequately characterizes covariate effects on PK in patients with UC. The model is also acceptable for predicting mirikizumab exposure following the proposed dosage in patients with UC.

Figure 35. Goodness-of-Fit Plots for Final Model



Loess in solid blue; Linear regression in dashed red. The lower limit of quantification is 0.1 ug/mL.
CWRES = conditional weighted residuals; DV = observed concentration; IPRED = individual prediction of concentration; PRED = population prediction of concentration; Run 004 = final population PK model run.
Source: Reviewer analysis

16.3.3.5. *Mirikizumab PK and Exposure*

Model-predicted exposure for the first induction dose and first maintenance dose are summarized in Table 96. The median PK concentration over time for proposed induction and maintenance dosing is presented in Figure 5. Steady state exposure is summarized in Table 10.

Table 96. Reviewer's Simulated Geometric Mean (CV%) Mirikizumab Exposure in Subjects With UC

	First Induction Dose of 300 mg IV in Study AMAN Patients (n=954)	First Maintenance Dose of 200 mg SC in Study AMBG Patients (n=389)
C_{max} (ug/mL)	96.2 (21.9)	11.4 (49.3)
C_{avg} (ug/mL)	18.5 (30.6)	6.6 (56.6)
AUC_{tau} (ug·day/mL)	517.5 (30.6)	184.3 (56.6)
C_{trough} (ug/mL)	2.6 (80.4)	2.0 (85.8)

In Study AMAN, 954 patients with UC received 300 mg IV infused over 30 minutes Q4W mirikizumab induction treatment. In Study AMBG, 389 patients who had previously achieved response with 300 mg IV Q4W mirikizumab induction treatment received 200 mg SC Q4W mirikizumab maintenance treatment.
AUC_{tau} = area under the concentration versus time curve over the dosing interval; C_{avg} = average concentration over the dosing interval; C_{max} = maximum concentration; C_{trough} = concentration at the end of the dosing interval; CV = coefficient of variation; IV = intravenous; popPK = population pharmacokinetic; Q4W = every 4 weeks; SC = subcutaneous; UC = ulcerative colitis.
Source: Reviewer analysis

The median individual predicted T_{max} following the first maintenance dose at Week 12 was 116 hours (i.e., 4.8 days) with a range of 59 to 141 hours (n=389). Based on popPK simulation in 1000 patients resampled from Study AMAN/AMBG, the median T_{max} following SC administration was 5 days (range = 3.08 to 6.75 days).

16.3.3.6. *Covariate Analysis*

Current evidence does not support alternative dosage according **to any patient covariates. The proposed induction dosage of 300 mg IV Q4W and the proposed maintenance dosage of 200 mg SC Q4W are acceptable from a clinical pharmacology perspective.**

Populati**on PK analysis identified the following statistically significant associations between patient covariates and mirikizumab PK:**

- Lower serum albumin associated with higher CL
- Higher baseline body weight associated with higher CL and V_d
- Higher baseline BMI associated with lower SC bioavailability.

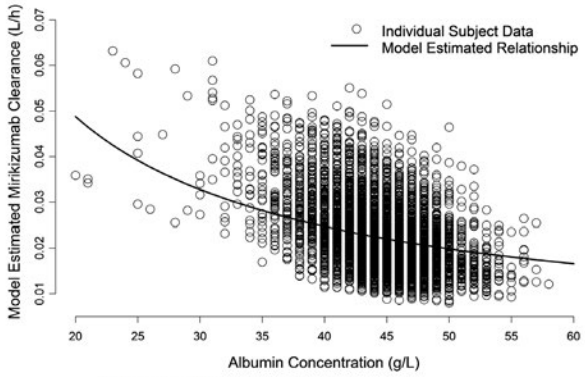
Although serum albumin, body weight, an**d BMI had statistically significant associations with mirikizumab PK parameters, no patient covariates had a clinically and statistically significant impact on mirikizumab exposure.**

Serum Albumin Concentrations versus Mirikizumab Exposure

Although low serum albumin concentration was associated with higher mirikizumab clearance, serum albumin is not expected to result in clinically relevant differences in mirikizumab exposure.

Patients with more severe UC disease tend to have lower serum albumin, which may be a result of low protein production and/or high protein clearance. Patients with high protein turnover tend to have faster clearance of both albumin and monoclonal antibodies such as mirikizumab. Figure 36 shows individual predicted mirikizumab clearance versus albumin concentration, which indicates that low serum albumin is associated with increased mirikizumab clearance.

Figure 36. Model-Estimated Clearance Versus Albumin Concentration Based on the Population PK Analysis Using Data From Phase 3 Studies AMAN and AMBG.



Source: Figure 9.3, Phase 3 Population PK Report, page 37, BLA 761279 SDN 1, submitted Mar. 30, 2022

Table 97 summarizes individual predicted mirikizumab exposure following the first dose of 300 mg IV Q4W by baseline serum albumin concentration in 954 patients with UC. Patients with baseline albumin concentration of 35 g/L or lower had 19% lower geometric mean AUC_{tau} than patients with baseline albumin concentration of 45 g/L or higher. A large degree of overlap in mirikizumab exposure was observed across all baseline albumin values, as shown in Figure 37.

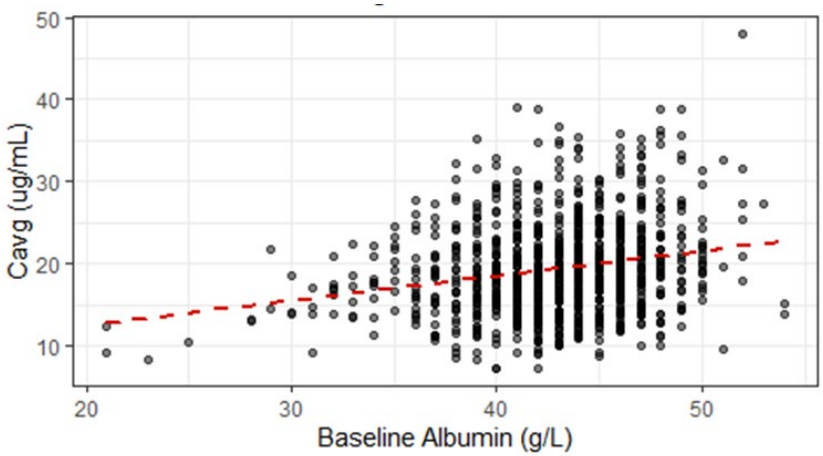
Table 97. Individual Predicted Exposure Following First Induction Dose of 300 mg IV According to Baseline Albumin Subgroup

		Baseline Serum Albumin Subgroup		
Covariate	**Statistic**	**35 g/L or lower**	**>35 to <45 g/L**	**45 g/L or higher**
Number of Subjects	N	45	572	337
Baseline Serum Albumin Concentration (g/L)	Geometric Mean (CV%)	31.5 (12.6)	41.2 (5.5)	46.8 (3.7)
	Median	33	42	46
	Min - Max	21 - 35	36 - 44	45 - 54
AUC_{tau}	Geometric Mean (CV%)	446.6 (26.2)	503.7 (30.5)	552.7 (29.8)
	Median	470.2	511.2	552.2
	Min - Max	232.4 - 685	199.5 - 1092.4	243.2 - 1345.8
C_{avg}	Geometric Mean (CV%)	16 (26.2)	18 (30.5)	19.7 (29.8)
	Median	16.8	18.3	19.7
	Min - Max	8.3 - 24.5	7.1 - 39	8.7 - 48.1
C_{max}	Geometric Mean (CV%)	102.6 (19.9)	96.8 (21.7)	94.3 (22.2)
	Median	99.5	97.5	94.1
	Min - Max	68.9 - 162.3	47.3 - 180	51.6 - 190.8

		Baseline Serum Albumin Subgroup		
Covariate	**Statistic**	**35 g/L or lower**	**>35 to <45 g/L**	**45 g/L or higher**
C_{trough}	Geometric Mean (CV%)	1.5 (79.7)	2.4 (79.5)	3.2 (72.8)
	Median	1.7	2.6	3.3
	Min - Max	0.2 - 5.2	0.2 - 13.3	0.5 - 14.3

Individual mirikizumab exposure calculated from individual predicted concentrations in 954 patients with UC from Study AMAN who received 300 mg IV infused over 30 minutes Q4W for induction treatment.
AUC_{tau} = area under the concentration versus time curve over the dosing interval; C_{avg} = average concentration over the dosing interval; C_{max} = maximum concentration; C_{trough} = concentration at the end of the dosing interval; CV = coefficient of variation; IV = intravenous; Q4W = every 4 weeks; UC = ulcerative colitis.
Source: Reviewer's analysis

Figure 37. Individual Predicted Exposure Following the First Dose of 300 mg IV for Induction Treatment Versus Baseline Albumin Concentration



Individual mirikizumab C_{avg} calculated from individual predicted concentrations in 954 patients with UC from Study AMAN who received 300 mg IV infused over 30 minutes Q4W for induction treatment.
C_{avg} = average concentration over the dosing interval; IV = intravenous; Q4W = every 4 weeks; UC = ulcerative colitis.
Source: Reviewer's analysis

When induction treatment effect was analyzed by baseline albumin category, lower albumin was associated with lower rates of remission and response (see Figure 10). This trend is also observed in the placebo arm, and therefore the association between albumin and efficacy is likely due to other patient factors (i.e., disease severity) instead of differences in mirikizumab exposure. Of note, within each serum albumin subgroup, numerically higher efficacy rates were observed in patients who received mirikizumab versus patients who received placebo.

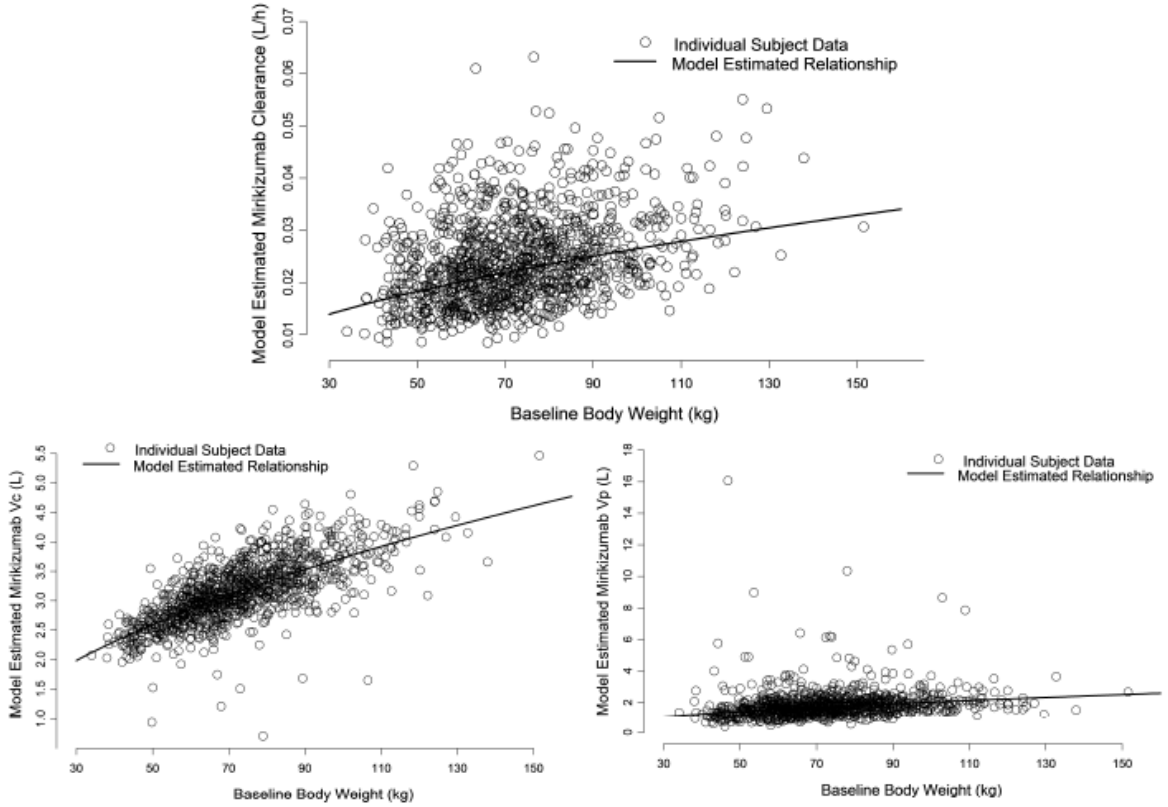
Body Weight and BMI versus Mirikizumab Exposure

Higher body weight and higher BMI were associated with lower mirikizumab exposure during induction and maintenance treatment. However, the difference in exposure according to body weight or BMI did not have a statistically significant impact on clinical efficacy or safety. Mirikizumab treatment has higher observed rates of efficacy compared to placebo across all body weight and BMI categories. Therefore, current evidence does not support alternative dosage according to body weight or BMI. The proposed induction dosage of 300 mg IV Q4W and the proposed maintenance dosage of 200 mg SC Q4W are acceptable across all body weights and BMI values.

In phase 3 studies AMAN and AMBG, body weight ranged from 34 to 152 kg, while BMI ranged from 13.8 to 53.5 kg/m^2. Higher body weight is associated with greater mirikizumab clearance and higher total volume of distribution. Figure 38 shows individual predicted clearance and volume of distribution versus body weight.

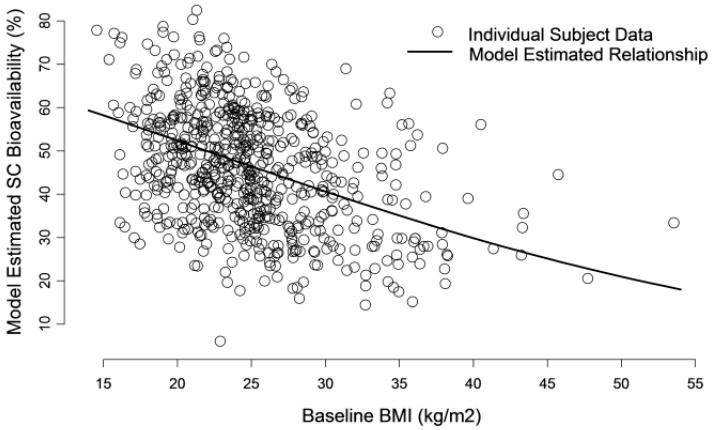
In addition to the impacts of body weight on PK parameters, higher BMI is associated with lower SC bioavailability. Figure 39 shows individual predicted SC bioavailability versus baseline BMI. BMI is a value derived from patient characteristics of height and weight, and so BMI is not a direct physiologic measurement. The association between mirikizumab SC bioavailability and BMI is likely due to patient factors that are associated with BMI but more difficult to quantify, such as distribution of subcutaneous adipose tissue. Therefore, inclusion of BMI in the final PPK model is acceptable for mirikizumab following SC administration.

Figure 38. Model-Estimated Clearance (top) and Volume of Distribution (Bottom) Versus Body Weight Based on the Population PK Analysis Using Data From Phase 3 Studies AMAN and AMBG



Vc = volume of distribution of the central compartment; Vp = volume of distr bution of the peripheral compartment.
Source: Figure 9.2, Phase 3 Population PK Report, page 36, BLA 761279 SDN 1, submitted Mar. 30, 2022

Figure 39. Model-Estimated SC Bioavailability Versus Baseline BMI Based on the Population PK Analysis Using Data From Phase 3 Studies AMAN and AMBG



BMI = body mass index; PK = pharmacokinetics; SC = subcutaneous.
Source: Figure 9.4, Phase 3 Population PK Report, page 38, BLA 761279 SDN 1, submitted Mar. 30, 2022

Following the first induction dose of 300 mg IV, patients weighing ≥90 kg are predicted to have 18% lower geometric mean C_{avg} compared to patients weighing less than 90 kg. Following the first maintenance dose of 200 mg SC, patients weighing ≥90 kg are predicted to have 32% lower geometric mean C_{avg} compared to patients weighing less than 90 kg. Exposure differences between weight categories are larger for maintenance compared to induction because induction doses are administered IV and therefore are not impacted by the association between BMI and SC bioavailability.

Exposures according to body weight category are summarized for the first induction dose and for the first maintenance dose in Table 98.

Table 98. Geometric Mean (CV%) Individual Predicted Exposure Following First Dose of Induction Treatment and First Dose of Maintenance Treatment by Weight Category

	First Dose of 300 mg IV Q4W Induction Treatment		**First Dose of 200 mg SC Q4W Maintenance Treatment**	
	<90 kg subjects with UC n=811	**≥90 kg subjects with UC** n=143	**<90 kg subjects with UC** n=336	**≥90 kg subjects with UC** n=53
C_{avg} [ug/mL]	19 (30.3%)	15.6 (25.5%)	6.9 (56%)	4.7 (45%)
C_{max} [ug/mL]	99 (20.9%)	81.5 (19.6%)	12.1 (48%)	8.2 (41%)
C_{trough} [ug/mL]	2.7 (82.2%)	2.3 (67.8%)	2.1 (88%)	1.5 (64%)

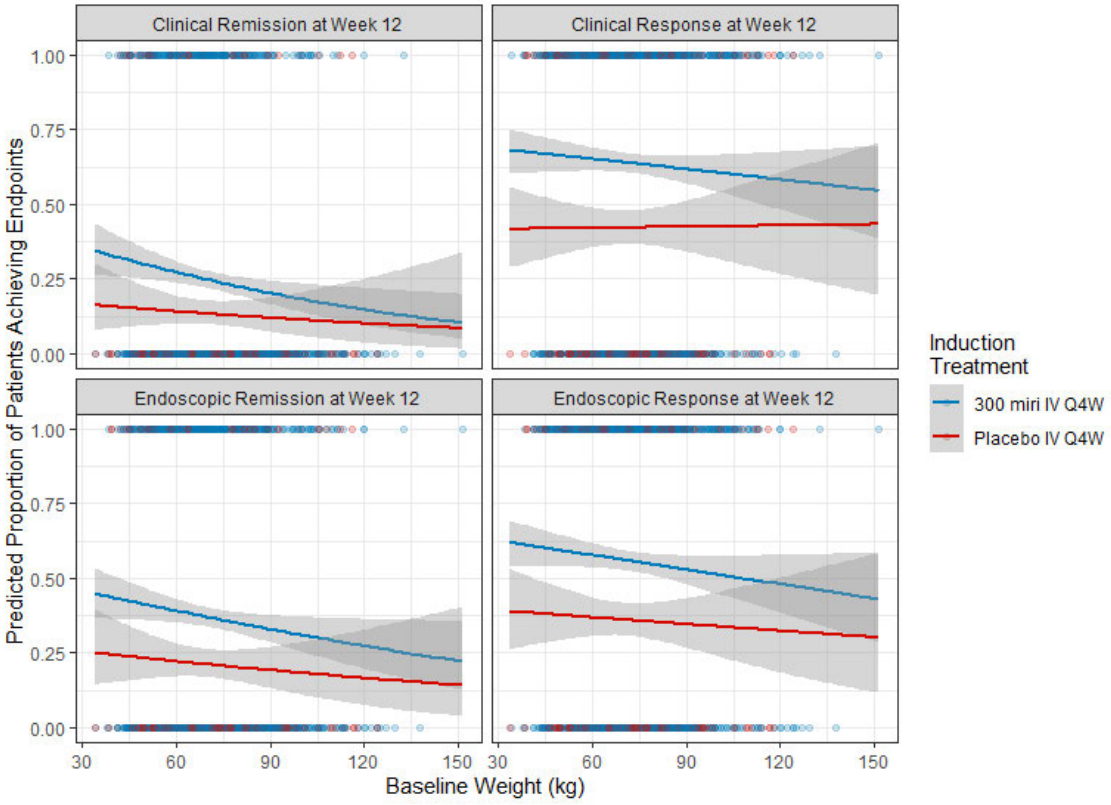
C_{avg} = average concentration over the dosing interval; C_{max} = maximum concentration; C_{trough} = concentration at the end of the dosing interval; CV = coefficient of variation; IV = intravenous; Q4W = every 4 weeks; SC = subcutaneous; UC = ulcerative colitis.
Source: Reviewer's analysis

To assess whether the differences in mirikizumab exposure according to body weight or BMI could be clinically significant, the reviewer compared efficacy and safety across weight and BMI for induction treatment and for maintenance treatment.

Analysis of Induction Efficacy According to Body Weight

For induction treatment, patients with higher body weight had lower rates of primary (i.e., clinical remission) and secondary efficacy endpoints following 300 mg IV Q4W mirikizumab (Figure 11). Patients who received placebo induction treatment displayed no clear associations between body weight and the rates of clinical remission or response. These findings were also supported by logistic regression, as shown in Figure 40. Although higher weight was also associated with a slightly higher proportion of patients with prior use of biologic or tofacitinib and longer duration of disease prior to mirikizumab treatment (see Table 99), the trend in mirikizumab efficacy across body weight in unlikely to be due to disease severity because the placebo arm did not display any clear trends in efficacy across the range of body weight.

Figure 40. Logistic Regression of Efficacy at Week 12 Versus Body Weight Following Induction Treatment With Mirikizumab 300 mg IV Q4W or Placebo IV Q4W in Study AMAN



Solid blue line = logistic regression in patients who received mirikizumab 300 mg IV Q4W during induction treatment (n=860). Solid red line = logistic regression in patients who received placebo IV Q4W during induction treatment (n=294). Points = observed patient data.
IV = intravenous; Q4W = every 4 weeks.
Source: Reviewer's Analysis of Applicant's Study AMAN E-R efficacy dataset

Table 99. Summary of Patient Disease Characteristics in Study AMAN Exposure-Response Dataset Across Weight Quartiles

		300 miri IV Q4W				Placebo IV Q4W			
	Statistic	34 to <60.1 kg	60.1 to <70.1 kg	70.1 to >83 kg	83 to ≤152 kg	34 to <60.1 kg	60.1 to <70.1 kg	70.1 to >83 kg	83 to ≤152 kg
	n	212	210	212	227	85	72	77	61
Baseline Body Weight (kg)	Mean	52.5	65.3	76.1	95.1	52.6	65.4	76.3	95.8
	SD	5.7	2.9	3.6	11.6	5.8	3.1	3.6	10.9
	Median	53.2	65.2	75.5	91.2	53.2	65.2	76	93.4
	Min - Max	34 - 60	60.1 - 70	70.1 - 82.9	83 - 151.5	33.8 - 60	60.1 - 70	70.3 - 82.9	83.1 - 124
Duration of UC from Diagnosis (years)	Mean	6.8	6.9	6.4	8.4	5.1	6.4	7.9	8.8
	SD	6.8	6.6	6.4	7.1	5.4	5.8	7.6	8.5
	Median	4.3	4.8	4.3	6.4	3	4.7	5.1	6.7
	Min - Max	0.3 - 35.7	0.4 - 44.3	0.3 - 40	0.2 - 39.7	0.2 - 28.7	0.4 - 21.7	0.2 - 33.9	0.4 - 47.6
Prior Use of Biologic or Tofacitinib	n (%)	81 (38%)	82 (39%)	88 (42%)	123 (54%)	22 (26%)	31 (43%)	40 (52%)	31 (51%)

IV = intravenous; Q4W = every 4 weeks; SD = standard deviation; UC = ulcerative colitis.
Source: Reviewer analysis of Applicant's Study AMAN exposure-response efficacy dataset

In order to assess the impact of exposure on induction efficacy independent of the impact from baseline disease characteristics, the reviewer conducted additional multivariate E-R analysis. The reviewer's multivariate E-R model confirmed that there was a statistically significant association between C_{avg} and rate of clinical remission, and C_{avg} had a stronger association with rate of clinical remission than C_{trough}. However, prior use of biologics or tofacitinib was also associated with a lower rate of clinical remission. Because patients with higher weight were more likely to have prior use of biologics or tofacitinib, the difference in induction efficacy across body weight is not entirely due to exposure differences alone. After controlling for baseline disease characteristics, the model-predicted rate of clinical remission had no statistically significant difference between patients weighing ≥90 kg and patients weighing <90 kg. The multivariate E-R model development and analysis are described with detail in Section 16.3.4.4.

The subgroup analysis and multivariate E-R model suggest that patients weighing ≥90 kg may be less likely to achieve efficacy (including the primary endpoint of clinical remission at Week 12) compared to patients weighing <90 kg due to lower mirikizumab C_{avg} following the proposed induction dose of 300 mg IV Q4W. However, the difference between body weight subgroups may not be statistically and/or clinically significant, could be confounded by other unknown factors, and could be limited by the single dose level trial design. Additionally, the proposed induction dosage resulted in greater efficacy compared to placebo across all body weights. Therefore, the currently available data do not support the need for alternative induction dosage according to body weight.

Analysis of Induction Efficacy According to *BMI*

Induction efficacy analysis according to BMI subgroups found that higher BMI was associated with smaller differences in efficacy between the mirikizumab and placebo arms (Table 100). All

BMI subgroups still had numerically better induction efficacy with mirikizumab treatment compared to placebo. These results support the same conclusions as the analysis of induction efficacy according to body weight, which is to be expected given the correlation between body weight and BMI. The currently available data do not support the need for alternative induction dosage according to BMI.

Table 100. Risk Difference in Achieving Week 12 Clinical Remission and Endoscopic Remission Across BMI Categories in Phase 3 Induction Study AMAN mITT Population

	Clinical Remission			Endoscopic Remission		
	Placebo n (%)	Miri n (%)	% Difference [95% CI]	Placebo n (%)	Miri n (%)	% Difference [95% CI]
All Subjects*	39 (13.3%)	210 (24.2%)	11.1% [3.2, 19.1%]	62 (21.1%)	315 (36.3%)	15.4% [6.3, 24.5%]
BMI <18.5 kg/m^2	5 (17.9%)	13 (23.6%)	N/A	10 (35.7%)	19 (34.5%)	N/A
BMI ≥18.5 to <25 kg/m^2	19 (12.8%)	125 (27.7%)	15% [8.2, 21.7%]	27 (18.1%)	179 (39.7%)	21.6% [13.9, 29.2%]
BMI ≥25 to <30 kg/m^2	9 (11.8%)	46 (19.5%)	7.6% [-1.2, 16.5%]	16 (21.1%)	76 (32.2%)	11.2% [0.2, 22.1%]
BMI ≥30 to <40 kg/m^2	6 (15.4%)	22 (19.3%)	3.9% [-9.5, 17.4%]	9 (23.1%)	35 (30.7%)	7.6% [-8.1, 23.3%]
BMI ≥40 kg/m^2	0 (0%)	4 (33.3%)	N/A	0 (0%)	6 (50%)	N/A

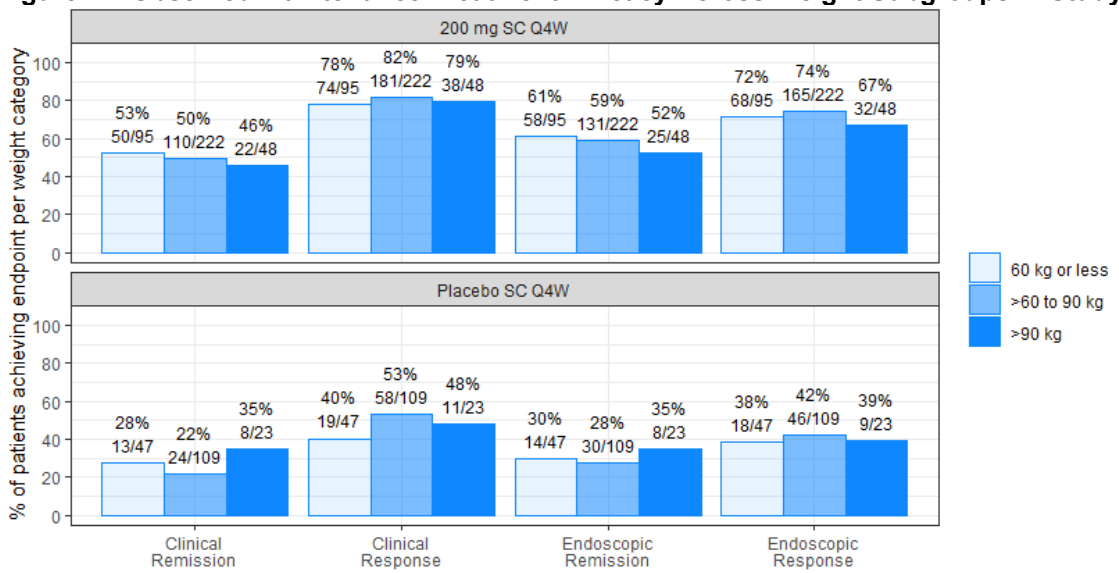
*Note that the confidence intervals reported for the All Subjects group is the 99.875% CI.
Subgroup risk comparison not conducted for BMI <18.5 kg/m^2 or BMI ≥40 kg/m^2.
BMI = body mass index; CI = confidence interval; Miri = mirikizumab; mITT = modified intent-to-treat; N/A = not available.
Source: Adapted from Table 2.7.3.12 and 2.7.3.13, Summary of Clinical Efficacy; and Interactive Forest Plots for Study AMAN and AMBG (Module 2.7.3), BLA 761279 SDN 1, submitted Mar. 30, 2022

Analysis of Maintenance Efficacy According to Body Weight

Although patients with higher weight have lower systemic exposure with the proposed 200 mg SC Q4W maintenance dosage, the exposure difference due to weight is not expected to result in any clinically relevant differences in maintenance efficacy.

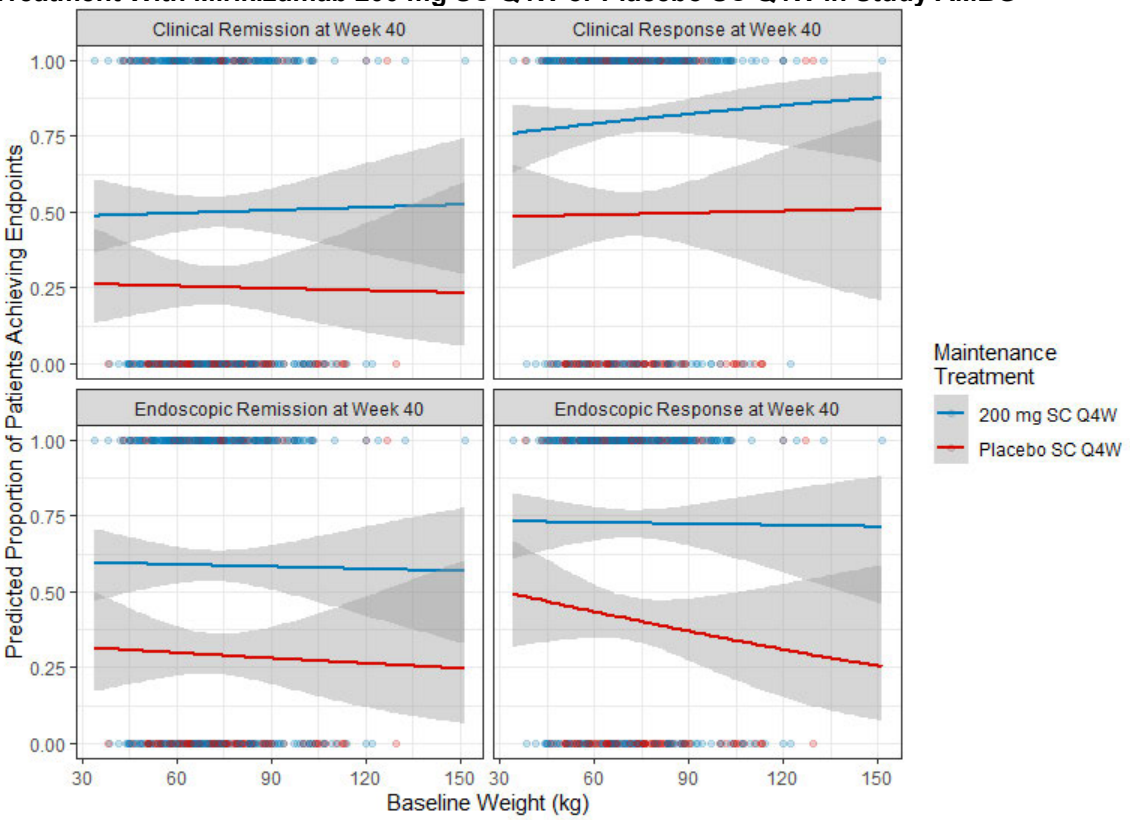
Observed rates of primary (i.e., clinical remission) and secondary efficacy endpoints following maintenance treatment are displayed according to weight category in Figure 41. When evaluated using logistic regression, there were no clear trends between maintenance efficacy and body weight (Figure 42). Thus, the proposed 200 mg SC Q4W maintenance dosage is acceptable for patients of all body weights.

Figure 41. Observed Maintenance Treatment Efficacy Across Weight Subgroups in Study AMBG



% and n/N displayed on top of each column.
Q4W = every 4 weeks; SC = subcutaneous.
Source: Reviewer analysis of Applicant's Study AMBG exposure-response efficacy dataset

Figure 42. Logistic Regression of Efficacy at Week 40 Versus Body Weight Following Maintenance Treatment With Mirikizumab 200 mg SC Q4W or Placebo SC Q4W in Study AMBG

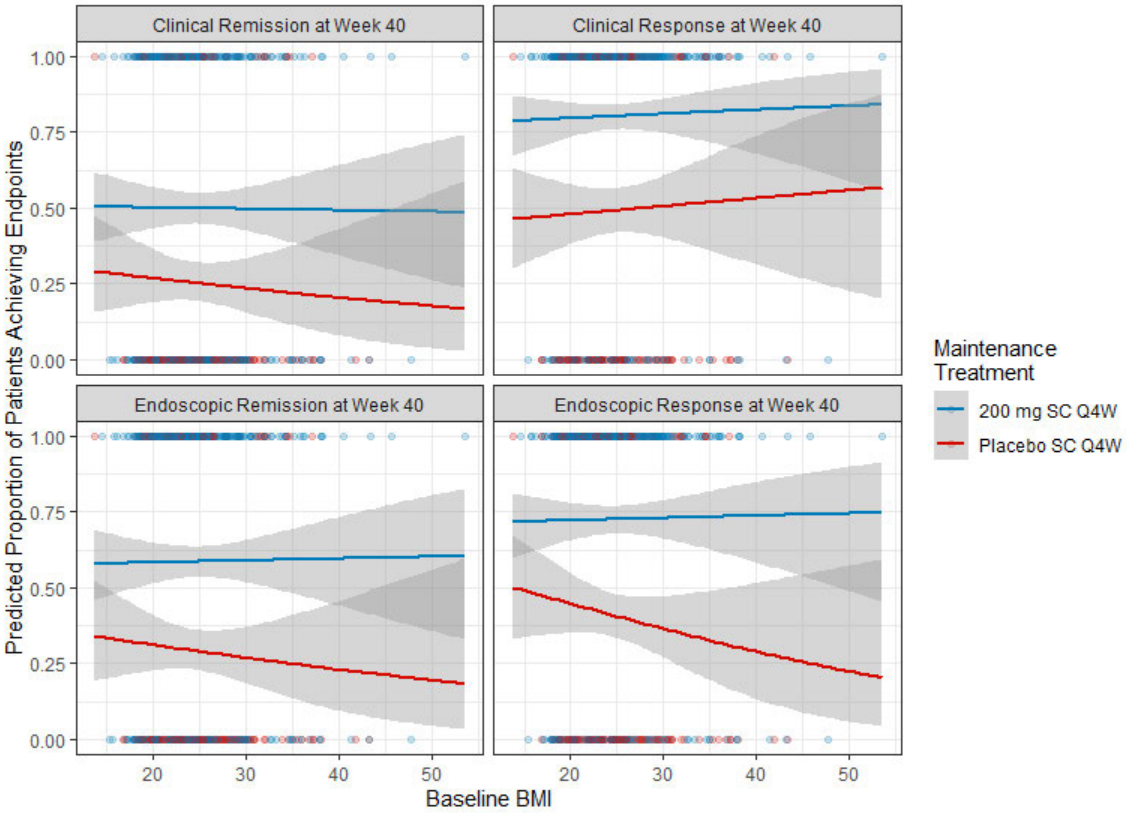


Solid blue line = logistic regression in patients who responded to mirikizumab 300 mg IV Q4W induction treatment and then received mirikizumab 200 mg SC Q4W during maintenance treatment (n=365). Solid red line = logistic regression in patients who responded to placebo induction treatment and then received placebo SC Q4W during maintenance treatment (n=179). Points = observed patient data.
IV = intravenous; Q4W = every 4 weeks; SC = subcutaneous.
Source: Reviewer's analysis of Applicant's Study AMBG E-R efficacy dataset

Analysis of *Maintenance Efficacy According to BMI*

Although higher BMI was associated with lower mirikizumab exposure during maintenance treatment, logistic regression indicates that maintenance efficacy does not differ significantly across BMI in patients who received the proposed mirikizumab maintenance dosage (Figure 43). Additionally, the risk difference between the mirikizumab and placebo arms did not differ according to BMI subgroups (Table 101). Therefore, no difference in maintenance efficacy is expected across the range of BMI values.

Figure 43. Logistic Regression of Efficacy at Week 40 Versus BMI Following Maintenance Treatment With Mirikizumab 200 mg SC Q4W or Placebo SC Q4W in Study AMBG



Solid blue line = logistic regression in patients who responded to mirikizumab 300 mg IV Q4W induction treatment and then received mirikizumab 200 mg SC Q4W during maintenance treatment (n=365). Solid red line = logistic regression in patients who responded to placebo induction treatment and then received placebo SC Q4W during maintenance treatment (n=179). Points = observed patient data.
IV = intravenous; Q4W = every 4 weeks; SC = subcutaneous.
Source: Reviewer analysis of Applicant's Study AMBG E-R efficacy dataset

Table 101. Risk Difference in Achieving Week 40 Clinical Remission and Endoscopic Remission Among Mirikizumab Induction Responders Across BMI Categories in Phase 3 Maintenance Study AMBG

	Clinical Remission			Endoscopic Remission		
	Placebo n (%)	**Miri n (%)**	**% Difference [95% CI]**	**Placebo n (%)**	**Miri n (%)**	**% Difference [95% CI]**
All Subjects	45 (25.1%)	182 (49.9%)	23.2% [15.2, 31.2%]	52 (29.1%)	214 (58.6%)	28.5% [20.2, 36.8%]
BMI <18.5 kg/m^2	2 (25%)	13 (50%)	N/A	2 (25%)	14 (53.8%)	N/A
BMI ≥18.5 to <25 kg/m^2	26 (26.8%)	100 (51.0%)	24.2% [13, 35.5%]	30 (30.9%)	113 (57.7%)	26.7% [15.2, 38.2%]
BMI ≥25 to <30 kg/m^2	8 (17.4%)	45 (46.4%)	29% [14.2, 43.8%]	10 (21.7%)	60 (61.0%)	40.1% [24.8, 55.5%]

	Clinical Remission			Endoscopic Remission		
	Placebo n (%)	Miri n (%)	% Difference [95% CI]	Placebo n (%)	Miri n (%)	% Difference [95% CI]
BMI ≥30 to <40 kg/m^2	9 (34.6%)	20 (51.3%)	16.7% [-7.4, 40.8%]	10 (38.5%)	23 (59.0%)	20.5% [-3.7, 44.8%]
BMI ≥40 kg/m^2	0 (0%)	4 (57.1%)	N/A	0 (0%)	4 (57.1%)	N/A

Subgroup risk comparison not conducted for BMI <18.5 kg/m^2 or BMI ≥40 kg/m^2.
BMI = body mass index; CI = confidence interval; Miri = mirikizumab; mITT = modified intent-to-treat; N/A = not available.
Source: Adapted from Table 2.7.3.20 and Table 2.7.3.21, Summary of Clinical Efficacy, page 103, and Interactive Forest Plots for Study AMAN and AMBG (Module 2.7.3), BLA 761279 SDN 1, submitted Mar. 30, 2022

Analysis of *Safety According to Body Weight and BMI*

No E-R safety associations were identified between exposure and various TEAEs in Study AMAN or Study AMBG (see Section 16.3.5). Additionally, there were no clear trends between body weight and incidence of TEAEs leading to dose modifications, infusion site reactions, injection site reactions, infections, opportunistic infections, serious infections, or hypersensitivity reactions in Study AMAN or Study AMBG. Although analysis is limited by the relatively small number of these safety events, incidence of these safety events is not expected to be impacted by exposure, body weight, or BMI.

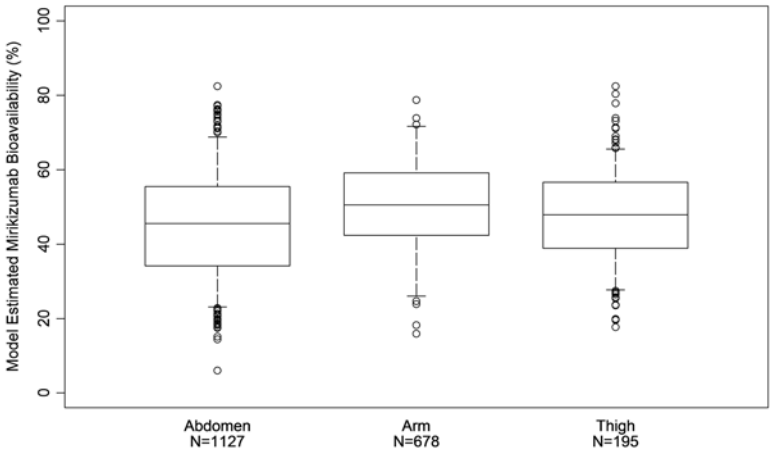
Body Weight and BMI Conclusions

Overall, current evidence does not indicate a strong need for alternative induction or maintenance dosage for patients according to body weight or BMI. The proposed induction dosage of 300 mg IV Q4W and the proposed maintenance dosage of 200 mg SC Q4W are acceptable for all body weights and BMI values.

Subcutaneous Injection Site versus Mirikizumab Exposure

Population PK analysis identified no statistically significant differences in mirikizumab bioavailability according to injection site (abdomen, arm, or thigh) following the proposed maintenance dose of 200 mg SC. Individual predicted SC bioavailability is summarized for each injection site in Figure 44.

Figure 44. Individual Predicted Subcutaneous Bioavailability Versus Injection Site



Note: The horizontal line in each box represents the median; the top and bottom sides of the box represent the 75th and 25th percentiles; the whiskers extend to the 95th and 5th percentiles; and circles represent data points outside of 5th or 95th percentile.
N = number of samples.
Source: Figure 9.5 from the Applicant's PopPK Report

Anti-drug Antibody Titers versus Mirikizumab Exposure

The final population PK model indicated no significant difference in mirikizumab clearance based on TE ADA status, neutralizing ADA status, or TE ADA titer. However, assessment of the effect of TE ADA titer was limited by the relatively small number of patients with higher ADA titer. There were only 10 patients in Studies AMAN and AMBG with popPK data and ADA titer ≥1280. See Figure 6 for a summary of model-estimated individual mirikizumab CL by TE ADA titer.

16.3.4. Exposure-Response Efficacy Analysis

16.3.4.1. *Executive Summary*

Exposure-response analyses found that higher mirikizumab exposure is generally associated with a higher response rate in both induction and maintenance treatment of UC. The E-R analyses also provide supportive evidence that the proposed induction dosage (300 mg IV Q4W) and the proposed maintenance dosage (200 mg SC Q4W) are acceptable from a clinical pharmacology perspective.

16.3.4.2. *Objectives*

The objectives of the exposure-response analysis of efficacy were*:*

- To characterize the relationship of mirikizumab systemic exposure with efficacy endpoints in patients with ulcerative colitis
- To identify covariates that can influence these relationships

16.3.4.3. *Data*

The Phase 2 Study AMAC E-R efficacy analysis evaluated efficacy endpoints at Week 12 of induction treatment using data from 248 total patients who had been randomized to receive 50 mg starting dose (n=63), 200 mg starting dose (n=62), 600 mg (n=60), or placebo (n=63) IV Q4W. Patients in the 50 mg starting dose and 200 mg starting dose cohorts received exposure-based dose adjustment, as described by Table 82 and in Section 6.3.2.2. Mirikizumab exposures are summarized according to dose cohort in Table 102.

Table 102. Predicted Induction Exposure According to Dose Cohort in Phase 2 Study AMAC Subjects With UC

	Statistic	50 mg starting dose cohort* (n=63)	200 mg starting dose cohort* (n=62)	600 mg cohort (n=60)
Mirikizumab C_{trough} at Week 4 (ug/mL)	Geo Mean (CV%)	2.9 (33.1%)	12.7 (31.1%)	37.5 (35.1%)
	Mean (SD)	3.0 (1.0)	13.3 (4.0)	39.7 (13.8)
	Median	2.9	13.6	37.5
	Min - Max	1.3 - 5.3	7.1 - 28.1	17.2 - 86.0
Mirikizumab C_{avg} during Induction Treatment (Week 0 through Week 12) (ug/mL)	Geo Mean (CV%)	5.0 (42.5%)	15.0 (35%)	37.0 (36.6%)
	Mean (SD)	5.4 (2.6)	15.7 (3.7)	39.3 (14.0)
	Median	5.0	16.0	37.2
	Min - Max	1.0 - 21.1	2.7 - 28.1	15.5 - 86.0

*Patients in the 50 mg and 200 mg starting dose cohorts received exposure-based dose adjustment at Week 4 and Week 8 up to a maximum dose of 600 mg.
C_{avg} = average mirikizumab concentration during one induction dosing interval; C_{trough} = mirikizumab concentration at the end of one induction dosing interval; CV = coefficient of variation; Geo Mean = geometric mean; SD = standard deviation; UC = ulcerative colitis.
Source: Reviewer's analysis of Applicant's Study AMAC PK/PD Dataset

The Phase 3 Study AMAN E-R efficacy analysis evaluated efficacy endpoints at Week 12 of induction treatment using data from 1156 total patients who received 300 mg IV Q4W (n=861) or placebo IV Q4W (n=295). Baseline characteristics of interest for each C_{avg} quartile are summarized in Table 103. Relative to subjects in higher exposure quartiles, subjects in the lower exposure quartiles tended to have more severe disease and higher levels of inflammatory markers including C-reactive protein and fecal calprotectin. Subjects in lower exposure quartiles were also more likely to have received prior treatment with biologics.

Subjects who achieved clinical response following mirikizumab 300 mg IV Q4W in Study AMAN tended to have higher C_{avg} and C_{trough} than subjects who did not achieve clinical response (see Table 16). However, the exposure ranges overlapped between responders and non-responders. Additionally, these results could be confounded with factors such as baseline disease characteristics.

Table 103. Baseline Characteristics of Patients in the Study AMAN Exposure-Response Efficacy Dataset According to Mirikizumab Induction Exposure Quartile

Covariate	Statistic	Placebo (N=295)	Mirikizumab C_{avg} Quartile during Induction			
			Q1 (N=210)	Q2 (N=217)	Q3 (N=217)	Q4 (N=217)
Induction C_{avg} (ug/mL)	Geo mean (CV%)	0	11.4 (27%)	17.6 (8.2%)	22.3 (6.8%)	31.1 (15%)
	Median	0	12.3	17.8	22.3	30.4
	Min - Max	0	3.7 - 15.1	15.1 - 20.0	20.0 - 25.3	25.3 - 53.5
Baseline Body Weight (kg)	Mean (SD)	70.8 (16.7)	78.2 (19.8)	77 (16.6)	71.6 (15.1)	64.1 (13.4)
	Median	69.5	75.4	76	70.1	64
	Min - Max	33.8 - 124	41 - 151.5	38.2 - 132.7	41.3 - 122.2	34 - 107.4
Baseline Albumin (g/L)	Mean (SD)	42.8 (4.1)	40.1 (4.8)	42.5 (3.6)	43.5 (3.4)	44.8 (3.1)
	Median	43	41	42	43	45
	Min - Max	28 - 54	21 - 52	29 - 50	32 - 54	35 - 53
Baseline C-Reactive Protein (mg/L)	n	291	207	214	215	214
	Mean (SD)	9.8 (16.9)	16.1 (21)	9.6 (14.3)	6.6 (9.5)	5 (8.1)
	Median	4.2	8.4	4.8	3.2	2.3
	Min - Max	0.1 - 173	0.1 - 150	0.1 - 91.9	0.1 - 49.9	0.1 - 68.6
Baseline Fecal Calprotectin (mg/kg)	n	231	161	173	167	172
	Mean (SD)	2648.1 (3489.7)	3369.3 (3998.2)	3185.1 (4387.8)	2619.3 (3816.7)	2257.3 (3637.5)
	Median	1475	1777	1795	1398	1365.5
	Min - Max	57 - 18954	65 - 21401	47 - 27287	63 - 18634	37 - 27295
Baseline Modified Mayo Score	n	294	210	217	217	217
	Mean (SD)	6.5 (1.3)	6.7 (1.3)	6.6 (1.3)	6.4 (1.3)	6.3 (1.3)
	Median	7	7	7	6	7
	Min - Max	4 – 9	3 – 9	4 – 9	4 – 9	4 - 9
Prior Use of Biologic or Tofacitinib	No prior use [n (%)]	171 (58%)	99 (47.1%)	111 (51.2%)	137 (63.1%)	140 (64.5%)
	Prior use [n (%)]	124 (42%)	111 (52.9%)	106 (48.8%)	80 (36.9%)	77 (35.5%)

Baseline values refer to baseline of study AMAN prior to receiving any mirikizumab treatment. Patients received 300 mg IV Q4W or placebo IV Q4W induction treatment.
C_{avg} = average mirikizumab concentration during one dosing interval; CV = coefficient of variation; geo mean = geometric mean; IV = intravenous; Q = quartile; Q4W = every 4 weeks; SD = standard deviation.
Source: Reviewer's analysis of Applicant's exposure-response efficacy dataset

The Phase 3 Study AMBG E-R efficacy analysis evaluated efficacy endpoints at Week 40 of maintenance treatment using data from 544 total patients. Patients were included in the E-R maintenance efficacy dataset if they had achieved clinical response with mirikizumab 300 mg IV Q4W induction treatment and then received 200 mg SC Q4W maintenance treatment (n=365), or if they had achieved clinical response with placebo IV Q4W induction treatment and then received placebo SC Q4W maintenance treatment (n=179). Baseline characteristics of interest for each C_{avg} quartile are summarized in Table 104. Relative to subjects in higher exposure quartiles, subjects in the lower exposure quartiles tended to have higher levels of inflammatory markers including C-reactive protein and fecal calprotectin, were more likely to have received prior treatment with biologics, and were less likely to have achieved clinical remission at Week 12 of induction treatment.

Table 104. Baseline Characteristics of Patients in the Study AMBG Exposure-Response Efficacy Dataset According to Mirikizumab Maintenance Exposure Quartile

Covariate	Statistic	Placebo (N=179)	Mirikizumab C_{avg} Quartile during Maintenance			
			Q1 (N=92)	Q2 (N=91)	Q3 (N=91)	Q4 (N=91)
Maintenance C_{avg} (ug/mL)	Geo mean (CV%)	0	3.2 (25.6%)	5.7 (12.5%)	7.8 (8.2%)	11.5 (17.8%)
	Median	0	3.4	5.8	7.9	11.3
	Min - Max	0	1.2 - 4.4	4.4 - 6.9	6.9 - 8.9	9.0 - 24.3
Baseline Body Weight (kg)	Mean (SD)	72.4 (17.2)	82.8 (18.5)	74.6 (15.5)	68.2 (14.6)	61.6 (12.5)
	Median	71.4	80	74.2	67.4	61.2
	Min - Max	38 - 129.5	44.5 - 151.5	43 - 120	43.5 - 132.7	34 - 97
Baseline Albumin (g/L)	Mean (SD)	43.1 (3.8)	42.1 (4.2)	43.1 (3.5)	43.2 (4.3)	44.1 (4.2)
	Median	44	42.5	43	44	45
	Min - Max	31 - 53	23 - 52	33 - 52	29 - 50	29 - 54
Baseline C-Reactive Protein (mg/L)	n	178	91	88	90	90
	Mean (SD)	7.3 (14.8)	7.7 (8.7)	10.3 (18)	9.4 (15.8)	8.2 (15)
	Median	3	4.9	4.7	3.2	2.7
	Min - Max	0.1 - 150	0.1 - 49.1	0.1 - 120	0.1 - 91.9	0.1 - 86.1
Baseline Fecal Calprotectin (mg/kg)	n	158	76	79	76	74
	Mean (SD)	3440.3 (4989.1)	2819.1 (4460.4)	3259.7 (5105)	2357.2 (3096.8)	3074.1 (5504.3)
	Median	1750	1456.5	1707	1373	1353.5
	Min - Max	15 - 31680	15 - 31680	85 - 31680	15 - 15984	15 - 31680
Baseline Modified Mayo Score	n	179	92	91	91	91
	Mean (SD)	6.6 (1.2)	6.5 (1.2)	6.6 (1.3)	6.5 (1.4)	6.4 (1.4)
	Median	7	6.5	6	7	7
	Min - Max	4 - 9	4 - 8	4 - 9	4 - 9	4 - 9
Prior Use of Biologic or Tofacitinib	No prior use [n (%)]	114 (63.7%)	52 (56.5%)	54 (59.3%)	63 (69.2%)	60 (65.9%)
	Prior use [n (%)]	65 (36.3%)	40 (43.5%)	37 (40.7%)	28 (30.8%)	31 (34.1%)
Clinical Remission Status at Week 12	Clinical Remission [n (%)]	65 (36.3%)	32 (34.8%)	29 (31.9%)	39 (42.9%)	43 (47.3%)
	No Clinical Remission [n (%)]	114 (63.7%)	60 (65.2%)	62 (68.1%)	52 (57.1%)	48 (52.7%)

Baseline values refer to baseline of study AMAN prior to receiving any mirikizumab treatment. Week 12 refers to week of induction treatment. Patients received 200 mg SC Q4W or placebo SC Q4W maintenance treatment.
C_{avg} = average mirikizumab concentration during one dosing interval; CV = coefficient of variation; geo mean = geometric mean; Q = quartile; Q4W = every 4 weeks; SC = subcutaneous; SD = standard deviation.
Source: Reviewer analysis of Applicant's exposure-response efficacy dataset

16.3.4.4. *Induction Treatment Analysis*

Phase 2 Study AMAC E-R Analysis and Potential Confounding Issues

In Study AMAC, the cohort with the 200 mg starting dose generally had higher rates of efficacy (clinical response, clinical remission, endoscopic response, and symptomatic response) at Week 12 than the cohort with the 50 mg starting dose or the placebo cohort. The 600 mg cohort appeared to have similar or slightly worse efficacy at Week 12 compared to the cohort

with the 200 mg starting dose. Study AMAC Week 12 observed rates of efficacy for each cohort are presented in Figure 7.

Efficacy trends across cohorts were similar to trends across exposure quartiles (Figure 9), as both analyses of Study AMAC showed a plateau of efficacy rates in higher dose/exposure quartiles. This is likely related to the significant impact of cohort on individual exposure.

Compared to the dose and exposure in the cohort with the 200 mg starting dose, efficacy may have appeared similar or worse with higher doses and exposures due to significant differences in disease severity between cohorts. Patients in the 600 mg induction cohort appeared to have higher baseline C-reactive protein concentration (median of 6.6 mg/L) compared to the placebo, 50 mg starting dose, and 200 mg starting dose cohorts (medians of 4.9, 4.9, and 3.7 mg/L, respectively) (Table 83). Other demographics and baseline characteristics did not appear to differ significantly between cohorts.

In addition to potential differences in disease severity, exposure-based dose increases were required in the 50 mg and 200 mg starting dose cohorts but prohibited in the 600 mg cohort. The different protocols regarding dose adjustment may also have impacted outcomes across cohorts independently of mirikizumab exposure. Because cohort had a significant impact on exposure, confounding affects both the cohort-response and exposure-response analyses for Study AMAC.

An induction dosage of 300 mg IV Q4W was selected for evaluation in phase 3 because 300 mg was similar to the average Week 8 dose of 290 mg in the cohort with the highest efficacy at Week 12 in Study AMAC (Table 82). The Phase 2 Study AMAC dose-response and E-R analyses suggested that induction doses above 300 mg IV Q4W would not result in better efficacy compared to 300 mg IV Q4W. However, the Phase 2 E-R analysis had significant limitations including confounding from disease severity and exposure-based dose adjustment which varied by dose cohort. The E-R analysis of data from Study AMAC did not account for differences in disease severity or dose adjustment between dose cohorts, which may have confounded relationships between exposure and response. Because the Phase 3 Study AMAN did not include exposure-based dose adjustment, the Study AMAN E-R analysis likely characterizes E-R associations more accurately.

Phase 3 Induction Study AMAN E-R Analysis

E-R analyses of data from Phase 3 study AMAN found that higher mirikizumab exposure was associated with higher rates of clinical remission, clinical response, endoscopic remission, endoscopic response, and symptomatic response at Week 12. Figure 1 and Table 15 show the observed rates of clinical remission, clinical response, endoscopic remission, endoscopic response, and symptomatic response in Study AMAN according to Study AMAN mirikizumab exposure quartile.

In study AMAN, rates of clinical efficacy endpoints did not appear to differ significantly between the patients in the first exposure quartile and patients who received placebo IV Q4W. This could be related to differences in disease severity across quartiles, as the lowest exposure quartile appeared to have higher mean C-reactive protein at baseline and a higher percentage of patients with prior biologic or tofacitinib experience compared to higher exposure quartiles (Table 103 above). These imbalances may have negatively impacted efficacy rates at lower exposures in Study AMAN.

Although the exposure ranges overlapped in studies AMAC and AMAN, the E-R analysis for AMAN did not show the same plateauing of efficacy as AMAC. This discrepancy in E-R trends at higher exposures may be related to differences in patient characteristics across exposure quartiles between the two studies. E-R efficacy associations in Study AMAC may also have been confounded by differences in protocol relating to exposure-based dose adjustment and differences in disease severity according to cohort, as discussed earlier in Section 16.3.4.4. In Study AMAC, baseline C-reactive protein, which is associated with disease severity, was higher in the 600 mg cohort compared to other cohorts (Table 83 above) which may have negatively affected efficacy in the 600 mg cohort. Conversely, in Study AMAN, higher exposure was associated with lower median C-reactive protein at baseline (Table 103 above) which may have positively affected efficacy rates at higher exposures. However, the comparisons of efficacy across mirikizumab exposure in Study AMAC and AMAN both indicate positive E-R efficacy associations and support the proposed induction dosage of 300 mg IV Q4W.

Association of Body Weight with Exposure and Efficacy

As described in Section 16.3.3.6, the reviewer assessed whether the difference in exposure according to body weight could have a clinically relevant impact on efficacy. Based on multivariate E-R analysis of Study AMAN data, the differences in induction exposure due to body weight do not have a statistically significant impact on induction efficacy. Therefore, no alternative dosage is recommended according to body weight.

In order to assess the impact of exposure on efficacy independent of baseline disease characteristics, multivariate E-R modeling was conducted for the primary efficacy endpoint of clinical remission using data from Study AMAN. The following covariates were investigated for impacts on clinical remission rate using forwards selection then backwards elimination: mirikizumab induction C_{avg}, mirikizumab induction C_{trough}, baseline age, race, baseline weight, weight category, baseline BMI, baseline serum albumin, baseline C-reactive protein, baseline fecal calprotectin, baseline CrCl, baseline bilirubin, duration of disease at baseline, prior biologic/tofacitinib experience, and baseline modified Mayo score and related subscores.

The multivariate E-R model with the best fit is summarized in Table 105. The model-predicted rate of clinical remission (24.9%) was similar to the observed rate of clinical remission (209/860 patients [24.3%]) in Study AMAN patients with E-R data who received mirikizumab induction.

Table 105. Final Multivariate Exposure-Response Model of Clinical Remission at Week 12

Covariate	Odds Ratio	95% CI	p-value
Induction C_{avg} (ug/mL)	1.04	1.03, 1.06	<0.001
Prior biologic or tofacitinib use (yes versus no)	0.54	0.39, 0.74	<0.001
Baseline Endoscopic Findings Subscore	0.64	0.45, 0.93	0.018
Baseline Rectal Bleeding Subscore	1.63	1.23, 2.16	<0.001
Baseline Modified Mayo Score	0.82	0.68, 0.98	0.028

C_{avg} = average mirikizumab concentration during induction treatment; CI = confidence interval.
Source: Reviewer's analysis of Applicant's Study AMAN exposure-response efficacy dataset and Study AMAN admayo.xpt

The multivariate E-R model predicted that Study AMAN patients weighing ≥90 kg would have a lower rate of clinical remission compared to those weighing <90 kg, which was consistent with the observed rates of clinical remission as shown in Table 106.

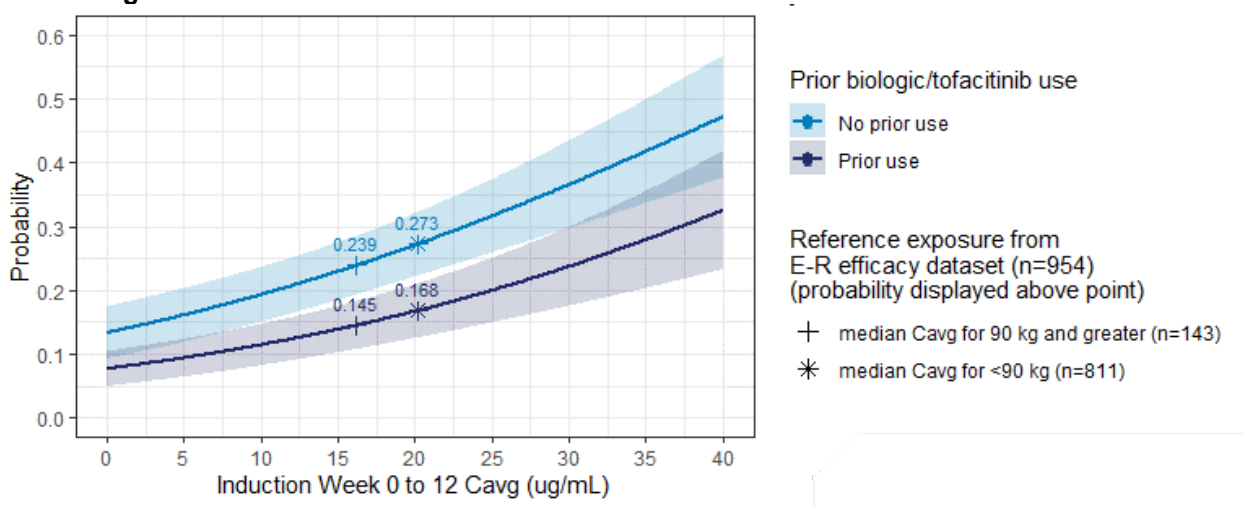
Table 106. Clinical Remission at Week 12 in Study AMAN Subjects With UC Following 300 mg IV Q4W Mirikizumab Induction Treatment

Weight Category	Number of Patients in Study AMAN with E-R Data	Observed Rate of Clinical Remission	Model-Predicted* Rate of Clinical Remission
Patients weighing <90 kg	732	25.5%	25.6%
Patients weighing ≥90 kg	128	17.2%	20.9%

*Model-predicted rates of clinical remission at Week 12 were determined by predicting individual induction C_{avg} with 10 replicates per patient, then predicting individual probability of clinical remission with multivariate exposure-response model, and then calculating the rate of clinical remission in 100,000 virtual trials.
C_{avg} = average mirikizumab concentration; E-R = exposure-response; IV = intravenous; Q4W = every 4 weeks; UC = ulcerative colitis.
Source: Reviewer's analysis of Applicant's Study AMAN exposure-response efficacy dataset and Study AMAN admayo.xpt

To control for differences in baseline disease characteristics, probability of clinical remission was predicted according to C_{avg} for virtual patients with Mayo subscore values fixed to the median baseline subscores in the E-R dataset. As shown in Figure 45, higher C_{avg} was associated with higher probability of clinical remission across a C_{avg} range from 0 to 40 ug/mL. With prior biologic or tofacitinib use, the probability of clinical remission is 23.9% in patients weighing ≥90 kg versus 27.3% in patients weighing <90 kg. With no prior biologic or tofacitinib use, the probability of clinical remission is 14.5% in patients weighing ≥90 kg versus 16.8% in patients weighing <90 kg. Virtual patients weighing ≥90 kg are predicted to have a numerically lower rate of clinical remission compared to patients weighing <90 kg. However, the difference between weight subgroups is not statistically significant.

Figure 45. Impact of Induction Exposure on Week 12 Clinical Remission Probability After Controlling for Baseline Disease Characteristics



Probability of clinical remission at Week 12 predicted in a virtual population using the multivariate logistic regression model which predicted clinical remission probability from C_{avg}, prior biologic or tofacitin b use, baseline rectal bleeding subscore, baseline endoscopic finding subscore, and baseline modified Mayo score.
Baseline rectal bleeding subscore in the virtual population was set to 2 which was the median value in E-R efficacy dataset.
Baseline endoscopic finding subscore in the virtual population was set to 3 which was the median value in E-R efficacy dataset.
Baseline modified Mayo score in the virtual population was set to 7 which was the median value in E-R efficacy dataset.
C_{avg} = average mirikizumab concentration; E-R = exposure-response.
Source: Reviewer's analysis

After controlling for baseline disease characteristics, the model-predicted rate of clinical remission had no statistically significant difference between patients weighing ≥90 kg and patients weighing <90 kg. Clinical analysis of efficacy and multivariate E-R analysis of clinical remission rate both indicate that mirikizumab induction treatment is more effective than placebo across all body weights. Therefore, the currently available data do not support the need for alternative induction dosage according to body weight.

Conclusion

The E-R analyses of efficacy in Study AMAC and in Study AMAN both indicate that higher mirikizumab exposure during induction treatment is associated with higher rates of primary and secondary efficacy endpoints. The discrepancy between the exposure-response relationship based on Phase 2 AMAC and Phase 3 AMAN indicates some uncertainty of both analyses given the limitations mentioned above for each trial. Differences in induction exposure due to body weight do not have a statistically significant impact on induction efficacy, which supports the acceptability of the proposed 300 mg IV Q4W dosage for all body weights.

16.3.4.5. *Maintenance Treatment Analysis*

Phase 3 Maintenance Study AMBG E-R Analysis

E-R analyses of data from Phase 3 study AMBG found that higher mirikizumab exposure was associated with higher rates of clinical remission, endoscopic remission, endoscopic response,

and symptomatic response at Week 40 of maintenance treatment with 200 mg SC Q4W. Rates of efficacy were higher in all exposure quartiles compared to placebo for each of these clinical efficacy endpoints, although efficacy appeared to plateau at higher exposures. The clinical response rate at Week 40 did not appear to differ significantly across exposure quartiles, although all exposure quartiles had higher rates of clinical remission compared to placebo. Figure 2 and Table 17 show the percentage of subjects achieving efficacy endpoints at Week 40 of maintenance treatment (i.e., Week 52 of mirikizumab treatment) for each quartile of exposure during maintenance treatment.

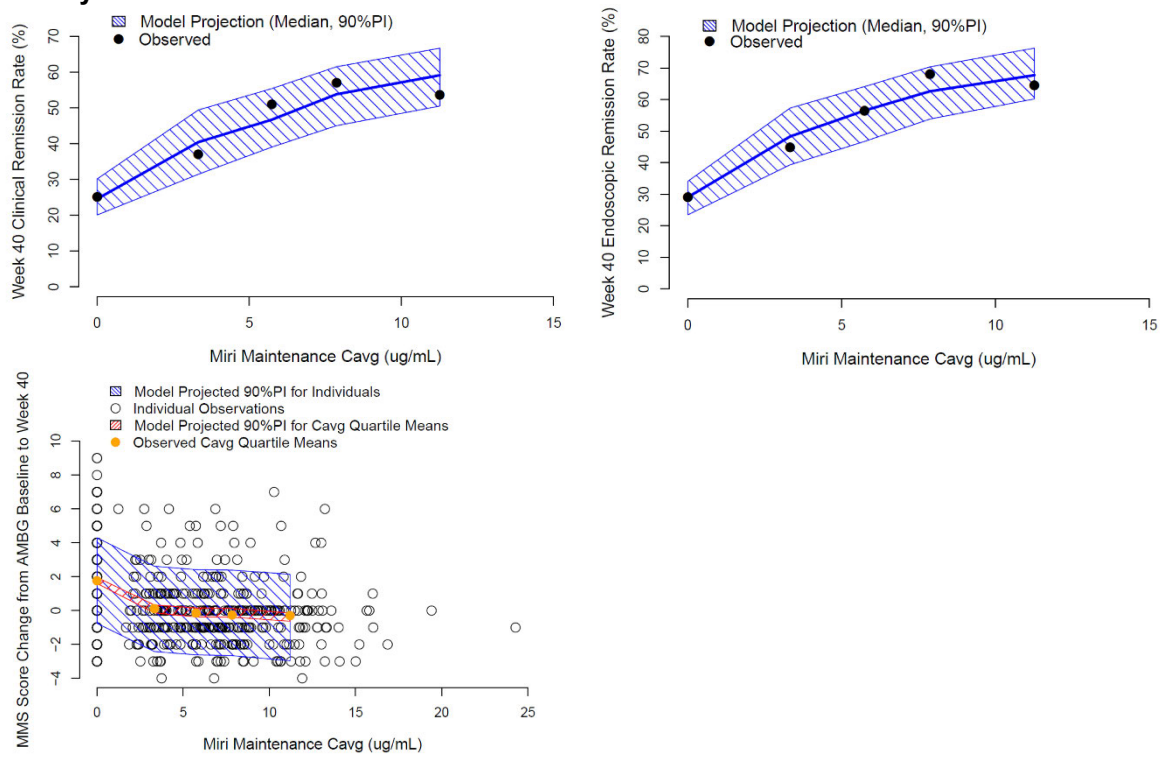
As shown in Table 104**,** maintenance exposure quartiles were slightly imbalanced with respect to baseline disease-relevant characteristics which may have introduced some confounding to the exposure-response relationships. Additionally, the E-R analysis of efficacy in Study AMBG only included mirikizumab exposure data in subjects who responded to mirikizumab 300 mg IV Q4W during induction treatment, and therefore it is unclear if E-R associations for maintenance treatment would differ in patients with different induction dosage, extended induction, or rescue induction.

Multivariate E-R modeling was also conducted using data from Study AMBG. Efficacy endpoints of clinical remission rate, endoscopic remission rate, and change in mMS at Week 40 were evaluated. The following covariates were investigated for impacts on efficacy: age, gender, race, body weight, BMI, prior biologic therapy or tofacitinib use, baseline albumin, baseline bilirubin, baseline C-reactive protein, baseline fecal calprotectin, TE ADA status, duration of disease, baseline use of corticosteroid or immunomodulator, clinical remission at the end of Study AMAN, mMS and related subscores before induction treatment, and mMS and related subscores at the end of Study AMAN.

The E-R modeling found that patients who achieved clinical remission at the end of Study AMAN (i.e., induction treatment) were more likely to have clinical remission at the end of Study AMBG (i.e., maintenance treatment). When clinical remission status at the end of Study AMAN was included as a covariate, there was no statistically significant association between maintenance efficacy and maintenance treatment C_{avg}. Predictions from the multivariate E-R analysis for maintenance treatment are displayed in Figure 46.

The E-R analysis of maintenance efficacy supports the proposed 200 mg SC Q4W dosage.

Figure 46. Visual Predictive Checks for Multivariate Mirikizumab Exposure-Response Models of Efficacy at Week 40 of Maintenance Treatment



Abbreviation: C_{avg} = average mirikizumab concentration; miri = mirikizumab; mMS = modified Mayo score; PI = prediction interval. The data points represent the percentage of patients that achieved clinical remission in the placebo group and the patients that received 300-mg mirikizumab subdivided into C_{avg} quartiles. The points are plotted along the x-axis at the median C_{avg} for each quartile.
Source: Figures ATT.13.22, ATT.13.25, and ATT.13.28 in Applicant's Population PK Report

Overall, data from studies AMAC, AMAN, and AMBG indicate that the proposed dosing results in exposure associated with clinical efficacy for both induction and maintenance. The E-R analyses provide supportive evidence of effectiveness for the proposed mirikizumab induction and maintenance dosing. Refer to Section 8 of this review for additional details regarding the study design and efficacy results from phase 3 studies AMAN and AMBG.

16.3.5. Exposure-Response Safety Analysis

16.3.5.1. *Executive Summary*

The E-R safety analysis investigated TEAEs leading to dose modification and select AESIs. No safety concerns were identified related to exposure following the proposed 300 mg IV Q4W induction dosage or exposure following the 200 mg SC Q4W maintenance dosage.

16.3.5.2. *Objectives*

The objectives of the exposure-response analysis of safety were*:*

- To characterize the relationship of mirikizumab systemic exposure with selected safety endpoints in patients with ulcerative colitis, and

- To identify covariates that can influence these relationships.

16.3.5.3. *Data*

The E-R safety analysis included data from Study AMAN and Study AMBG in 1275 unique patients.

In Study AMAN, 1273 patients had exposure and safety data for induction treatment (952 patients with 300 mg IV Q4W plus 321 patients with placebo IV Q4W).

In Study AMBG, 524 patients had exposure and safety data for maintenance treatment (389 patients with 200 mg SC Q4W and 135 patients with placebo SC Q4W). Study AMBG placebo patients were only included if they had previously received placebo IV Q4W in Study AMAN and achieved response before starting placebo SC Q4W in Study AMBG.

16.3.5.4. *Induction and Maintenance Treatment Analysis*

In Study AMAN, there were no clear associations across exposure quartiles (C_{avg} during induction treatment) and incidence of TEAE leading to dose modification, infusion site reactions, infections, opportunistic infections, serious infections, or hypersensitivity reactions. Many safety events had relatively low incidence overall in Study AMAN which may limit the ability to accurately characterize the E-R safety relationships. See Table 107 for the incidence of safety events with induction treatment across exposure quartiles.

In Study AMBG, there were no clear associations across exposure quartiles (C_{avg} during maintenance treatment) and incidence of TEAE leading to dose modification, injection site reactions, infections, opportunistic infections, serious infections, or hypersensitivity reactions. See Table 108 for the incidence of safety events with maintenance treatment across exposure quartiles.

Table 107. Percent of Subjects in Study AMAN Experiencing Adverse Events of Special Interest During Induction Treatment by Exposure Quartile

	Placebo (n=321)	Mirikizumab C_{avg} Quartile During Induction			
		Q1 (n=238)	Q2 (n=238)	Q3 (n=238)	Q4 (n=238)
Median mirikizumab C_{avg} (ug/mL)	--	12.7	17.6	22.0	30.0
Any TEAE [n (%)]	150 (46.7%)	110 (46.2%)	108 (45.4%)	91 (38.2%)	117 (49.2%)
TEAE leading to dose modification*	28 (8.7%)	7 (2.9%)	4 (1.7%)	2 (0.8%)	5 (2.1%)
TEAE leading to dose interruption	6 (1.9%)	2 (0.8%)	1 (0.4%)	2 (0.8%)	2 (0.8%)
TEAE leading to drug discontinuation	22 (6.9%)	5 (2.1%)	3 (1.3%)	1 (0.4%)	3 (1.3%)
Hypersensitivity reaction [n (%)]	11 (3.4%)	5 (2.1%)	10 (4.2%)	14 (5.9%)	8 (3.4%)
Infection [n (%)]	45 (14%)	41 (17.2%)	39 (16.4%)	32 (13.4%)	33 (13.9%)
Infusion site reaction [n (%)]	1 (0.3%)	0 (0%)	2 (0.8%)	1 (0.4%)	1 (0.4%)
Opportunistic Infection [n (%)]	4 (1.2%)	4 (1.7%)	1 (0.4%)	0 (0%)	2 (0.8%)
Serious Infection [n (%)]	2 (0.6%)	2 (0.8%)	5 (2.1%)	0 (0%)	0 (0%)

*Dose modification = dose interruption or drug discontinuation.
Opportunistic infection plots include opportunistic infections defined by narrow search terms and potential opportunistic infections defined by broad search terms. Hypersensitivity reaction plots include immediate events defined by both broad and narrow search terms and nonimmediate events defined by narrow search terms.
C_{avg} = average mirikizumab concentration during one dosing interval; Q = quartile; TEAE = treatment emergent adverse event.
Source: Reviewer analysis of Applicant's exposure-response safety dataset submitted in response to 18May2022 Information Request; and Applicant's Study AMAN adae.xpt dataset

Table 108. Percent of Subjects in Study AMBG Experiencing Adverse Events of Special Interest During Maintenance Treatment by Exposure Quartile

	Placebo **(n=135)**	Mirikizumab C_{avg} Quartile During Maintenance			
		Q1 **(n=98)**	Q2 **(n=96)**	Q3 **(n=98)**	Q4 **(n=97)**
Median mirikizumab C_{avg} (ug/mL)	--	3.5	5.9	7.8	11.4
Any TEAE **[n (%)]**	85 (63%)	58 (59.2%)	61 (63.5%)	68 (69.4%)	66 (68%)
TEAE leading to dose modification*	2 (1.5%)	5 (5.1%)	2 (2.1%)	0 (0%)	5 (5.2%)
TEAE leading to dose interruption	1 (1.7%)	4 (4.1%)	0 (0%)	0 (0%)	2 (2.1%)
TEAE leading to drug discontinuation	1 (1.7%)	1 (1.0%)	2 (2.1%)	0 (0%)	3 (3.1%)

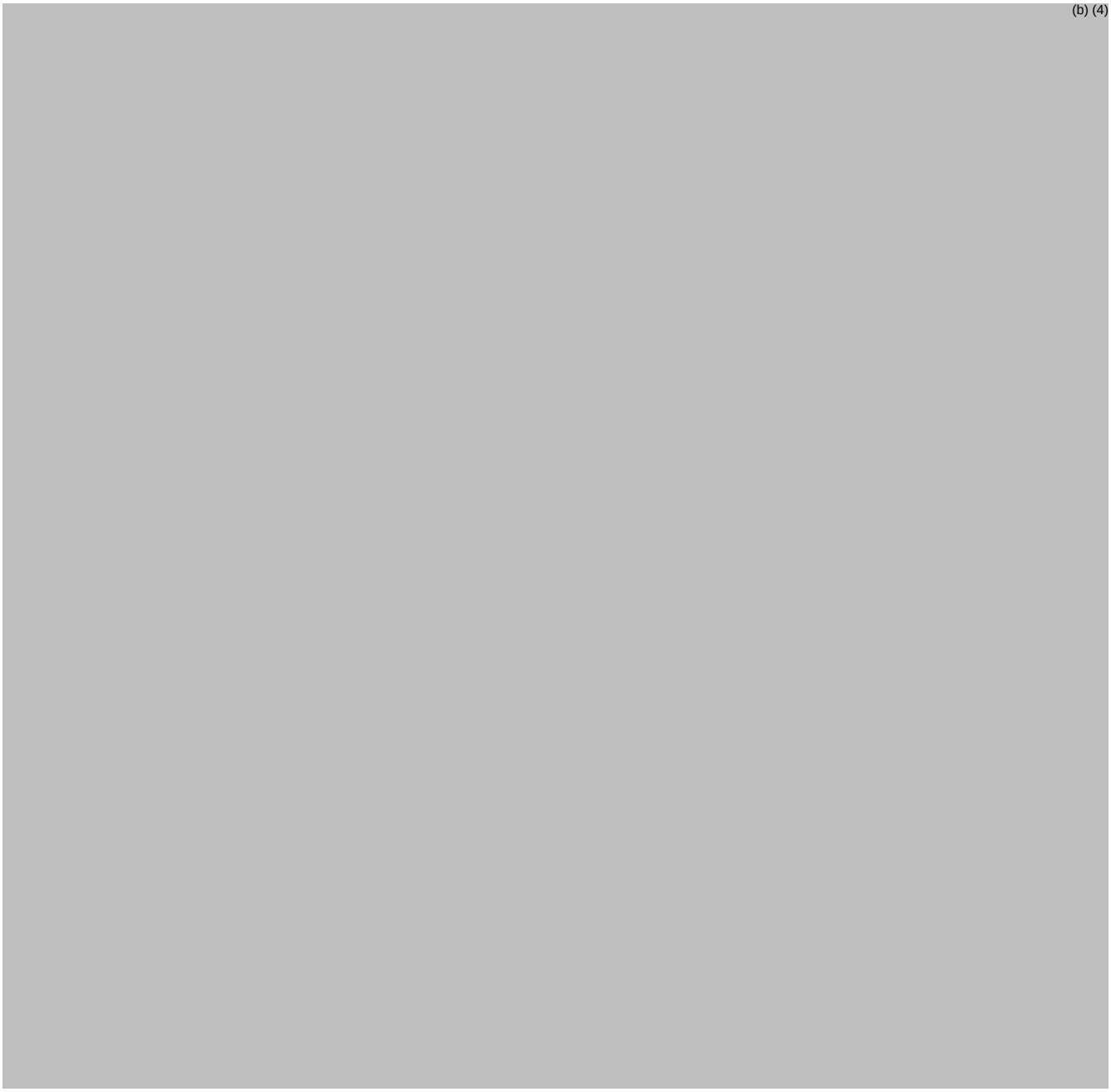
Hypersensitivity reaction **[n (%)]**	4 (3%)	5 (5.1%)	10 (10.4%)	4 (4.1%)	13 (13.4%)
Infection **[n (%)]**	30 (22.2%)	23 (23.5%)	22 (22.9%)	22 (22.4%)	26 (26.8%)
Infusion site reaction **[n (%)]**	3 (2.2%)	7 (7.1%)	11 (11.5%)	5 (5.1%)	11 (11.3%)
Opportunistic infection **[n (%)]**	3 (2.2%)	3 (3.1%)	2 (2.1%)	2 (2%)	0 (0%)
Serious infection **[n (%)]**	3 (2.2%)	0 (0%)	2 (2.1%)	1 (1%)	0 (0%)

*Dose modification = dose interruption or drug discontinuation.
The placebo group column in the table represents subjects who were considered placebo responders in study AMAN and received placebo in study AMBG. Opportunistic infection plots include opportunistic infections defined by narrow search terms and potential opportunistic infections defined by broad search terms. Hypersensitivity reaction plots include immediate events defined by both broad and narrow search terms and nonimmediate events defined by narrow search terms.
C_{avg} = average mirikizumab concentration during one dosing interval; Q = quartile; TEAE = treatment emergent adverse event.
Source: Reviewer analysis of Applicant's exposure-response safety dataset submitted in response to 18May2022 Information Request; and Applicant's Study AMBG adae.xpt dataset

Overall, the E-R safety analysis did not identify any safety concerns related to exposure following the proposed 300 mg IV Q4W induction dose or exposure following the 200 mg SC Q4W maintenance dose.

16.4. Patient Reported Outcome (PRO) Measures Proposed in Labeling

The Applicant proposed the following language in the draft label for Omvoh (mirikizumab):



16.4.1. Urgency Numeric Rating Scale (NRS)

The Urgency NRS is a single-item PRO measure assessing severity of a patient's urgency (the sudden or immediate need) to have a bowel movement within the past 24 hours using an 11-point NRS ranging from 0 ("No urgency") to 10 ("Worst possible urgency"). Daily total scores were recorded using an 11-point NRS ranging from 0 ("No urgency") to 10 ("Worst possible urgency") and weekly Urgency NRS scores are calculated as the mean score over a 7-day period. If there are fewer than 4 available daily Urgency NRS scores over the relevant 7-day period, then the Urgency NRS score is recorded as missing.

The Urgency NRS was developed and refined based on a targeted literature review, expert input (n=2; one gastroenterologist and one expert in clinical outcome assessments), real world data from the prospective, longitudinal *Study of a Prospective Adult Research Cohort with IBD (SPARC-IBD; n=582 adult participants with UC)*, 1:1 concept elicitation (CE) interviews (n=21 participants with mild to severe UC), cognitive interviews (n=16 participants with mild to severe UC), hybrid CE/cognitive interviews (n=20 participants with moderate to severe UC), and a 2-week daily diary pilot study (n=41 participants with mild to severe UC) to assess the Urgency NRS measurement properties. The demographic and clinical characteristics of the participating population in the qualitative and quantitative studies was similar to those in studies AMAN and AMBG.

The results of the qualitative research demonstrated that urgency is a relevant and important symptom that was spontaneously reported by the majority of participants across all UC severity levels. Participants most commonly described urgency severity in terms of the amount of time available to a participant to find a bathroom (e.g., “you got a couple of seconds to get to the bathroom”, “can’t wait 2-3 minutes”, “I really had to drop everything… and rush to the restroom”) to avoid an accident. Based on the qualitative evidence submitted by the Applicant, the Urgency NRS appears to have content validity for the proposed context of use. Of note, frequency of having a BM appears to be a potential confounder with urgency severity.

16.4.2. Qualitative Input for Meaningful Change in Urgency NRS Scores

In the cognitive and hybrid CE/cognitive interviews, 36 participants were asked to describe the amount of change they would consider a meaningful improvement based on the Urgency NRS response scale. Of all participants, the proportion of participants reporting a 1-category, 2-category, 3-category, and ≥ 4-category change as reflecting meaningful improvement was 47% (n=17), 22% (n=8), 8% (n=3), 3% (n=1), and 19% (n=7), respectively.

Approximately 56% (n=20) of participants interviewed reported having an Urgency NRS score ≤ 6 and approximately 44% (n=16) of participants interviewed reported having an Urgency NRS score > 6. For participants that reported an Urgency NRS score ≤ 6, the majority reported a 1-category change as a meaningful improvement (n=13, 65%). However, for participants that reported an Urgency NRS score > 6, only 25% (n=4) reported a 1-category change as a meaningful improvement. Half of participants with more severe urgency reported meaningful improvement as ≥ 4-category change in Urgency NRS scores (n=8) suggesting that patients with more severe urgency need a greater amount of change to consider it as a meaningful improvement.

16.5. Qualitative Evidence to Support the **Urgency** NRS Weekly Average Score of 0 or 1 Endpoint

The cognitive interview participants (N=16) were asked what score they would need to achieve on the Urgency NRS to consider an ideal treatment a success. The largest proportion of participants (n=5, approximately 31%) reported they would need to achieve an Urgency NRS

score of 1. Only 1 participant (approximately 6%) reported they would need to achieve an Urgency NRS score of 0.

Amongst participants in the hybrid CE/cognitive interviews (N=21), 9 participants described an improvement in bowel urgency in the past as times when bowel urgency had gone completely, and 9 participants described an improvement in bowel urgency as times when their bowel urgency had "reduced" or "improved".

16.6. Interpretation of Change From Baseline in the Urgency NRS Score

For development programs utilizing COA-based endpoints, it is important to evaluate how well results of a COA-based endpoint correspond to a treatment benefit that is meaningful to subjects. The anchor scale(s) are used as external criteria to define subjects who have or have not experienced a meaningful change in their condition, with the change in COA score evaluated in these sets of subjects.

This section details how clinically meaningful within-subject change (improvement) from baseline to Week 12 (AMAN) and to Week 40 (AMBG) in the Urgency NRS score was determined to support the determination of clinical meaningfulness for the Urgency NRS-based multiplicity controlled secondary endpoint results.

16.6.1. Anchor Assessment

Two anchor scales were used in the Applicant's anchor-based analyses, the Patient Global Rating of Severity (PGRS) and the Patient Global Rating of Change (PGRC). The PGRS is not an ideal anchor scale for the primary anchor-based analysis to interpret Urgency NRS scores given that it asks subjects to rate their overall UC symptoms rather than asking specifically about the bowel urgency concept. However, based on the correlations described in Section 16.6.2.2.2 and clear separation of curves in the empirical cumulative distribution function (eCDF) plots in Figure 47 and Figure 49, the PGRS appears to function as an appropriate anchor scale for interpretation of Urgency NRS scores.

The PGRC is not an ideal anchor scale due to concern for recall bias but is considered acceptable as a secondary analysis support the primary analysis based on the PGRS.

Patient Global Rating of Change (PGRS)

The PGRS is a single-item PRO measure assessing the severity of a patient's overall UC symptoms in the past 24-hours using a 6-category verbal response scale (VRS), as shown in Table 111 below. The PGRS was assessed daily from screening to Week 12 in AMAN and Week 0 to Week 40 in AMBG.

Table 111. Patient Global Rating of Change (PGRS) Item and Scoring

Question	Response option	Score
How would you rate your overall Ulcerative Colitis symptoms over the past 24 hours?	None	1
	Very mild	2
	Mild	3
	Moderate	4
	Severe	5
	Very severe	6

Source: Reviewer's table, adapted from page 9/28 of the Applicant's Subject Facing Screen Report-eDiary

Patient Global Rating of Change (PGRC)

The PGRC is a single-item PRO measure assessing a patient's global rating of change in his/her UC symptoms now compared to how they were before starting the study medication using a 7-category VRS, as shown in Table 112 below. The PGRC was assessed at Weeks 4, 8, and 12 in AMAN and at Week 40 in AMBG.

Table 112. Patient Global Rating of Change (PGRC) Item and Scoring

Question	Response option	Score
Mark the box that best describes how your Ulcerative Colitis symptoms are now, compared to how they were before you started taking this medicine	Very much better	1
	Much better	2
	A little better	3
	No change	4
	A little worse	5
	Much worse	6
	Very much worse	7

Source: Reviewer's table, adapted from page 12/154 of the Applicant's Subject Facing Screen Report-Slate

16.6.2. Anchor-Based Analyses

Anchor-based methods supplemented with eCDF curves were used to establish a range of thresholds that constitutes a clinically meaningful within-subject change from baseline in the Urgency NRS score for both Studies AMAN and AMBG. The anchor-based analyses were conducted separately using mITT subjects with an induction baseline mMS ≥5 based on pooled data (across arms) in Studies AMAN and AMBG, and by both the Applicant and the review team. While the review team replicated the Applicant's analyses, the review team does not agree with the Applicant's conclusion regarding the range of clinically meaningful within-subject change thresholds in the Urgency NRS score for both Studies AMAN and AMBG. The following sections provide a comprehensive review of the analyses conducted by the Applicant and the review team.

16.6.2.1. *Applicant's Original Analyses in the PRO Dossier*

According to the prespecified scoring algorithm described in Section 5.12 and Appendix 1 of the SAP Version 4 dated January 14, 2021, a weekly Urgency NRS score and a weekly PGRS score are calculated as follows: "all available days of the 7 days will be averaged and rounded to the nearest integer to calculate the weekly score for each subject. If fewer than 4 days are available (i.e., not missing), the patient will be considered to be missing data for that week." Therefore,

the Applicant's primary anchor-based analysis included in the PRO dossier (dated March 08, 2022) was conducted using rounded weekly Urgency NRS and rounded weekly PGRS scores.

In addition to the anchor-based analyses supplemented by the eCDF curves, the Applicant also calculated sensitivity, specificity, positive predictive value, negative predictive value, and the Youden Index (specificity + sensitivity - 1) for a sequence of thresholds for improvement on the Urgency NRS against the binary classifier based on the predefined target anchor change threshold at Week 12 for AMAN and Week 40 for AMBG. Threshold associated with the largest Youden's index was considered a candidate for meaningful within-patient change in the Urgency NRS score.

Lastly, the Applicant conducted two sensitivity analyses to examine the consistency of the primary anchor-based analysis:

- Using a single daily PGRS score as anchor: only the diary entry closest to the visit date within the appropriate visit window was used at Baseline and Week 12
- Using a rounded weekly PGRS improvement of at least 2 categories from Baseline and requiring each daily PGRS score at Week 12 to be less than the maximum of daily PGRS score at Baseline

Based on results of the 3 approaches, the Applicant's original anchor-based analyses determined that a threshold of ≥ 3 points improvement on the Urgency NRS is clinically meaningful to subjects for both Studies AMAN and AMBG.

16.6.2.2. *Agency's Evaluation*

16.6.2.2.1. *Additional Analyses Requested by the Review Team*

The review team does not agree with the SAP prespecified scoring algorithm that allows rounding of the Urgency NRS and PGRS scores, as rounding could bias the individual-level change in scores by either overestimating or underestimating the actual improvement. In addition, the recall period used in the PGRS (i.e., "the past 24 hours") did not match the assessment period used to calculate the Urgency NRS score. While the Applicant attempted to calculate a weekly PGRS score to match the assessment period of the Urgency NRS score, the approach to round the weekly PGRS score to the nearest integer complicates the interpretability of whether a change in the anchor scores represents a clinically meaningful improvement to subjects on the anchor scale. Given the limitations of the Applicant's analyses, the review team could not agree that the Applicant's proposed threshold of ≥ 3 points improvement reflected a clinically meaningful within-subject change and subsequently issued an information request (IR) on June 30, 2022, requesting additional anchor-based analyses using the following approaches:

For both AMAN and AMBG:

- Use the worst PGRS score within an assessment week as an anchor (i.e., at baseline and Week 12 of AMAN or Week 40 of AMBG)
- Use each of the 7 daily PGRS score within an assessment week (i.e., at baseline and Week 12 of AMAN or Week 40 of AMBG) as anchors

For AMAN only:

- Use the PGRC as an anchor, with un-rounded weekly Urgency NRS scores

The Applicant provided the requested analyses in written responses on July 22, 2022. Upon further review of the BLA and the Applicant's July 22, 2022, IR response, the review team identified and notified the Applicant that for both studies AMAN and AMBG, the clinically meaningful within-subject change in Urgency NRS score that incorporated the subjects' perspectives reflects a range of thresholds greater than the Applicant's originally proposed threshold of ≥ 3 points improvement in the Urgency NRS score. In addition, both qualitative and quantitative assessments conducted by the review team indicate that the meaningful change threshold range varies by subjects' baseline urgency severity status. As such, the review team issued another IR on September 8, 2022, requesting the Applicant to propose a revised range of clinically meaningful within-subject change threshold in the Urgency NRS score, along with justification, for both AMAN and AMBG. The Applicant provided the requested analyses on September 26, 2022, and proposed a meaningful change range between 3- and 5-point improvement, inclusive, in the Urgency NRS score for both AMAN and AMBG. The Applicant's justification of the lower bound of the change in the Urgency NRS (i.e., 3-point improvement) was based on the lower 25th percentile of the range of thresholds derived using different types of anchors (i.e., the worst PGRS score, day 1 to day 7 within a 7-day period of the PGRS score). When deriving the range of thresholds, the Applicant also considered median and 75th percentile of change from baseline on Urgency NRS for patients who had no change, a 1-point improvement, 2-point improvement, 3-point improvement. Further, the lower bound of the threshold is confirmed using the Youden Index as described in Section 16.6.2.1,. the review team does not agree with the Applicant's revised range as the lower bound (a 3-point improvement) may not represent clinically meaningful improvement for subjects with higher symptom severity at baseline. Refer to Sections 16.6.2.2.2 and 16.6.2.2.6, below, for a more detailed discussion of these assessments.

16.6.2.2.2. *Correlations Between Change from Baseline in Urgency NRS Score and Anchors*

The review team replicated the Applicant's Spearman correlation analyses (included in Section 4.2.1.4 of the September 26, 2022, IR response) to investigate the strength and magnitude of the relationship between change from baseline to Week 12 (AMAN) or Week 40 (AMBG) in Urgency NRS score and the anchors (Table 113). Overall, the change in PGRS has consistent and moderately higher correlation with the change in Urgency NRS score in both studies whereas

PGRC has moderately lower correlation with change in Urgency NRS score at Week 12 and low correlation at Week 40. Of note, the overall relatively modest correlation was expected as both PGRS and PGRC measure overall UC symptoms instead of specifically about bowel urgency as discussed in Section 16.6.1. The review team's anchor-based analysis focused on using the PGRS as an anchor, given the lower correlation and the potential long recall bias (i.e., a 12-week recall in AMAN and a 52-week [12-week induction + 40-week maintenance] in AMBG) with the PGRC.

Table 113. Spearman Correlations Between Absolute Change From Baseline to Week 12/ Week 40 in Urgency NRS Score and Anchor Scores

Anchor	Spearman Correlation with Change in Urgency NRS score	
	AMAN	AMBG
PGRC at Week 12 (AMAN) or Week 40 (AMBG)	0.5	0.3
Change from baseline to Week 12 (AMAN) or Week 40 (AMBG)		
Worst PGRS	0.6	0.6
Day 1 of the 7-day period in PGRS	0.6	0.6
Day 2 of the 7-day period in PGRS	0.6	0.6
Day 3 of the 7-day period in PGRS	0.6	0.6
Day 4 of the 7-day period in PGRS	0.7	0.6
Day 5 of the 7-day period in PGRS	0.6	0.6
Day 6 of the 7-day period in PGRS	0.6	0.6
Day 7 of the 7-day period in PGRS	0.6	0.6

Source: PFSS reviewer generated table. Analysis was verified by reviewer using Applicant submitted data adsl.xpt and addd4.xpt using only modified intend-to-treat subjects with Baseline Modified Mayo Score ≥ 5.
Abbreviation: PGRC = Patient Global Rating of Change, Urgency NRS = Urgency numerical rating scale, mITT = modified intent to treat

16.6.2.2.3. *Distribution of Baseline and Change from Baseline in Urgency NRS Score*

In order to understand the change in Urgency NRS score that is considered meaningful to subjects, the review team examined the distribution of baseline Urgency NRS score and the change from baseline to Week 12 (AMAN) or Week 40 (AMBG) in Urgency NRS score by treatment arm and by study (Table 114) The Urgency NRS score at baseline had similar distribution between the two studies. In AMAN, the mean and median change from baseline to Week 12 in Urgency NRS are -2.9 and -2.5 and -1.9 and -1.6 for subjects in the treatment and placebo groups, respectively. In AMBG, the mean and median change from baseline to Week 40 in Urgency NRS score are -4.0 and -4.0 and -3.9 and -4.3 for subjects in the treatment and placebo groups, respectively.

Table 114. Distribution of Baseline Urgency NRS Score and Change From Baseline in Urgency NRS Score by Study and Treatment Arm

	Statistics	AMAN			AMBG		
		300 miri IV Q4W (N=795)	Placebo IV Q4W (N=267)	All Subjects (N=1062)	Miri Responder 200 miri SC (N=337)	Miri Responder placebo SC (N=169)	All Subjects (N=506)
Baseline	Min / Max	0.0 / 10.0	0.0/ 10.0	0.0 / 10.0	0.0 / 10.0	0.9 / 10.0	0.0 / 10.0
	Median [IQR]	6.6 [4.9; 7.9]	6.7 [4.9; 8.0]	6.6 [4.9; 7.9]	6.4 [4.7;7.7]	6.7 [5.0;7.7]	6.5 [4.9;7.7]
	Mean (SD)	6.2 (2.1)	6.3 (2.1)	6.3 (2.1)	6.1 (2.1)	6.3 (1.9)	6.2 (2.1)
	N (Missing)	788 (7)	263 (4)	1051 (11)	333 (4)	169 (0)	502 (4)
Change from Baseline	Min / Max	-9.8 / 6.7	-8.4 / 6.4	-9.8 / 6.7	-9.7 / 1.9	-8.3 / 2.9	-9.7 / 2.9
	Median [IQR]	-2.5 [-4.4; -0.9]	-1.6 [-3.4; -0.1]	-2.3 [-4.3; -0.7]	-4.0 [-6.0; -2.1]	-4.3 [-5.8; -1.9]	-4.1 [-6.0; -2.1]
	Mean (SD)	-2.7 (2.5)	-1.9 (2.5)	-2.5 (2.5)	-4.0 (2.5)	-3.9 (2.6)	-4.0 (2.5)
	N (Missing)	755 (40)	229 (38)	984 (78)	291 (46)	97 (72)	388 (118)

Source: PFSS reviewer generated table. Analysis was verified by reviewer using Applicant submitted data adsl.xpt and addd4.xpt using only modified intend-to-treat subjects with Baseline Modified Mayo Score ≥ 5.
Abbreviations: IQR =interquartile range, SD = standard deviation, N =sample size, Min = minimum, Max = maximum

16.6.2.2.4. *Target Anchor Change Category*

Ideally, a target anchor change category should be pre-specified by the Applicant and agreed upon by FDA during the IND phase. Of note, while the Applicant's PRO dossier specified that "patients who improved by 2 or more categories on the PGRS were considered to have experienced large and important improvement," a formal agreement between FDA and the Applicant was not made. Based on discussions among the Clinical, DCOA, and Statistical review teams, a 2-category improvement on the 6-category PGRS was determined to be reasonable to support further anchor-based meaningful change analyses. A 2-category improvement on the 6-category PGRS could occur in the following ways:

- Change from "Very severe" to "Moderate"
- Change from "Severe" to "Mild"
- Change from "Moderate" to "Very Mild"
- Change from "Mild" to "None"

What subjects consider to be clinically meaningful improvement may be impacted by their baseline symptom severity. Subjects' baseline symptom severity should be considered when determining clinically meaningful within-subject improvement thresholds. Table 115 and Table 116 show the distribution of change patterns in the worst PGRS score between baseline and Week 12 for AMAN and between baseline and Week 40 for AMBG, respectively, using data pooled across arms. Note that change patterns on Day 1 to Day 7 within a 7-day period show a similar trend as observed in the worst PGRS score and are not included in this review.

What subjects consider to be clinically meaningful improvement may be impacted by their baseline symptom severity. Subjects' baseline symptom severity should be considered when determining clinically meaningful within-subject improvement thresholds.

In both AMAN and AMBG, the majority of subjects reported having moderate to severe disease severity at baseline. However, subjects in AMAN and AMBG reported different change patterns in the worst PGRS. For AMAN (Table 115), the majority of subjects starting with moderate symptom reported "no change" (42.1%) at Week 12, followed by a 1-category improvement (27.9%) and 2-cateogry improvement (19.3%). For subjects who started with severe symptom at baseline, the majority reported a 1-category improvement (37.2%), followed by a 2-category improvement (22.3%) and "no-change" (19.7%). For AMBG (Table 116), most subjects starting with moderate symptom reported a 1-category improvement (32.3%) at Week 40, followed by a 2-cateogry improvement (27.1%) and a 3-cateogry improvement (23.3%). For subjects who started with severe symptom at baseline, the majority reported a 4-category improvement (33.9%), followed by a 3-category improvement (24.9%) and a 2-category improvement (19.6%). There is also a notable number of subjects who started with "very severe" symptoms reporting improvement of more than 2 categories on the PGRS.

Table 115. Category Change (n (%)) in PGRS From Baseline to Week 12 by Baseline PGRS (mITT With mMS ≥ 5 in AMAN)

Worst PGRS at Baseline	Change from Baseline to Week 12 in the Worst PGRS							
	Improved 5 categories (N=2)	Improved 4 categories (N=47)	Improved 3 categories (N=93)	Improved 2 categories (N=212)	Improved 1 category (N=326)	No change (N=267)	Worsen 1 category (N=33)	Worsen 2 categories (N=3)
None (N=1)	0	0	0	0	0	1 (100.0%)	0	0
Very mild (N=6)	0	0	0	0	2 (33.3%)	3 (50.0%)	1 (16.7%)	0
Mild (N=42)	0	0	0	7 (16.7%)	16 (38.1%)	14 (33.3%)	5 (11.9%)	0
Moderate (N=337)	0	0	19 (5.6%)	65 (19.3%)	94 (27.9%)	142 (42.1%)	14 (4.2%)	3 (0.9%)
Severe (N=476)	0	33 (6.9%)	53 (11.1%)	106 (22.3%)	177 (37.2%)	94 (19.8%)	13 (2.7%)	0
Very severe (N=121)	2 (1.7%)	14 (11.6%)	21 (17.4%)	34 (28.1%)	37 (30.6%)	13 (10.7%)	0	0

Source: PFSS reviewer generated table. Analysis was verified by reviewer using Applicant submitted data adsl.xpt and addd4.xpt with only modified intend-to-treat subjects with Baseline Modified Mayo Score ≥ 5.
Abbreviation: PGRS = Patient Global Rating of Severity, mMS = Modified Mayo Score, mITT = modified intent to treat

Table 116. Category Change (n (%)) in PGRS From Induction Baseline to Week 40 by Baseline PGRS (mITT With mMS ≥ 5 in AMBG)

Worst PGRS at Baseline	Change from Baseline to Week 40 in the Worst PGRS							
	Improved 5 categories (N=11)	Improved 4 categories (N=73)	Improved 3 categories (N=83)	Improved 2 categories (N=93)	Improved 1 category (N=88)	No change (N=37)	Worsen 1 category (N=2)	Worsen 2 categories (N=1)
None (N=0)	0	0	0	0	0	0	0	0
Very mild (N=3)	0	0	0	0	1 (33.3%)	2 (66.7%)	0	0
Mild (N=19)	0	0	0	5 (26.3%)	10 (52.6%)	4 (21.1%)	0	0
Moderate (N=133)	0	0	31 (23.3%)	36 (27.1%)	43 (32.3%)	21 (15.8%)	1 (0.8%)	1 (0.6%)
Severe (N=189)	0	64 (33.9%)	47 (24.9%)	37 (19.6%)	31 (16.4%)	9 (4.8%)	1 (0.5%)	0
Very severe (N=44)	11 (25.0%)	9 (20.5%)	5 (11.4%)	15 (34.1%)	3 (6.8%)	1 (2.3%)	0	0

Source: PFSS reviewer generated table. Analysis was verified by reviewer using Applicant submitted data adsl.xpt and addd4.xpt with only modified intend-to-treat subjects with Baseline Modified Mayo Score ≥ 5.
Abbreviation: PGRS = Patient Global Rating of Severity, mMS = Modified Mayo Score, mITT = modified intent to treat

16.6.2.2.5. *AMAN Results: Clinically Meaningful Change From Baseline to Week 12 in Urgency NRS Score*

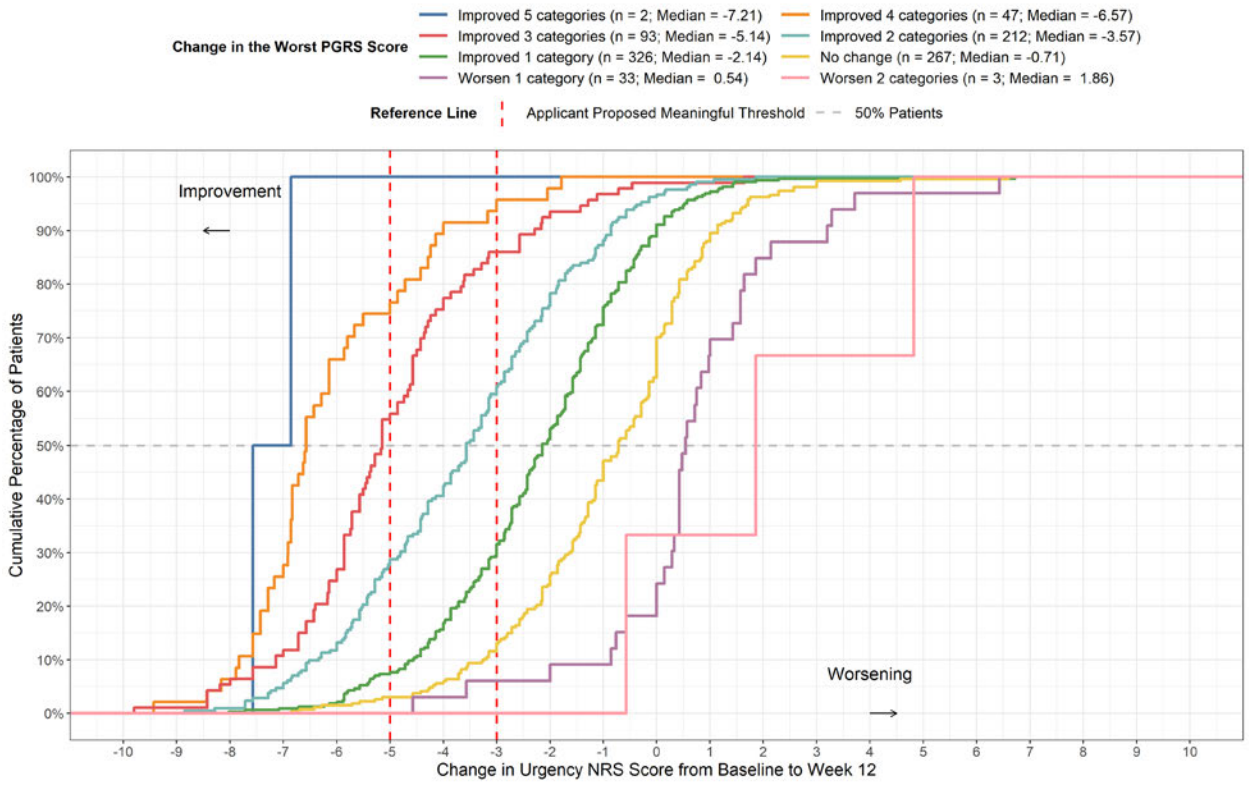
As previously mentioned in the Applicant's PRO dossier and confirmed by the Applicant's IR response submitted on September 26, 2022, the Applicant proposed that a threshold of ≥ 3 points improvement on the Urgency NRS is considered clinically meaningful to subjects for both Studies AMAN and AMBG. The review team does not agree with the Applicant's proposed threshold of ≥ 3 point improvement. As shown in Table 117 and Table 118, for AMAN subjects who experienced a 2-category improvement in the anchors, the median change in the Urgency NRS score is larger than a 3-point improvement on all anchors. Table 117 also summarizes the percentile of change in the Urgency NRS score from baseline for subjects with a 2-category improvement in the PGRS. When looking at the eCDF plot of change from baseline in the Urgency NRS score by the worst PGRS category of change from baseline for AMAN (Figure 47), the eCDF plot shows clear and consistent separation between the "2-category improvement", "1-category improvement", and "no change" curves, further supporting the use of a 2-category improvement on the PGRS from a quantitative perspective. The eCDF plots of change from baseline in the Urgency NRS score by PGRS change category of Day 1 to Day 7 within the 7-day period show similar trend and are not included in this review.

Table 117. Change From Baseline to Week 12 in Urgency NRS Score for Subjects With a 2-Category Improvement in PGRS Category of Change (mITT With mMS ≥ 5 in AMAN)

		Change From Baseline in Urgency NRS				
Anchor	N	10th percentile	25th percentile	50th percentile	75th percentile	90th percentile
Day 1 PGRS	182	-6.0	-4.9	-3.6	-2.1	-1.0
Day 2 PGRS	171	-6.3	-5.3	-3.7	-2.4	-1.0
Day 3 PGRS	184	-6.6	-5.3	-3.9	-2.4	-1.1
Day 4 PGRS	182	-5.9	-5.1	-3.6	-2.4	-1.6
Day 5 PGRS	180	-6.2	-5.2	-3.7	-2.0	-0.9
Day 6 PGRS	186	-6.2	-5.3	-3.8	-2.0	-0.9
Day 7 PGRS	175	-6.0	-4.8	-3.3	-1.8	-0.9
Worst PGRS	212	-6.3	-5.2	-3.6	-2.1	-0.9

Source: PFSS reviewer generated table. Analysis was verified by reviewer using Applicant submitted data adsl.xpt and addd4.xpt with only modified intend-to-treat subjects with Baseline Modified Mayo Score ≥ 5.
Abbreviation: PGRS = Patient Global Rating of Severity, mMS = Modified Mayo Score, mITT = modified intent to treat

Figure 47. eCDF, Change From Baseline to Week 12 in Urgency NRS Score by Change in the Worst PGRS Category (mITT With mMS ≥ 5 in AMAN)



Source: PFSS reviewer generated figure.

When subjects' baseline PGRS score was taken into account, the median change from baseline to Week 12 in PGRS score varied for different baseline bowel urgency severity levels (see Table 118). Specifically, subjects with more severe bowel urgency severity at baseline would require a higher change in the Urgency NRS score to consider the change a meaningful improvement. This quantitative observation is also supported by qualitative evidence (see Section 16.4.2). For instance, for subjects with at least a 2-category improvement in the corresponding PGRS anchor, the median change in the Urgency NRS score ranges from -3.9 to -3.2 and -5.1 to -4.4 for subjects with moderate and severe baseline bowel urgency severity, respectively. However, to minimize misclassifying subjects who did not experience a meaningful improvement (e.g., no change, 1-category worsening) on the PGRS as experiencing a meaningful improvement, a minimal improvement of 3.3 points in the Urgency NRS score should be considered. Of note, the Applicant's threshold (≥ 3 points) resulted in classifying >20% of subjects who did not experience meaningful change on the PGRS as experiencing meaningful change. The review team additionally considered the baseline Urgency NRS score. As shown in Table 117 above, the 25th percentile of the baseline Urgency NRS score is 4.9, which means that 75% of the subjects can have a change of 4.9 points. Therefore, the review team's anchor-based analysis suggested that the meaningful within-subject improvement threshold range should be between 3.2- and 4.9-point.

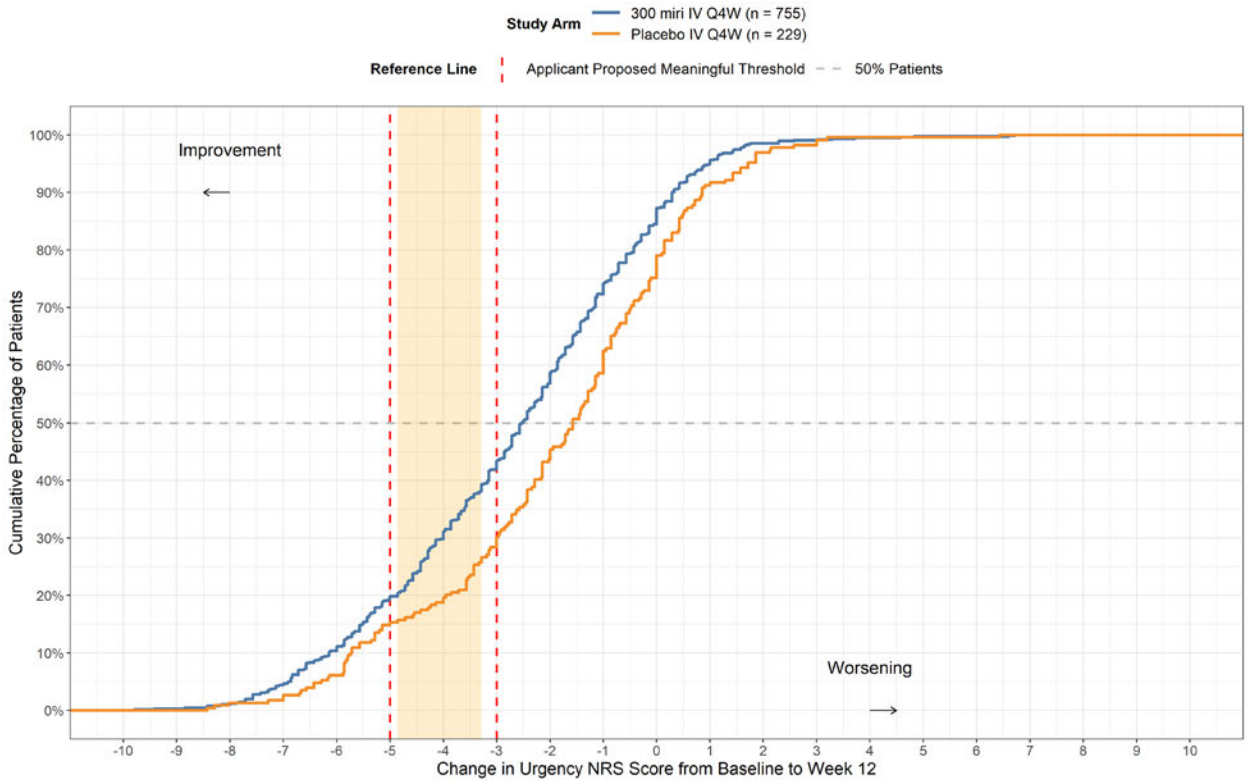
Table 118. Median Change From Baseline to Week 12 in Urgency NRS Score by PGRS for Subjects With ≥ 2-Category Improvement in the Corresponding PGRS Score (mITT With mMS ≥ 5 in AMAN)

	Baseline PGRS			
Anchor	**Mild**	**Moderate**	**Severe**	**Very Severe**
Day 1 PGRS	-4.1 (N=13)	-3.6 (N=127)	-4.7 (N=129)	-4.2 (N=32)
Day 2 PGRS	-4.1 (N=13)	-3.6 (N=124)	-5.1 (N=146)	-4.7 (N=29)
Day 3 PGRS	-4.7 (N=19)	-3.9 (N=115)	-4.7 (N=157)	-5.4 (N=29)
Day 4 PGRS	-4.1 (N=12)	-3.7 (N=133)	-4.6 (N=150)	-5.6 (N=27)
Day 5 PGRS	-4.6 (N=11)	-3.8 (N=136)	-4.7 (N=145)	-4.3 (N=35)
Day 6 PGRS	-5.0 (N=10)	-3.7 (N=137)	-4.4 (N=157)	-5.6 (N=31)
Day 7 PGRS	-4.9 (N=13)	-3.4 (N=132)	-4.4 (N=162)	-4.9 (N=35)
Worst PGRS	-2.3 (N=7)	-3.2 (N=84)	-4.7 (N=192)	-5.3 (N=71)

Source: PFSS reviewer generated table. Analysis was verified by reviewer using Applicant submitted data adsl.xpt and addd4.xpt with only modified intend-to-treat subjects with Baseline Modified Mayo Score ≥ 5.
Abbreviation: PGRS = Patient Global Rating of Severity, mMS = Modified Mayo Score, mITT = modified intent to treat

Furthermore, the eCDF plot of within-subject changes in the Urgency NRS score from baseline to Week 12 by treatment arm for AMAN is shown in Figure 48. The orange shaded area indicates FDA-derived meaningful change threshold range of 3.3-point to 4.9-point improvement. Based on visual inspection, while the eCDF plot shows consistent separation between treatment arms, the difference in the proportion of subjects experiencing a meaningful improvement between the treatment arms is notably smaller at the lower bound of the threshold range (-4.9). At the lower bound and upper bound of the review team-determined meaningful threshold range, the differences in response rates by treatment arm (mirikizumab – placebo) are 4.6% and 12.3%, respectively.

Figure 48. eCDF, Change From Baseline to Week 12 in Urgency NRS Score by Treatment Arm (mITT With mMS ≥ 5 for AMAN)



Source: PFSS reviewer generated figure.

16.6.2.2.6. *AMBG Results: Clinically Meaningful Change From Induction Baseline to Week 40 in Urgency NRS Score*

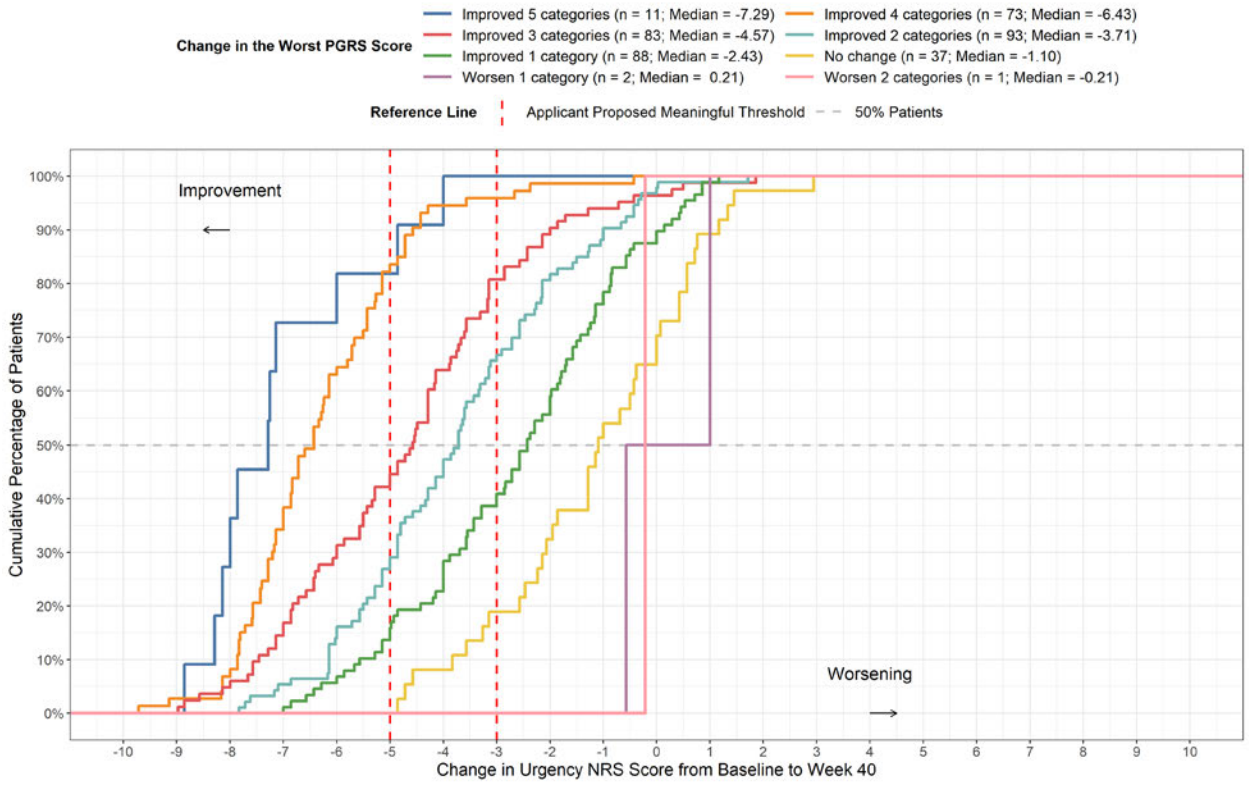
Similarly, the review team does not agree with the Applicant's proposed threshold of ≥ 3 points improvement as clinical meaningful within-subject change in the AMBG. As shown in Table 119, for AMBG subjects who experienced a 2-category improvement in the anchors, the median change in the Urgency NRS score is larger than a 3-point improvement on all anchors. When looking at the eCDF plot of change from baseline in the Urgency NRS score by the worst PGRS category of change from baseline for AMBG (Figure 49), the eCDF plot shows clear and consistent separation between the "2-category improvement", "1-category improvement", and "no change" curves, further supporting the use of a 2-category improvement on the PGRS from a quantitative perspective. The eCDF plots of change from baseline in the Urgency NRS score by PGRS change category for Day 1 to Day 7 within the 7-day period show similar trend and are not included in this review.

Table 119. Change From Baseline to Week 40 in Urgency NRS Score for Subjects With a 2-Category Improvement in PGRS Category of Change (mITT With mMS ≥ 5 in AMBG)

		Change From Baseline in Urgency NRS				
Anchor	N	10th percentile	25th percentile	50th percentile	75th percentile	90th percentile
Day 1 PGRS	85	-6.1	-5.3	-4.0	-2.6	-1.3
Day 2 PGRS	90	-5.9	-4.9	-3.7	-2.6	-1.3
Day 3 PGRS	86	-6.3	-5.4	-4.1	-2.6	-1.3
Day 4 PGRS	70	-6.1	-5.1	-3.9	-2.7	-1.9
Day 5 PGRS	94	-6.2	-5.3	-4.0	-2.6	-0.7
Day 6 PGRS	87	-6.1	-5.1	-3.9	-2.6	-1.0
Day 7 PGRS	86	-6.1	-5.0	-3.8	-2.1	-0.5
Worst PGRS	93	-6.1	-5.1	-3.7	-2.3	-1.0

Source: PFSS reviewer generated table. Analysis was verified by reviewer using Applicant submitted data adsl.xpt and addd4.xpt with only modified intend-to-treat subjects with Baseline Modified Mayo Score ≥ 5.
Abbreviation: PGRS = Patient Global Rating of Severity, mMS = Modified Mayo Score, mITT = modified intent to treat

Figure 49. eCDF, Change From Baseline to Week 40 in Urgency NRS Score by Change in the Worst PGRS Category (mITT With mMS ≥ 5 in AMBG)



Source: PFSS reviewer generated figure.

When subjects' baseline PGRS score was taken into account, the median change from baseline to Week 40 in PGRS score varied for different baseline bowel urgency severity levels (see Table 120). Specifically, subjects with more severe bowel urgency severity at baseline would require an even higher change in the Urgency NRS score when compared with AMAN. For instance, for subjects with at least a 2-category improvement in the corresponding PGRS anchor, the median

change in the Urgency NRS score ranges from -4.3 to -3.6 and -6.0 to -5.5 for subjects with moderate and severe baseline bowel urgency severity, respectively. However, to minimize misclassifying subjects who did not experience a meaningful improvement (e.g., no change, 1-category worsening) on the PGRS as experiencing a meaningful improvement, a minimal improvement of 4.7 points in the Urgency NRS score should be considered. As previously shown in Table 119, the 25th percentile of the baseline Urgency NRS score is 4.9, suggesting that the meaningful within-subject improvement threshold range should be between 4.7- and 4.9-point.

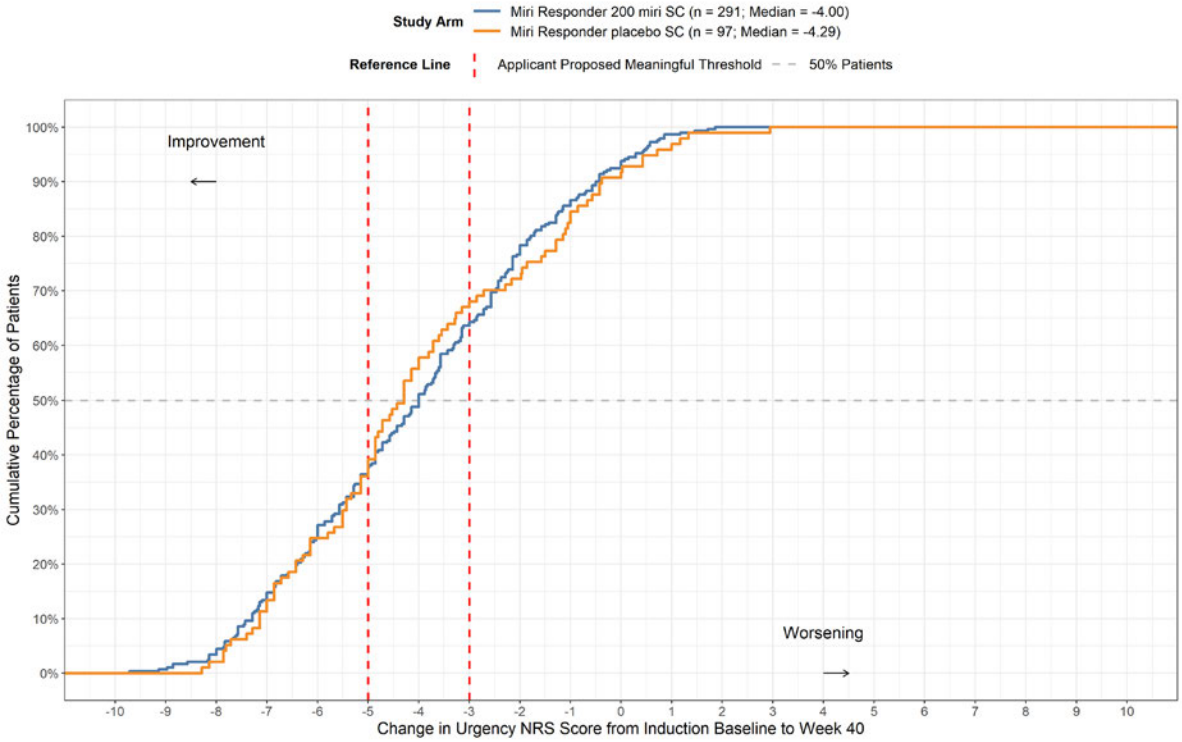
Table 120. Median Change From Baseline to Week 40 in Urgency NRS Score by PGRS for Subjects With ≥ 2-Category Improvement in the Corresponding PGRS Score (mITT With mMS ≥ 5 in AMBG)

	Baseline PGRS			
Anchor	**Mild**	**Moderate**	**Severe**	**Very Severe**
Day 1 PGRS	-5.4 (N=14)	-4.0 (N=94)	-6.0 (N=92)	-5.3 (N=15)
Day 2 PGRS	-3.4 (N=13)	-4.3 (N=104)	-6.0 (N=104)	-6.0 (N=13)
Day 3 PGRS	-4.8 (N=14)	-4.3 (N=91)	-6.0 (N=99)	-6.1 (N=15)
Day 4 PGRS	-4.8 (N=5)	-4.3 (N=98)	-5.6 (N=96)	-7.3 (N=19)
Day 5 PGRS	-4.6 (N=12)	-4.2 (N=104)	-6.0 (N=104)	-6.2 (N=18)
Day 6 PGRS	-4.8 (N=9)	-4.2 (N=98)	-6.0 (N=111)	-6.2 (N=17)
Day 7 PGRS	-4.9 (N=12)	-4.3 (N=96)	-6.0 (N=103)	-6.0 (N=21)
Worst PGRS	-4.8 (N=5)	-3.6 (N=67)	-5.5 (N=148)	-6.1 (N=40)

Source: PFSS reviewer generated table. Analysis was verified by reviewer using Applicant submitted data adsl.xpt and addd4.xpt with only modified intend-to-treat subjects with Baseline Modified Mayo Score ≥ 5.
Abbreviation: PGRS = Patient Global Rating of Severity, mMS = Modified Mayo Score, mITT = modified intent to treat

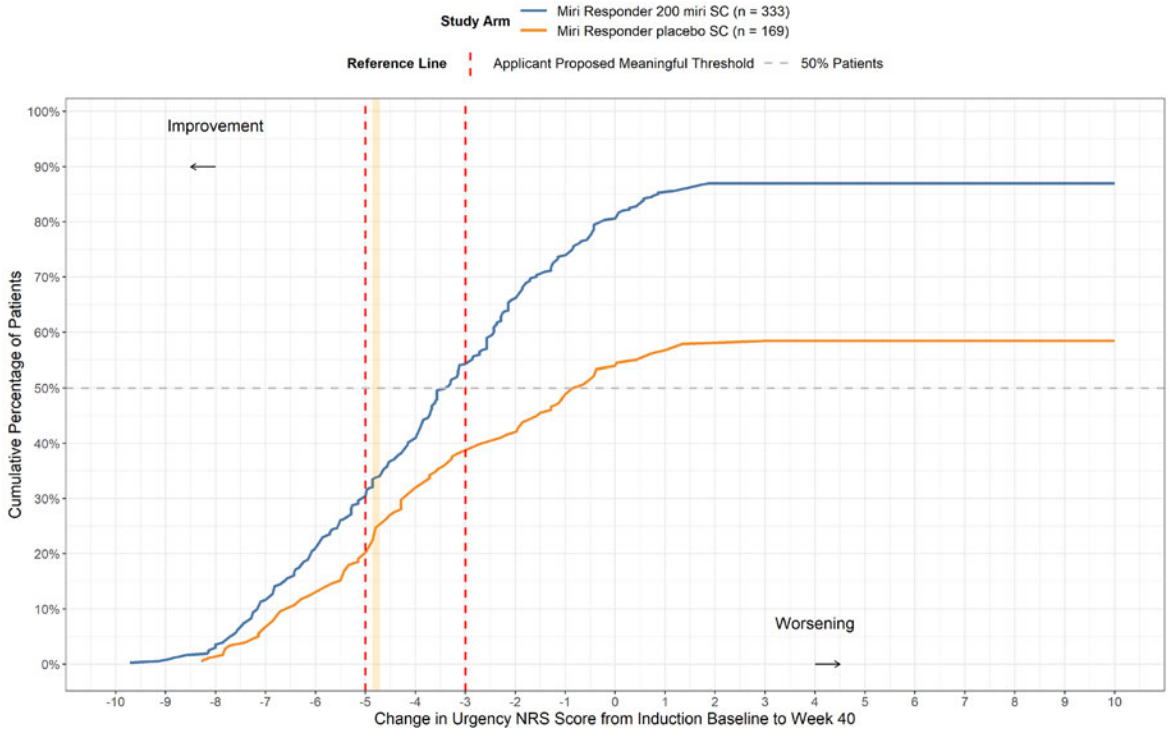
The eCDF plot of within-subject changes in the Urgency NRS scores from the induction Baseline to Week 40 by treatment arm using observed data (see Figure 50) shows overlaps and no clear separation between treatment arms based on visual inspection across all possible change scores. In the July 22, 2022, IR response, the Applicant stated that the overlap between the treatment arms is due to differential dropout rates between the placebo and treatment groups contributed by a lack of treatment effect in the placebo group. To investigate the Applicant's claim, the review team examined the AMBG data by treating all dropouts as non-responders at each cutoff value and visualized the within-subject changes in the Urgency NRS scores by treatment arm (see Error! Reference source not found.). Note that treating all dropouts as non-responders favors the treatment group. Even with the bias toward the treatment group, the differences in the response rates by treatment arm (mirikizumab – placebo) are 10.3% and 11.1%, at the lower bound and upper bound of the review team-determined meaningful threshold range.

Figure 50. eCDF, Change From Induction Baseline to Week 40 in Urgency NRS Score by Treatment Arm Using Observed Data (mITT With mMS ≥ 5 for AMBG)



Source: PFSS reviewer generated figure.

Figure 51. eCDF, Change From Induction Baseline to Week 40 in Urgency NRS Score by Treatment Arm Treating Dropouts as Non-Responders at Each Cutoff Value (mITT With mMS ≥ 5 for AMBG)



Source: PFSS reviewer generated figure.

16.6.3. Agency's Conclusion Regarding Clinically Meaningful Change in Urgency NRS Score

Based on the review team's comprehensive quantitative anchor-based analyses and qualitative assessment, the review team does not agree with the Applicant's proposed clinically meaningful within-subject change threshold range of between 3- and 5-point improvement in the Urgency NRS score for both Studies AMAN and AMBG. For both AMAN and AMBG, subjects with higher UC symptom severity at baseline would require a larger change in Urgency NRS score to feel that the improvement is meaningful. However, data collected from Studies AMAN and AMBG do not provide strong evidence to support the meaningfulness of the observed improvement in the urgency severity for subjects with higher severity at baseline, given that the difference between mirikizumab and placebo groups was modest despite of the statistically significant results reported on the multiplicity controlled secondary endpoint of change from baseline in the Urgency NRS score at Week 12 (AMAN) or Week 40 (AMBG). The review team concludes that the evaluation of this multiplicity-controlled secondary endpoint for Studies AMAN and AMBG did not demonstrate that subjects treated with mirikizumab had meaningful improvement compared to those treated with placebo.

Of note, in response to the review team's information request dated December 7, 2022, the Applicant proposed alternative labeling pertaining to the inclusion of Urgency NRS weekly average score of 0 or 1 (b) (4)

(b) (4)

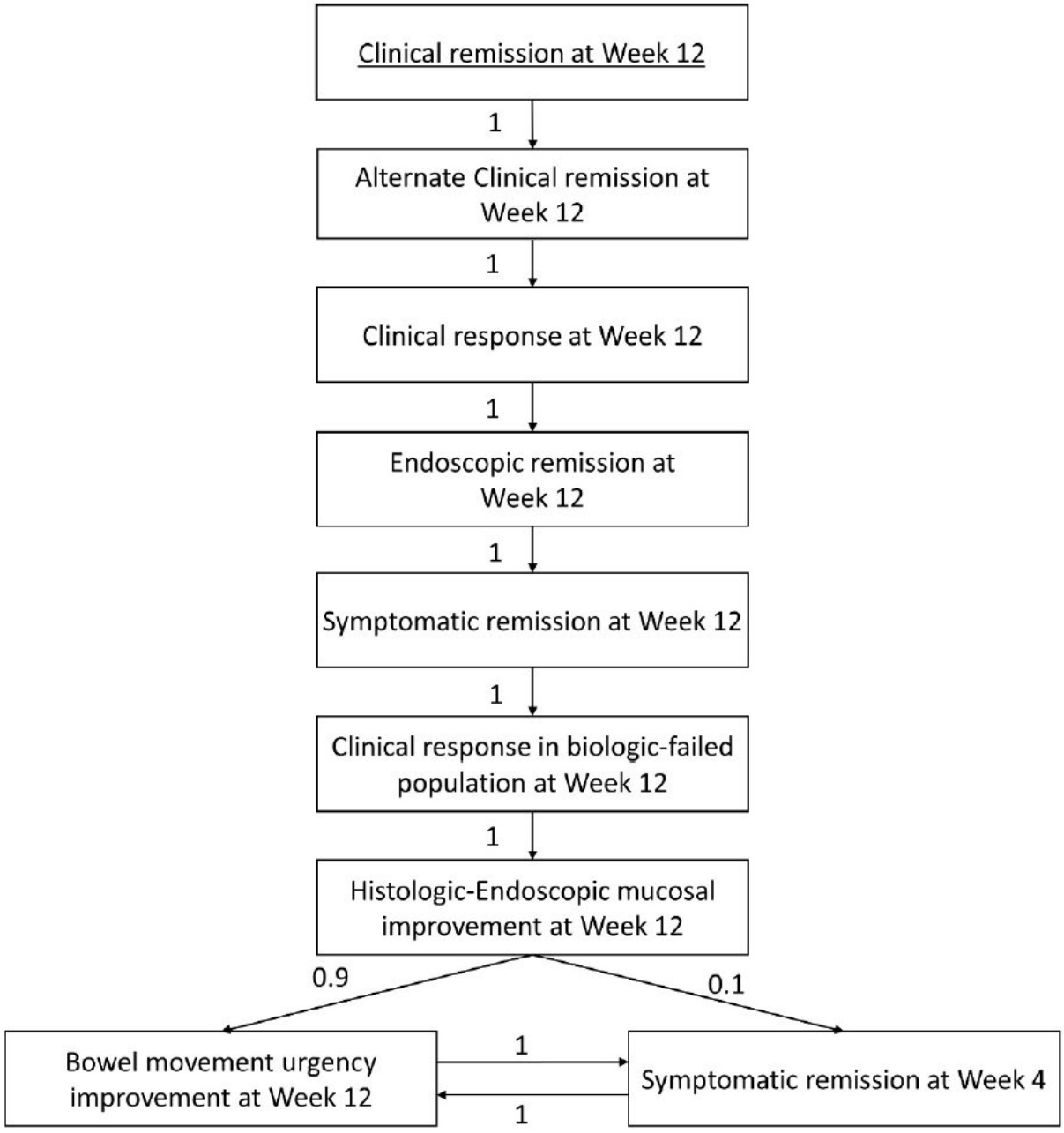
It is important to point out that the Applicant's newly proposed labeling of Urgency NRS weekly average score of 0 or 1 should be viewed as a separate issue from the meaningfulness of the change from baseline in Urgency NRS score. As such, the review team's evaluation on change from baseline in bowel Urgency NRS does not influence the review team's decision on whether the Applicant's newly proposed labeling of Urgency NRS weekly average score of 0 or 1 should be considered.

16.7. Supplemental Efficacy Analyses

16.7.1. Multiple Testing Procedure

A prespecified graphical multiple testing approach was implemented to control the overall Type I error rate at 2-sided alpha of 0.00125 for all primary and multiplicity-controlled secondary endpoints for AMAN, as shown in Figure 52.

Figure 52. Graphical Approach to Control the Type I Error Rate for AMAN

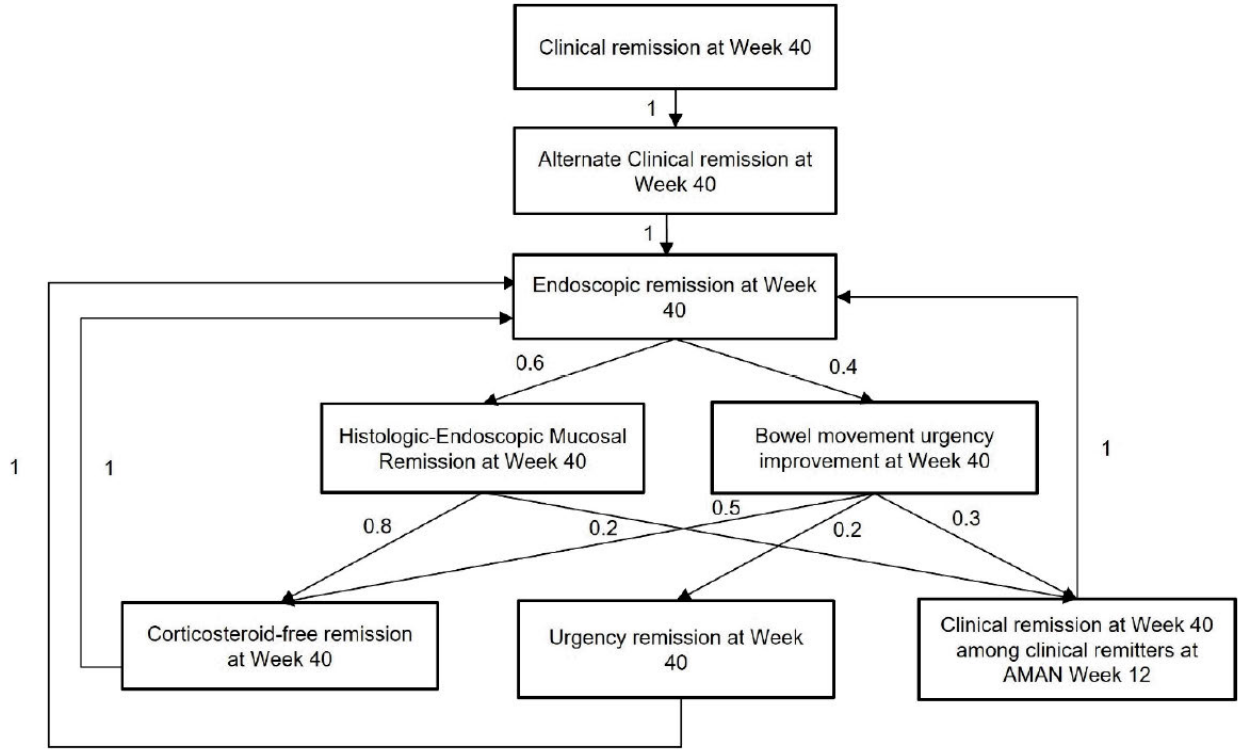


Note: The underlined endpoint is the primary endpoint.

Source: Statistical Analysis Plan (Version 4.0) for study AMAN, Figure AMAN.5.1 (page 28).

A prespecified graphical multiple testing approach was implemented to control the overall Type I error rate at 2-sided alpha of 0.05 for all primary and multiplicity-controlled secondary endpoints for AMBG, as shown in Figure 53.

Figure 53. Graphical Approach to Control the Type I Error Rate for AMBG



Source: Statistical Analysis Plan (Version 4.0) for study AMBG, Figure AMBG.5.1 (page 34).

16.7.2. Baseline Demographic Characteristics, FDA Preferred Analysis Population

Table 121 and Table 122 display the baseline demographic characteristics for FDA preferred analysis population for Study AMAN and Study AMBG, respectively. Of note, the reduced number of subjects in Eastern Europe were mostly due to eCOA transcription error (see Section 7.2).

Table 121. Baseline Demographic Characteristics, Study AMAN, 12 Week Induction Period (FDA Preferred Analysis Population)

Characteristic	Mirikizumab 300 mg IV Q4W N=795	Placebo N=267	Total N=1062
Sex, n (%)			
Female	307 (39)	120 (45)	427 (40)
Male	488 (61)	147 (55)	635 (60)
Age, years			
Mean (SD)	43 (14)	41 (14)	43 (14)
Median (min, max)	41 (18, 79)	39 (18, 75)	41 (18, 79)
Age group, years, n (%)			
<65	731 (92)	250 (94)	981 (92)
≥65	64 (8)	17 (6)	81 (8)
Age group ≥75, years, n (%)			
≥75	10 (1)	1 (0.3)	11 (1)

Characteristic	Mirikizumab 300 mg IV Q4W N=795	Placebo N=267	Total N=1062
Weight, kg			
Mean (SD)	72 (17)	71 (17)	72 (17)
Median (min, max)	70 (38, 152)	69 (34, 124)	70 (34, 152)
Weight group, kg (%)			
<80	543 (68)	197 (74)	740 (70)
≥80	252 (32)	70 (26)	322 (30)
Race, n (%)			
White	588 (70)	199 (75)	757 (71)
Asian	207 (26)	62 (23)	269 (25)
American Indian or Alaska Native	10 (1)	2 (1)	12 (1)
Black or African American	9 (1)	2 (1)	11 (1)
Multiple	1 (0.1)	1 (0.4)	2 (0.2)
Native Hawaiian or Other Pacific Islander	1 (0.1)	0	1 (0.1)
Missing	9 (1)	1 (0.4)	10 (1)
Ethnicity, n (%)			
Not Hispanic or Latino	581 (73)	205 (77)	786 (74)
Hispanic or Latino	25 (3)	10 (4)	35 (3)
Not reported	189 (24)	52 (19)	241 (23)
Region of participation, n (%)			
Eastern Europe	126 (16)	47 (18)	173 (16)
Asia	196 (25)	57 (21)	253 (24)
Rest of the World	175 (22)	66 (25)	241 (23)
Western Europe	161 (20)	51 (19)	212 (20)
North America	122 (15)	43 (16)	165 (16)
Central America/South America	15 (2)	3 (1)	18 (2)

Source: adsl.xpt; Software: R
Abbreviations: IV, intravenous; N, number of patients in treatment group; n, number of patients with given characteristic; Q4W, once every 4 weeks; SD, standard deviation
Region of participation: Eastern Europe: Czech Republic, Hungary, Latvia, Lithuania, Poland, Romania, Slovakia; Asia: China, India, Japan, South Korea, Malaysia, Taiwan; Rest of the world: Australia, Israel, Russian Federation, Serbia, Turkey, Ukraine; Western Europe: Austria, Belgium, Denmark, France, Germany, Ireland, Italy, Netherlands, Spain, Switzerland, United Kingdom; North America: Canada, United States of America; Central/South America: Argentina, Mexico.

Table 122. Baseline Demographic Characteristics, Study AMBG, 40 Week Maintenance Period (FDA Preferred Analysis Population)

Characteristic	Mirikizumab Responders to Mirikizumab 200 mg SC Q4W N=337	Mirikizumab Responders to Placebo N=169	Mirikizumab Responders in Total N=506	Placebo Responders to Placebo N=116
Sex, n (%)				
Female	138 (41)	72 (43)	210 (42)	55 (47)
Male	199 (59)	97 (57)	296 (58)	61 (53)
Age, years				
Mean (SD)	43 (14)	41 (12)	43 (14)	41 (13)
Median (min, max)	42 (18, 79)	39 (21, 74)	40 (18, 79)	38 (19, 70)

Characteristic	Mirikizumab Responders to Mirikizumab 200 mg SC Q4W N=337	Mirikizumab Responders to Placebo N=169	Mirikizumab Responders in Total N=506	Placebo Responders to Placebo N=116
Age group, years, n (%)				
<65	307 (91)	162 (96)	469 (93)	110 (95)
≥65	30 (9)	7 (4)	37 (7)	6 (5)
Age group ≥75, years, n (%)				
≥75	4 (1)	0	4 (1)	0
Weight, kg				
Mean (SD)	72 (17)	72 (17)	72 (17)	71 (19)
Median (min, max)	70 (38, 152)	69 (38, 130)	70 (38, 152)	68 (39, 124)
Weight group, kg, n (%)				
<80	238 (71)	120 (71)	358 (71)	85 (73)
≥80	99 (29)	49 (29)	148 (29)	31 (27)
BMI, kg/m^2				
Mean (SD)	25 (6)	25 (5)	25 (5)	25 (5)
Median (min, max)	24 (15, 54)	23 (14, 43)	24 (14, 54)	24 (15, 43)
Race, n (%)				
White	240 (71)	117 (69)	357 (71)	86 (74)
Asian	86 (26)	49 (29)	135 (27)	27 (23)
Black or African American	6 (2)	0	6 (1)	0
American Indian/Alaska Native	3 (1)	1 (1)	4 (1)	2 (2)
Multiple	0	0	0	1 (1)
Missing	2 (1)	2 (1)	4 (1)	0
Ethnicity, n (%)				
Hispanic or Latino	15 (4)	1 (1)	16 (3)	2 (2)
Not Hispanic or Latino	254 (75)	128 (76)	382 (75)	96 (83)
Not Reported	68 (20)	40 (24)	108 (21)	18 (16)
Region of participation, n (%)				
Eastern Europe	53 (15)	32 (19)	85 (17)	22 (19)
Asia	82 (24)	48 (28)	130 (26)	25 (22)
Rest of the World	82 (24)	39 (23)	121 (24)	35 (30)
Western Europe	67 (20)	27 (16)	94 (19)	20 (17)
North America	46 (14)	22 (13)	68 (13)	12 (10)
Central America/South America	7 (2)	1 (1)	8 (2)	2 (2)

Source: adsl.xpt; Software: R
Abbreviations: N, number of patients in treatment group; n, number of patients with given characteristic; Q4W, once every 4 weeks; SC, subcutaneous; SD, standard deviation

16.7.3. Applicant's Original Analyses on mITT Population

Table 123, and Table 124 display analysis results for the primary and multiplicity-controlled secondary endpoints in Study AMAN using the mITT population. All endpoints were statistically significant. All multiplicity-controlled endpoints were tested at an alpha level of 0.00125 as prespecified in the SAP.

Table 123. Clinical Remission at Week 12, MITT Population, Study AMAN

Parameter	Mirikizumab 300 mg IV Q4W (N=868)	Placebo (N=294)
Clinical Remission at Week 12, n (%)	210 (24.2)	39 (13.3)
Treatment Difference[1], (99.875% CI)	11.1 (3.2, 19.1)	
P-value[2]	0.00006	
Alternate Clinical Remission at Week 12, n (%)	191 (25.6)	39 (14.6)
Treatment Difference[1], (99.875% CI)	11.1 (3.0, 19.3)	
P-value[2]	0.00007	

Source: Reviewer analysis using Applicant submitted data admayo.xpt; based on Clinical Study Report (Table AMAN.8.10, Table AMAN.8.12)

1 The common risk difference is the difference in proportions adjusted for the stratification factors: prior biologic or tofacitinib failure (yes/no), baseline corticosteroid use (yes/no), baseline disease activity (mMS: <7 or ≥7), and region (North America/Europe/Other), where the confidence intervals are calculated using Mantel-Haenszel-Sato method.

2 Cochran-Mantel-Haenszel (CMH) test adjusted by prior biologic or tofacitinib failure (yes/no), baseline corticosteroid use (yes/no), baseline disease activity (mMS: <7 or ≥7), and region (North America/Europe/Other).

Abbreviations: MITT, modified intent-to-treat; N, number of patients in treatment group; Q4W, once every 4 weeks; IV, intravenous; CI, confidence interval.

Table 124**. Results for Secondary Efficacy Endpoints, MITT Population, Study AMAN**

Endpoints	Parameter	Mirikizumab 300 mg IV Q4W (N=868)	Placebo (N=294)	Treatment Difference[1] versus Placebo (99.875% CI)	P-value[2]
Clinical Response at Week 12	%	63.5	42.2	21.4 (10.8, 32.0)	<0.00001
Endoscopic Remission[3] at Week 12	%	36.3	21.1	15.4 (6.3, 24.5)	<0.00001
Symptomatic Remission at Week 12	%	45.5	27.9	17.5 (7.5, 27.6)	<0.00001
Clinical Response in the Biologic-Failed Population at Week 12	(N) %	(361) 54.6	(118) 29.7	25.0 (9.0, 41.1)	<0.00001
Histologic-Endoscopic Mucosal Improvement at Week 12	%	27.1	13.9	13.4 (5.5, 21.4)	<0.00001
Symptomatic Remission at Week 4	%	21.8	12.9	9.2 (1.4, 16.9)	0.00064
Change from Baseline in Urgency NRS Score	(N_{obs}) LSMEAN (SE)	(829) -2.67 (0.083)	(258) -1.63 (0.141)	-0.95 (-1.47, -0.44)	<0.00001[3]

Source: Reviewer analysis using Applicant submitted data admayo.xpt; based on Clinical Study Report (Table AMAN.8.13 – Table AMAN.8.25) and the Applicant's Information Request response submitted on July 22, 2022; verified by reviewer using Applicant submitted data addd4.xpt

[1] For binary endpoints, the common risk difference is the difference in proportions adjusted for the stratification factors: prior biologic or tofacitinib failure (yes/no), baseline corticosteroid use (yes/no), baseline disease activity (mMS: <7 or ≥7), and region (North America/Europe/Other), where the confidence intervals are calculated using Mantel-Haenszel-Sato method; for continuous endpoint, The treatment difference, 95% CI, and p-value were calculated using a mixed model with repeated measures including treatment, baseline value, visit, interaction of baseline value-by-visit, interaction of treatment-by-visit, and stratification factors.

[2] For binary endpoints, computation was based on Cochran-Mantel-Haenszel (CMH) test adjusted by prior biologic or tofacitin b failure (yes/no), baseline corticosteroid use (yes/no), baseline disease activity (mMS: <7 or ≥7), and region (North America/Europe/Other). For the continuous endpoint, computation was based on a mixed model with repeated measures including treatment, baseline value, visit, interaction of baseline value-by-visit, interaction of treatment-by-visit, prior biologic or tofacitin b failure (yes/no), baseline corticosteroid use (yes/no), baseline disease activity (mMS: <7 or ≥7), and region (North America/Europe/Other) as covariates.

[3] This endpoint is called "endoscopic improvement" in the label.

Abbreviations: MITT, modified intent-to-treat; N, number of patients in treatment group; Q4W, once every 4 weeks; IV, intravenous; CI, confidence interval; NRS, Numeric Rating Scale; LSMEAN, least squares mean; SE, standard error; N_{obs}, number of observed values.

Table 125, and Table 126 display analysis results for the primary and multiplicity-controlled secondary endpoints in Study AMBG using the mITT population. All endpoints were statistically significant.

Table 125. Clinical Remission at Week 40, MITT - Mirikizumab Induction Responders, Study AMBG

Parameter	Mirikizumab 200 mg SC Q4W (N=365)	Placebo SC (N=179)
Clinical remission at Week 40, n (%)	182 (49.9)	45 (25.1)
Treatment Difference[1], (95% CI)	23.2 (15.2, 31.2)	
P-value[2]	<0.001	
Alternate clinical remission at Week 40, n (%)	189 (51.8)	47 (26.3)
Treatment Difference[1], (95% CI)	24.1 (16.0, 32.2)	
P-value[2]	<0.001	

Source: Reviewer analysis using Applicant submitted data admayo.xpt; based on Clinical Study Report (Table AMBG.8.21, Table AMBG.8.23)
[1] The common risk difference is the difference in proportions adjusted for the stratification factors: prior biologic or tofacitinib failure (yes/no), baseline corticosteroid use (yes/no), AMAN clinical remission status (yes/no), and region (North America/Europe/Other), where the confidence intervals are calculated using Mantel-Haenszel-Sato method.
[2] Cochran-Mantel-Haenszel (CMH) test adjusted by prior biologic or tofacitinib failure (yes/no), baseline corticosteroid use (yes/no), AMAN clinical remission status (yes/no), and region (North America/Europe/Other).
Abbreviations: MITT, modified intent-to-treat; N, number of patients in treatment group; Q4W, once every 4 weeks; SC, subcutaneous; CI, confidence interval.

Table 126. Results for Secondary Efficacy Endpoints, MITT - Mirikizumab Induction Responders, Study AMBG

Endpoints	Parameter	Mirikizumab 200 mg SC Q4W (N=365)	Placebo SC (N=179)	Treatment Difference[1] versus Placebo (95% CI)	P-value[2]
Clinical remission at Week 40 among subjects in clinical remission at Week 12 in AMAN	(N)	(143)	(65)		
	%	63.6	36.9	24.8 (10.4, 39.2)	<0.001
Endoscopic remission at Week 40	%	58.6	29.1	28.5 (20.2, 36.8)	<0.001
Corticosteroid-free remission at Week 40	%	44.9	21.8	21.3 (13.5, 29.1)	<0.001
Histologic-endoscopic mucosal remission at Week 40	%	43.3	25.0	18.1 (9.8, 26.4)	<0.001
Change from AMAN baseline in urgency NRS score	(N_{obs})	(316)	(104)		
	LSMEAN (SE)	-3.80 (0.139)	-2.74 (0.202)	-1.06 (-1.51, -0.61)	<0.001

Source: Reviewer analysis using Applicant submitted data admayo.xpt; based on Clinical Study Report (Table AMBG.8.23 – Table AMBG.8.31, P 255 – P 349) and the Applicant's Information Request response submitted on July 22, 2022; verified by reviewer using Applicant submitted data addd4.xpt
[1] For binary endpoints, the common risk difference is the difference in proportions adjusted for the stratification factors: previous biologic therapy failure status (yes/no), baseline corticosteroid use (yes/no), region (North America/Europe/Other) and AMAN clinical remission status (yes/no), where the confidence intervals are calculated using Mantel-Haenszel-Sato method; for continuous endpoint, the treatment difference, 95% CI, and p-value were calculated using a mixed model with repeated measures including treatment, baseline value, visit, interaction of baseline value-by-visit, interaction of treatment-by-visit, and stratification factors.
[2] For binary endpoints, Cochran-Mantel-Haenszel (CMH) test adjusted by prior biologic or tofacitinib failure (yes/no), baseline corticosteroid use (yes/no), AMAN clinical remission status (yes/no), and region (North America/Europe/Other).

16.7.4. Sensitivity Analysis on Histologic-Endoscopic Mucosal Improvement

The table below provides a summary of the baseline histologic disease activity as assess on the Geboes score. Approximately 6.6% subjects had a baseline Geboes score of ≤3.1, despite having active endoscopic disease (ES of 2 or 3) at enrollment. Among subjects who entered the

maintenance study (Study AMBG), approximately 3.2% subjects had a baseline Geboes score of < 2.0.

Table 127. Baseline Histologic Activity at Study AMAN and Study AMBG, FDA Preferred Analysis Population

	Study AMAN			Study AMBG		
	Mirikizumab 300 mg IV (N = 795)	**Placebo (N = 267)**	**Total (N = 1062)**	**Mirikizumab responder, Mirikizumab 200 mg SC (N = 337)**	**Mirikizumab responder, Placebo SC (N = 169)**	**Total (N = 506)**
Subjects with Geboes score ≤3.1 at baseline, n (%)	53 (6.7)	17 (6.4)	70 (6.6)	30 (9.0)	12 (7.1)	42 (8.3)
Subjects with Geboes score <2.0 at baseline, n (%)	22 (2.8)	3 (1.1)	25 (2.4)	12 (3.6)	4 (2.4)	16 (3.2)
Missing	14 (1.8)	3 (1.1)	17 (1.6)	8 (2.4)	1 (0.6)	9 (1.8)

Source: Reviewer's analysis using Applicant submitted data adsl.xpt, and adhist.xpt.
Abbreviation: IV, intravenous; SC, subcutaneous.

A sensitivity analysis was conducted to evaluate the "Histologic Endoscopic Mucosal Improvement" endpoint that excluded subjects who met the definition of histologic improvement, defined using the Geboes score ≤3.1, at baseline in Study AMAN. Another sensitivity analysis was conducted to evaluate the "Histologic Endoscopic Mucosal Remission" endpoint in Study AMBG that excluded subjects who met the definition of histologic remission, defined using the Geboes score <2, at the induction baseline (Table 128). The results were consistent with the results in the overall FDA preferred analysis population.

Table 128. Proportion of Subjects Achieving "Histologic Endoscopic Mucosal Improvement" at Week 12 (Sensitivity Analysis Excluding Those With Geboes Score ≤3.1) and Proportion of Subjects Achieving "Histologic Endoscopic Mucosal Remission" at Week 12 (Sensitivity Analysis Excluding Those With Geboes Score <2.0), FDA Preferred Analysis Population

Histologic-Endoscopic Mucosal Improvement at Week 12	**Mirikizumab 300 mg IV**	**Placebo**	**Treatment Difference Mirikizumab vs Placebo (99.875% CI)**
Study AMAN			
All	N = 728 22.8%	N = 247 13.0%	10.3% (1.97, 18.63)
Biologic and JAKi naive	N = 406 32.0%	N = 141 17.0%	
Prior biologic or JAKi failure	N = 310 11.3%	N = 101 6.9%	
Histologic-Endoscopic Mucosal Improvement at Week 40	**Mirikizumab** responder, **Mirikizumab 200 mg SC**	**Mirikizumab** responder, **Placebo SC**	**Treatment Difference Mirikizumab vs Placebo (95% CI)**
Study AMBG			
All	N = 317 42.9%	N = 164 22.0%	19.9% (11.84, 28.06)
Biologic and JAKi naive	N = 195 47.7%	N = 105 26.7%	
Prior biologic or JAKi failure	N = 116 34.5%	N = 58 13.8%	

Source: Reviewer's analysis using Applicant submitted data adsl.xpt, and adhist.xpt.
Abbreviation: IV, intravenous; SC, subcutaneous; CI, confidence interval.

16.7.5. Efficacy Analyses by Demographic Subgroups in Study AMAN and Study AMBG

Subgroup analyses were conducted to assess the potential for differences in the treatment effect for various demographics. Overall, the treatment effect of mirikizumab compared to placebo appeared consistent across demographic subgroups of sex, race, and ethnicity. The observed treatment effect in Study AMAN and in Study AMBG was lower in the subgroup of subjects who were 65 years of age and older, but the sample size of this subgroup limited the ability to form definitive conclusions about the relative efficacy in the ≥65 years of age population.

Table 129. Subgroup Analyses, Clinical Remission (FDA Preferred Definition) at Week 12, FDA Preferred Analysis Population, Study AMAN

	Mirikizumab 300 mg IV Q4W (N=795)		**Placebo (N=267)**		**Treatment difference (95% CI)[1]**
Group	**n/N**	**%**	**n/N**	**%**	
Sex					
Male	93/488	19.1	19/147	12.9	6.1 (-0.3, 12.6)
Female	94/307	30.6	18/120	15.0	15.6 (7.4, 23.8)
Age					
<65	179/731	24.5	34/250	13.6	10.9 (5.6, 16.2)
≥65	8/64	12.5	3/17	17.6	-5.2 (-25, 14.7)

	Mirikizumab 300 mg IV Q4W (N=795)		Placebo (N=267)		Treatment difference (95% CI)[1]
Group	**n/N**	**%**	**n/N**	**%**	
Race					
White	123/558	22.0	26/199	13.1	9.0 (3.2, 14.8)
Asian	59/207	28.5	8/62	12.9	15.6 (5.2, 26.0)
Other[2]	5/30	16.7	3/6	50.0	-33.3 (-75.5, 8.8)
Ethnicity					
Hispanic or Latino	5/25	20.0	1/10	10.0	10.0 (-14.3, 34.3)
Not Hispanic or Latino	143/581	24.6	31/205	15.1	9.5 (3.5, 15.5)

Source: Reviewer generated table based on Applicant submitted data admayo.xpt, and adsl.xpt.
[1] The 95% confidence intervals of the treatment effects were constructed by Wald approach.
[2] Black or African American, Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native, and Multiracial people.
Abbreviations: N, number of patients in treatment group; Q4W, once every 4 weeks; IV, intravenous; CI, confidence interval.

Table 130. Subgroup Analyses, Clinical Remission (FDA Preferred Definition) at Week 40, FDA Preferred Analysis Population, Study AMBG

	Mirikizumab responders Mirikizumab 200 mg SC Q4W (N=337)		Mirikizumab responders Placebo SC (N=169)		Treatment difference (95% CI)[1]
Group	**n/N**	**%**	**n/N**	**%**	
Sex					
Male	104/199	52.3	24/97	24.7	27.5 (16.5, 38.6)
Female	66/138	47.8	20/72	27.8	20.0 (6.8, 33.3)
Age					
<65	155/307	50.5	40/162	24.7	25.8 (17.1, 34.5)
≥65	15/30	50	4/7	57.1	-7.1 (-47.9, 33.6)
Race					
White	124/240	51.7	31/117	26.5	25.2 (15.0, 35.4)
Asian	39/86	45.3	13/49	26.5	18.8 (2.6, 35.0)
Other[2]	7/11	63.6	0/3	0	63.6 (35.2, 92.1)
Ethnicity					
Hispanic or Latino	6/15	40.0	0/1	0	40.0 (15.2, 64.8)
Not Hispanic or Latino	132/254	52.0	35/128	27.3	24.6 (14.8, 34.5)

Source: Reviewer generated table based on Applicant submitted data admayo.xpt, and adsl.xpt.
[1] The 95% confidence intervals of the treatment effects were constructed by Wald approach.
[2] Black or African American, Native Hawaiian or Other Pacific Islander.
Abbreviations: N, number of patients in treatment group; Q4W, once every 4 weeks; IV, intravenous; CI, confidence interval.

16.7.6. Efficacy Analyses on Open-Label Extended Induction Period

A total of 405 subjects (133 placebo induction nonresponders and 272 mirikizumab induction nonresponders) received open-label extended induction treatment with mirikizumab 300 mg IV Q4W for 12 weeks. Clinical remission was achieved by 31 (11.4%) mirikizumab induction nonresponders and 27 (20.3%) placebo induction nonresponders (Table 131).

Table 131. Clinical Remission at Week 12, Extended Induction Period, mITT Population, AMBG

Parameter	Mirikizumab induction nonresponders (N=272)	Placebo induction nonresponders (N=133)
Clinical Remission at Week 12, n (%)	31 (11.4)	27 (20.3)
95% CI	(7.6, 15.2)	(13.5, 27.1)

Source: AMBG clinical study report, Table AMBG.5.34., verified by the review team
Abbreviations: mITT, modified intent-to-treat; N, number of subjects in treatment group; n, number of subjects with given characteristic; CI, confidence interval

Overall, the rate of clinical remission in mirikizumab induction nonresponders appears lower than mirikizumab naïve subjects (AMAN). Due to the open-label design, relatively small sample size, and lack of comparator, a conclusion cannot be made whether extended induction treatment with mirikizumab is effective. Additionally, as noted in Section 8.2.6.3.1, a drug-induced liver injury occurred in a subject who received extended induction treatment. Therefore, a favorable benefit-risk assessment for extended induction treatment with mirikizumab cannot be made.

16.7.7. Efficacy Analyses on Open-Label Loss of Response Rescue Period

A total of 59 subjects (40 mirikizumab responders to placebo and 19 mirikizumab responders to mirikizumab) received open-label loss of response rescue treatment with mirikizumab 300 mg IV Q4W for 12 weeks. Of note, endoscopy was not performed at the end of the loss of response rescue period; therefore, endpoints related to endoscopy could not be analyzed (e.g., clinical remission). Among subjects who received open-label rescue, symptomatic remission was achieved by 7 (36.8%) mirikizumab induction responders re-randomized to mirikizumab and 24 (60.0%) mirikizumab induction responders re-randomized to placebo (Table 132)

Table 132. Symptomatic remission at Week 12, Loss of Response Rescue Period, mITT Population, AMBG

Parameter	Mirikizumab induction responders to Mirikizumab 200 mg SC Q4W (N=19)	Mirikizumab responders to Placebo (N=40)
Symptomatic Remission at Week 12, n (%)	7 (36.8)	24 (60.0)
95% CI	(15.2, 58.5)	(44.8, 75.2)

Source: AMBG clinical study report, Table AMBG.8.101., verified by the review team
Abbreviations: mITT, modified intent-to-treat; N, number of subjects in treatment group; n, number of subjects with given characteristic; CI, confidence interval

The absence of endoscopic assessment limits the interpretability of the results of the loss of response rescue period, as symptoms and endoscopic findings may vary independently. Additionally, due to the open-label design, small sample size, and lack of comparator, a conclusion cannot be made whether loss of response rescue treatment with mirikizumab is effective. Therefore, a favorable benefit-risk assessment for loss of response rescue treatment with mirikizumab cannot be made.

16.8. Supplemental Safety Analyses Supplemental Safety Analyses

Table 133. AESI-Infections. Pathogens and/or Presentations of Specific Pathogens to be Considered as Opportunistic (or 'Indicator') Infections in the Setting of Biologic Therapy (Level of Evidence I–V).

Table 2 Pathogens and/or presentations of specific pathogens to be considered as opportunistic (or 'indicator') infections in the setting of biologic therapy (level of evidence I–V)

Definite*†	Probable‡
Pneumocystis jirovecii (II)	Paracoccidioides infections (V)
BK virus disease including PVAN (V)	*Penicillium marneffei* (V)
Cytomegalovirus disease (V)	*Sporothrix schenckii* (V)
Post-transplant lymphoproliferative disorder (EBV) (V)	Cryptosporidium species (chronic disease only) (IV)
Progressive multifocal leucoencephalopathy (IV)	Microsporidiosis (IV)
Bartonellosis (disseminated disease only) (V)	Leishmaniasis (Visceral only) (IV)
Blastomycosis (IV)	Trypanosoma cruzi infection (Chagas' disease) (disseminated disease only) (V)
Toxoplasmosis (IV)	Campylobacteriosis (invasive disease only) (V)
Coccidioidomycosis. (II)	Shigellosis (invasive disease only) (V)
Histoplasmosis (II)	Vibriosis (invasive disease due to *Vibrio vulnificus*) (V)
Aspergillosis (invasive disease only) (II)	HCV progression (V)
Candidiasis (invasive disease or pharyngeal) (II)	
Cryptococcosis (II)	
Other invasive fungi: Mucormycosis (zygomycosis) (Rhizopus, Mucor and Lichtheimia), *Scedosporium/Pseudallescheria boydii*, *Fusarium* (II)	
Legionellosis (II)	
Listeria monocytogenes (invasive disease only) (II)	
Tuberculosis (I)	
Nocardiosis (II)	
Non-tuberculous mycobacterium disease (II)	
Salmonellosis (invasive disease only) (II)	
HBV reactivation (IV)	
Herpes simplex (invasive disease only) (IV)	
Herpes zoster (any form) (II)	
Strongyloides (hyperinfection syndrome and disseminated forms only) (IV)	

*Generally does not occur in the absence of immunosuppression and whose presence suggests a severe alteration in host immunity.
†Can occur in patients without recognised forms of immunosuppression, but whose presence indicates a potential or likely alteration in host immunity.
‡Published data is currently lacking, but expert opinion believes that risk is likely elevated in the setting of biologic therapy.
EBV, Epstein-Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; PVAN, polyomavirus-associated nephropathy.

Winthrop KL, *et al*. *Ann Rheum Dis* 2015;**74**:2107–2116. doi:10.1136/annrheumdis-2015-207841 2113

Withrop at al. used "Oxford evidence based medicine criteria" defining level of evidence I to V that was published in 2009.

- Level Ia: Systematic review (with homogeneity) of RCTs
- Level Ib: Individual RCT (with narrow Confidence Interval)
- Level Ic: All or none (Met when all patients died before treatment became available, but some now survive on treatment; or when some patients died before treatment became available, but none now die on treatment)
- Level IIa: Systematic review (with homogeneity) of cohort studies
- Level IIb: Individual cohort study (including low quality RCT; e.g., <80% follow-up)
- Level IIc: "Outcomes" Research; Ecological studies
- Level IIIa: Systematic review (with homogeneity) of case-control studies
- Level IIIb: Individual case-control studies
- Level IV: Case-series (and poor-quality cohort and case-control studies)
- Level V: Expert opinion without explicit critical appraisal, or based on physiology, or bench research

Table 134. Clinical Laboratory Tests, AMAN

I6T-MC-AMAN(a) Clinical Protocol **Page 99**

Clinical Laboratory Tests

Hematology[a,b]	**Clinical Chemistry**[a,b]
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBCs)	Chloride
Mean cell volume	Bicarbonate
Mean cell hemoglobin	Potassium
Mean cell hemoglobin concentration	Total bilirubin
Leukocytes (WBCs)	Total protein
Cell morphology	Direct bilirubin
Neutrophils, segmented	Alkaline phosphatase (ALP)
Lymphocytes	Alanine aminotransferase (ALT)
Monocytes	Aspartate aminotransferase (AST)
Eosinophils	Gamma-glutamyl transferase (GGT)
Basophils	Blood urea nitrogen (BUN)
Platelets	Creatinine
	Uric acid
Urinalysis[a,b]	Calcium
Specific gravity	Glucose
pH	Albumin
Protein	Cholesterol (total)
Glucose	Triglycerides
Ketones	Lipid Panel (fasting)[c]
Bilirubin	High-density lipoprotein
Urobilinogen	Low-density lipoprotein
Blood	Creatine kinase (CK)
Nitrite	
Urine leukocyte esterase	**Other Tests**[a]
Microscopic examination of sediment	Hepatitis B core antibody[b,d]
	Hepatitis B surface antigen[b,d]
	HBV DNA[b,e]
	Hepatitis C antibody[b,d,f]
	HIV[b,d]
	Pregnancy test (serum[b,d] and urine[g])
	FSH[b]
	QuantiFERON-TB Gold test[d] or T-SPOT or TST
	Exploratory storage samples (serum, plasma, whole blood, RNA, tissue RNA, and fecal sample)
	Pharmacogenomic sample
	Anti-mirikizumab antibodies (immunogenicity)
	Serum mirikizumab concentration (PK)
	C-reactive protein, high-sensitivity
	Clostridium difficile[b,h] and Stool Culture[b,h]
	Fecal calprotectin
	Tryptase[i]
	Complement (C3/C4)[i]
	Cytokine panel[i]

Abbreviations: ADA = anti-drug antibody; ETV = early termination visit; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; HIV = human immunodeficiency virus; PK = pharmacokinetics; RB = rectal bleeding; RBC = red blood cell; SF = stool frequency; TST – tuberculin skin test; UV = unscheduled visit; V = visit; WBC = white blood cell.
a Assayed by Lilly-designated laboratory.
b Results will be confirmed by the Central Laboratory/other at the time of initial testing.
c For the fasting lipid profile, patients should not eat or drink anything except water for 12 hours prior to test.
d Performed at screening only.
e Hepatitis B DNA testing will be performed in patients who test positive for anti-hepatitis B core antibody (at protocol-specified intervals).

f A positive hepatitis C antibody laboratory assessment will be confirmed with an additional test method.
g Urine pregnancy test will be evaluated locally.
h Clostridium difficile tests at V5 and ETV may be performed for patients who do not move into Study AMBG. Clostridium difficile test at UV may be performed if visit is due to worsening SF and/or RB.
i Test performed only in the event of systemic allergic/hypersensitivity events, along with ADA and PK.

Table 135. Schedule of Activities, AMAN

Table AMAN.1. Schedule of Activities

Procedure	Treatment Period								Post-Treatment Follow-Up Period		Notes:
Visit	V0	V1	V2[a]	V3	V4	V5	ETV[b]	V997 (UV)[c]	V801	V802	
Week		0	2	4	8	12			LV + 4	LV + 16	
Day and/or Visit Interval Tolerance	≤28 from V1	1	15 ± 3	29 ± 3	57 ± 3	85 ± 7			± 4	± 4	
All activities should be completed prior to any study drug administration unless otherwise stated below. Post-treatment Follow-up visits should only occur if the patient is not proceeding to Study AMBG.											
Informed consent	X										
Explain UC remission stool frequency question to patient	X										Investigator or site staff should explain the purpose of UC remission question in the TrialSlate (tablet) device before the patient answers the question to ensure accurate data capture. Errors in response cannot be corrected once response is saved and confirmed by the patient.
Inclusion and exclusion criteria	X	X									
Demographic information	X										
Medical history and pre-existing conditions	X										Includes relevant surgical history
Concomitant medication	X	X	X	X	X	X	X	X	X	X	
Review AEs	X	X	X	X	X	X	X	X	X	X	
Tobacco/nicotine use	X					X	X				
Alcohol/caffeine use	X										
IP Administration											
Randomization		X									
IP administration		X		X	X						
Physical Examination											
Vital signs (T, BP, PR)	X	X		X	X	X	X	X	X	X	

Procedure	Treatment Period								Post-Treatment Follow-Up Period		Notes:
Visit	V0	V1	V2[a]	V3	V4	V5	ETV[b]	V997 (UV)[c]	V801	V802	
Week		0	2	4	8	12			LV + 4	LV + 16	
Day and/or Visit Interval Tolerance	≤28 from V1	1	15 ± 3	29 ± 3	57 ± 3	85 ± 7			± 4	± 4	
All activities should be completed prior to any study drug administration unless otherwise stated below. Post-treatment Follow-up visits should only occur if the patient is not proceeding to Study AMBG.											
Weight		X				X	X				
Height		X									
Physical examination	X	X				X	X				
Evaluate for EIMs	X	X		X	X	X	X	X			
12-lead ECG (locally read)	X					X	X				
Laboratory Investigations											
Urinalysis	X										
Urine pregnancy test		X		X	X			X	X	X	Only in women of childbearing potential. Done locally and prior to dosing.
HIV testing	X										
HBV, HCV testing	X										
HBV DNA[d]	X					X	X			X	For patients with the following HBV serology at screening: HBsAg-, anti-HBc+, HBV DNA not detected.
Hematology	X	X		X	X	X	X	X	X	X	
Chemistry	X	X		X	X	X	X	X	X	X	
Fasting lipid profile[e]		X				X	X				
hsCRP[e]		X				X	X				
FSH (optional in women to confirm nonchild-bearing potential)[e]	X	X		X	X	X	X	X			Optional, to confirm post-menopausal status in women ≥50 with amenorrhea >1 year.
Serum pregnancy test[e]	X										Only in women of childbearing potential.
Serum and plasma for cytokines		X		X		X	X				
PK assessment											Serum for PK assessment and

Procedure	Treatment Period								Post-Treatment Follow-Up Period		Notes:
Visit	V0	V1	V2[a]	V3	V4	V5	ETV[b]	V997 (UV)[c]	V801	V802	
Week		0	2	4	8	12			LV + 4	LV + 16	
Day and/or Visit Interval Tolerance	≤28 from V1	1	15 ± 3	29 ± 3	57 ± 3	85 ± 7			± 4	± 4	
All activities should be completed prior to any study drug administration unless otherwise stated below. Post-treatment Follow-up visits should only occur if the patient is not proceeding to Study AMBG.											
Pre-dose PK sample		X		X	X						mirikizumab assay development. Patients with potential hypersensitivity or infusion-related event should have sample taken as soon as possible after event occurs and at 4 and 12 to 16 weeks after the event.
Post-dose PK sample		X		X							
PK sample						X	X	X		X	
ADA assessment		X		X	X	X	X	X		X	Patients with potential hypersensitivity or infusion-related event should have sample taken as soon as possible after event occurs and at 4 and 12 to 16 weeks after the event.
Pharmacogenetic sample		X									Can be obtained after starting study drug if not obtained at V1
Serum, plasma and whole blood for exploratory biomarkers		X		X		X	X				
Interferon-γ release assay (or tuberculin skin test)	X										
Additional Screening Tests											
CXR	X										
C-SSRS, Self-Harm Supplement Form, Self-Harm "Follow-Up" Form	X										
QIDS-SR16		X				X	X				
Stool Samples											
Stool culture	X										Additional local stool testing (for

Procedure	Treatment Period								Post-Treatment Follow-Up Period		Notes:
Visit	V0	V1	V2[a]	V3	V4	V5	ETV[b]	V997 (UV)[c]	V801	V802	
Week		0	2	4	8	12			LV + 4	LV + 16	
Day and/or Visit Interval Tolerance	≤28 from V1	1	15 ± 3	29 ± 3	57 ± 3	85 ± 7			± 4	± 4	
All activities should be completed prior to any study drug administration unless otherwise stated below. Post-treatment Follow-up visits should only occur if the patient is not proceeding to Study AMBG.											
C. difficile testing	X					X[f]	X[f]	X[g]			example, ova & parasites) is allowed at the investigator's discretion
Fecal calprotectin and exploratory fecal biomarkers		X		X		X	X				
Endoscopic Procedure											
Endoscopy with biopsies	X					X	X				Screening endoscopy within 14 days of V1. Please refer to Section 9.1.1.3 for procedure clarification.
UC Activity Assessments											
Patient diary dispensed	X										
Patient diary compliance review		X	X	X	X	X	X	X			
PGA		X		X	X	X	X				
Review Modified Mayo Score		X				X	X				
Patient diary collected						X	X				
Health Outcome Assessments											
IBDQ		X				X	X				
EQ-5D 5L		X				X	X				
SF-36		X				X	X				
WPAI:UC		X				X	X				
PGRC				X	X	X	X				

Abbreviations: ADA = anti-drug antibody; AE = adverse event; anti-HBc+ = positive for anti-hepatitis B core antibody; BP = blood pressure; C-SSRS = Columbia-Suicide Severity Rating Scale; CXR = chest x-ray; DNA = deoxyribonucleic acid; ECG = electrocardiogram; EIM = extraintestinal manifestation; EQ-5D-5L = European Quality of Life 5–Dimension 5 Level; ETV = early termination visit; FSH = follicle-stimulating hormone; HBsAg- = negative for hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hsCRP = high-sensitivity C-reactive protein; IBDQ = Inflammatory Bowel Disease Questionnaire; IP = investigational product; LV = last visit; PGA = Physician's Global Assessment; PGRC = Patient's Global Rating of Change; PK = pharmacokinetic; PR = pulse rate; QIDS-SR16 = Quick Inventory of Depressive Symptomatology-Self Report (16 items); RB = rectal bleeding; SF = stool frequency; SF-36 = Medical Outcomes Study 36-Item Short Form Health Survey; T = temperature; UV = unscheduled visit; V = visit; WPAI:UC = Work Productivity and Activity Impairment Questionnaire Ulcerative Colitis.
a Visit 2 (Week 2) is a telephone visit. These assessments will be made by a telephone call to the patient.
b ETV may occur on any day without regard to visit interval.
c Additional study procedures can be performed at an unscheduled visit at the discretion of the investigator.
d This test will be performed on a sub-set of study patients, as described in the Notes column of the applicable row.
e These tests will be run from the "chemistry" sample.
f Clostridium difficile tests at V5 and ETV may be performed for patients who do not move into Study AMBG.
g Clostridium difficile test at UV may be performed if visit is due to worsening SF and/or RB.

Table 136. Reviewer's Preferred Term (PT) Grouping Strategy for Assessment for Adverse Drug Reactions

Group Term	Preferred Terms Included in Each Grouping
Dermatitis	Dermatitis, dermatitis contact, dermatitis acneiform, and dermatitis allergic, hand dermatitis, injections site dermatitis, perioral dermatitis
Herpes simplex infections	Herpes zoster, oral herpes, genital herpes, herpes simplex reactivation, and herpes simplex
Hypertension (HTN)	HTN, and elevated blood pressure
Pyrexia	Pyrexia and hyperpyrexia
Rash	Rash, rash macular, rash maculo-papular, rash papular, rash erythematous and rash pruritic
Transaminase elevation	Aspartate aminotransferase increased, alanine aminotransferase increased, hepatic function abnormal, liver function test increased, and hepatic enzyme increased
Upper respiratory tract infections	Acute sinusitis, COVID-19, nasopharyngitis, pharyngitis, rhinitis, sinusitis, tonsillitis, upper respiratory tract infection, and viral upper respiratory tract infection

Source: Reviewer generated table
Coded as MedDRA 24.0 preferred term

BLA 761279 mirikizumab

Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Cross-Disciplinary Project Manager	Kelly Richards	OND/ORO/DROII	Sections 3.1, 3.2 ☒ Authored ☐ Approved
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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Pharmacology/Pharmacometrics	Jiang Liu	OTS/OCP/DPM	Sections 6, 16.3 ☐ Authored ☒ Approved
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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Pharmacology/Toxicology	Carmen Booker	OND/OII/DPTII	Section 5 ☐ Authored ☒ Approved
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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Clinical Outcome Assessment	David Reasner	OND/ODES/DCOA	Sections 16.4, 16.5 ☐ Authored ☒ Approved
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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
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/s/

KELLY D RICHARDS
04/07/2023 10:32:41 AM

JULIE G BEITZ
04/07/2023 10:38:42 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY IND ASSESSMENT AND EVALUATION

Application Number*:	125444
Supporting Document Number/s:	0097
CDER Receipt Date:	4/25/2019
Sponsor:	Eli Lilly & Co.
Product:	LY3074828/Mirikizumab
Pharmacologic Class:	Interleukin 23-receptor blocking antibody
Indication:	Ulcerative Colitis
Therapeutic area:	Gastroenterology
Review Division:	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Reviewer:	Tamal Chakraborti, PhD
Supervisor/Team Leader:	Sushanta Chakder, PhD
Acting Division Director:	Dragos Roman, MD
Project Manager:	Kelly Richards, RN
Purpose of Review:	Study Report Review
Alternative Assays:	N/A
Reviewer Completion Date:	September 18, 2019

Template Version: May 23, 2019

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Background

Mirikizumab (LY3074828) is a humanized immunoglobulin G4 (IgG4) monoclonal antibody that binds to the p19 subunit of interleukin (IL)-23 and does not bind IL-12. (b) (4) [redacted] In this submission, the Sponsor submitted the final report of the ePPND study (Study No. 20102344), which is reviewed here.

Studies Submitted

Studies Reviewed

An Assessment of the Effect of LY3074828 on Pre- and Postnatal Development When Administered by Intravenous Injection Twice Weekly to Pregnant Cynomolgus Monkeys (Report No. 20102344)

Studies Not Reviewed

N/A

Reproductive and Developmental Toxicology

Prenatal and Postnatal Development (PPND)+

Study Title: An Assessment of the Effect of LY3074828 on Pre- and Postnatal Development When Administered by Intravenous Injection Twice Weekly to Pregnant Cynomolgus Monkeys (Report No. 20102344)

Study no.:	20102344
Study report location:	EDR 4.2.3.5.3
Conducting laboratory and location:	(b) (4) [redacted]
GLP compliance:	Yes
Drug, lot #, and % purity:	LY3074828, EL01913-009-API, 99.3%
Enhanced PPND Study:	Y

Methods

Doses:	0 and 300 mg/kg
Frequency of dosing:	Twice weekly. Adult females were dosed initially on gestation day (GD) 21, GD25, GD28, and twice every 7 days thereafter (i.e., every 4 then 3 days, GD32, GD35, GD39, GD42, etc.) until parturition (GD160, for a total of approximately 42 doses/animal).
Number/Sex/Group:	15 pregnant females
Dose volume:	5 mL/kg
Formulation/Vehicle:	10 mM Sodium citrate, 150 mM sodium chloride, 0.03% polysorbate 80, pH 5.5
Route of administration:	INTRAVENOUS BOLUS
Species:	Monkey
Strain:	Cynomolgus
Comment on Study Design and Conduct:	The study design is shown below. Only one dose was used in this study. However, the Sponsor provided justification for the dose selection, which is discussed below.
Dosing Solution Analysis:	Dosing solutions were analyzed for concentrations, homogeneity and stability. Mean LY3074828 concentrations for dose formulations sampled and used at the 1st, 10th, and 19th preparations were 98.7% to 100.7% of theoretical values. The results of the stability studies indicated the test material was stable over the course of use.

The study design is shown in the table below (from page 24 of the report).

Text Table 4
Experimental Design

Group Identification	Route	Dose Level mg/kg/dose[a]	Dose Concentration mg/mL	No. of Pregnant Females
1 Vehicle Control	IV	0	0	15
2 LY3074828	IV	300	60	15

IV = intravenous.
[a] The dose volume was 5 mL/kg. Doses were administered twice weekly as slow bolus injections (target 4 to 5 mL/minute). Concentrations were corrected for lot specific test article content.

Basis of Dose Selection: The dose (300 mg/kg) level for the ePPND study was set based upon the results of previous toxicity studies with LY3074828 in cynomolgus monkeys. Previously, 4-week and 6-month toxicity studies in cynomolgus monkeys were conducted using weekly dosing via subcutaneous (SC) or intravenous (IV) route.

In the 4-week study, no significant treatment-related changes were observed at 1 and 30 mg/kg SC, or 100 mg/kg IV. In the 6-month study, no significant treatment-related changes were observed in any organs at SC doses of 10 and 100 mg/kg. In addition, in a 6-month IV study in cynomolgus monkeys, twice-weekly administration of LY3074828 at 100 mg/kg was not associated with any significant test article-related changes. At 300 mg/kg IV, there were no clear target organ toxicities identified; however, changes considered likely related to LY3074828 were observed at Day 180 in 1 animal at 300 mg/kg. This animal had hematologic, clinical chemistry, and morphologic changes indicative of an idiosyncratic (low-incidence and non-dose responsive) immune-mediated hemolytic effect of LY3074828 administration. Based on these, 300 mg/kg was selected for the ePPND study.

Observations and Results

F0 Dams

During gestation, adult females were observed for clinical signs and changes in food consumption, body weight and body weight gain, pregnancy and embryo/fetal status and heart rate and clinical pathology. Blood samples were collected at various time points throughout the study for hematology, clinical chemistry, toxicokinetics (TK), immunogenicity (anti-drug antibody [ADA] formation), and lymphocyte phenotyping.

For adult females during gestation and postpartum period, there were no significant LY3074828-related changes in clinical signs, food consumption, body weight, and hematology parameters. LY3074828-related changes in clinical chemistry parameters for adult females were limited to non-adverse minimal increased levels of cholesterol compared to controls on GD 140. There were no significant treatment-related changes in fetal heart rates through gestation for the fetuses exposed to LY3074828 in utero.

There were no LY3074828-related effects on embryo/fetal losses. Incidences of embryo/fetal loss were higher in the LY3074828-treated group compared to the control group (6.7% [1 of 15] at 0 mg/kg and 26.7% [4 of 15] at 300 mg/kg); however, the values were within the range of historical control data for embryo/fetal loss at the testing facility (76 embryo/fetal losses out of 349 pregnancies [21.8%]; range 6.7 to 38.9%). Total number of male:female fetuses/infants in each group and the mean gestation lengths at delivery of live infants were comparable between the 0 and 300 mg/kg/dose groups. There were no LY3074828-related changes in lymphocyte subsets in adult females.

F1 Generation

Infants were evaluated for up to 6 months following birth for growth, development, behavior, TK, immunomodulation, immunogenicity, and external, visceral, and skeletal (developmental) endpoints.

In addition, for up to 6 months postpartum/postnatal, infants were evaluated for clinical signs, body weight and body weight gain. Infants also underwent physical, ophthalmology, neurobehavioral, neurological, and external, visceral, and skeletal (developmental) examinations. Blood samples were collected from infants at various time points for hematology, TK, lymphocyte phenotyping, natural-killer (NK) cell activity, T-cell dependent antibody response (TDAR), and immunogenicity. Surviving infants were euthanized on birth day (BD) 183 and a full necropsy was conducted on all infants, including macroscopic and microscopic tissue examinations.

A total of 12 and 11 infants were delivered by natural birth at 0 and 300 mg/kg, respectively. In addition, 2 control group infants were delivered by C-section because the adult females had not delivered their infants by GD172 or GD174. Therefore, 14 and 11 infants were evaluated in the 2 respective dose groups. There were no LY3074828-related effects on infant survival. Two of 25 delivered infants (1 each in the control and LY3074828 group) died or were euthanized within 7 days postpartum. Both infant losses, including the control, resulted from circumstances unrelated to treatment and were considered due to maternal neglect. Therefore, these deaths were not attributed to maternal treatment with LY3074828.

Combined fetal and infant losses were 33% at 300 mg/kg compared to the historical control range of 20 to 42.9% at the testing facility. In addition, combined fetal/infant losses for the test article-treated group were within expected outcomes based on the published literature for live-birth studies of this type in cynomolgus monkeys (Jarvis P, et al., 2010, The Cynomolgus Monkey as a Model for Developmental Toxicity Studies: Variability of Pregnancy Losses, Statistical Power Estimates, and Group Size Considerations, Birth Defects Research (Part B), 89:175-187).

In surviving infants (13 and 10 at 0 and 300 mg/kg, respectively), there were no LY3074828-related changes in clinical signs, body weight, neurobehavioral or neurologic evaluations, external evaluations, morphometric measurements, ophthalmology, and respiration or heart rates. There were no LY3074828-related changes in hematology parameters for infants through BD183. There were no LY3074828-related changes in lymphocyte subsets in infants. In addition, there were no changes in innate or humoral immunity, as evaluated by NK cell activity and TDAR, respectively, in infants exposed to maternal doses of LY3074828.

For fetuses that were aborted, infants that died or were euthanized early, and infants that survived until the scheduled terminal necropsy on BD183, there were no significant LY3074828-related effects on fetal or infant macroscopic or microscopic pathology, morphometric measurements, or external, visceral, or skeletal (infants only) evaluations.

F2 Generation

N/A

Toxicokinetics and Lactation (exposures)

Maternal and infant serum samples were collected per the following schedule (from page 1370 of the report).

Text Table 2
TK Sample Collection Schedule

Adult Female Sample Collection Time Points		
Group No(s).	**Study Day**	**Time Points (Relative to Dosing)**
1 and 2	GD21 ± 1	1 hr Post
	GD70	Pre, 1, 8, 24, 48, and 96 hr Post
	GD140	Pre and 1 hr Post
	PPD14	NR
	PPD28	NR
	PPD56	NR
	PPD84	NR
	PPD112	NR
	PPD140	NR
Day of abortion/pregnancy loss confirmation (including stillbirth and any C-sections) and infant losses.	As applicable	NR
Unscheduled necropsy of adult female	As applicable	NR

Pre – Predose; Post – Postdose; hr – hour; NR = not relevant

Infant Sample Collection Time Points	
Group No(s).	**Study Day**
1 and 2	BD14
	BD28
	BD56
	BD84
Unscheduled necropsy of infant (including rejection or health reasons)	As applicable

Maternal: Maximum serum concentrations of LY3074828 were observed at 1 h postdose on GD70. Mean serum concentrations at 1 h postdose were similar on GD 21, GD70, and GD140, indicating no apparent accumulation after repeated dosing. All treated adult females were exposed to LY3074828 with C0 (concentration at 0 time point) ranging from 5570 to 12000 µg/mL and $AUC_{(0-96)}$ ranging from 82000 to 178000 hr.µg/mL on GD70.

Infant: LY3074828 was quantifiable on BD28 for 10 of 10 surviving infants, on BD56 for 4 of 10 infants, and on BD84 for 1 of 10 infants. No clear gender differences were observed in the infant serum concentration values. Maximum quantifiable serum concentrations occurred at BD14 and ranged from 5.41 to 17.8 µg/mL in males and 2.16 to 12.3 µg/mL in females.

Infant to Mother Serum Concentration Ratios**:** Concentration ratios of LY3074828 in infant serum to mother serum ranged from 1.09 to 19.2 on PPD14 and from 0.696 to 18.0 on PPD28. The following table (from page 1389 of the report) shows the infant to mother ratio.

Table 3.1: Ratio of LY3074828 Concentrations Post Parturition in Cynomolgus Monkey Mother Serum and Infant Serum

	Mother												
	2501	2502	2503	2504	2506	2507	2508	2511	2514	2515	N	Mean	SD
Day	Concentration (µg/mL)												
PPD14	4.28	BQL	0.925	2.19	0.596	1.12	BQL	0.37	1.93	3.31	10	1.47	1.44
PPD28	0.786	BQL	0.28	0.44	BQL	0.368	BQL	BQL	0.409	0.861	10	0.314	0.324
PPD56	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	10	0.00	0.00
PPD84	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	10	0.00	0.00
	Infant												
	2016	2026	2031	2046	2066	2071	2081	2116	2146	2156	N	Mean	SD
Day	Concentration (µg/mL)												
BD14	4.66	12.3	17.8	5.62	2.62	6.34	5.41	2.16	7.40	6.21	10	7.05	4.70
BD28	0.547	2.06	5.05	0.933	0.683	0.981	1.32	0.278	1.65	1.19	10	1.47	1.36
BD56	BQL	BQL	1.44	BQL	BQL	0.254	0.364	BQL	0.255	BQL	10	0.231	0.447
BD84	BQL	BQL	0.416	BQL	BQL	BQL	BQL	BQL	BQL	BQL	10	0.0416	0.132
Day	Infant to Mother Ratio										N	Mean	SD
PPD14	1.09	NA	19.2	2.57	4.40	5.66	NA	5.84	3.83	1.88	8	5.56	5.78
PPD28	0.696	NA	18.0	2.12	NA	2.67	NA	NA	4.03	1.38	6	4.82	6.57
PPD56	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0	NA	NA
PPD84	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0	NA	NA

BD = Birth Day; BQL = Below quantitation limit (LLOQ = 0.200 µg/mL); NA = Not applicable; PPD = Postpartum Day.

The following tables (from page 53 and 1387of the report) show the maternal TK parameters.

Text Table 29
Mean and SD Exposure Parameters

	Administered Dose (mg/kg/dose)
Parameter	**300**
Sex	**Females (N = 15)**
LY3074828	
GD70	
C0 (µg/mL)	7720 ± 1660
$AUC_{(0-96)}$ (hr*µg/mL)	127000 ± 33700

$AUC_{(0-96)}$ = area under the curve from 0 to 96 hours postdose; C0 = theoretical concentration at time zero; N = sample size.

Table 2.1: Individual and Summary LY3074828 Toxicokinetic Parameters in Maternal Cynomolgus Monkey Serum on GD70 Following Twice Weekly IV Bolus Injection of LY3074828 at 300 mg/kg/dose from GD21 ± 1 Through Parturition

Dose (mg/kg/dose)	Day	Animal	C0 (µg/mL)	$AUC_{(0-96)}$ (hr*µg/mL)	$AUC_{(0-96)}$/D (hr*µg/mL/(mg/kg))
300	GD70	2501	6640	136000	452
		2502+	6140	82000	273
		2503+	6690	152000	507
		2504	8320	178000	593
		2505+	8370	141000	471
		2506+	7000	88400	295
		2507+	5570	120000	399
		2508+	7520	119000	397
		2510+	7630	103000	343
		2511+	7740	154000	513
		2512+	12000	174000	579
		2513+	8590	108000	359
		2514+	6870	98300	328
		2515	10200	173000	578
		2516	6490	83000	277
		N	15	15	15
		Mean	7720	127000	424
		SD	1660	33700	112

GD = Gestation Day; + At predose on GD70, this animal was confirmed ADA positive.

Infant serum concentrations are shown in the tables (from page 1385 of the report) below.

Table 1.5: Individual and Summary Infant Male Cynomolgus Monkey Serum LY3074828 Concentrations from Mothers Given Twice Weekly IV Bolus Injection of 300 mg/kg/dose LY3074828 from Gestation Day 21 ± 1 Through Parturition

					Animal					
					2031	2071	2081	N	Mean	SD
TK Sample	Dose (mg/kg)	Gender	Day	Time (hr)	Concentration (µg/mL)					
Infant	300	Male	BD14	NA	17.8	6.34	5.41	3	9.86	6.92
			BD28	NA	5.05	0.981	1.32	3	2.45	2.26
			BD56	NA	1.44+	0.254+	0.364+	3	0.686	0.655
			BD84	NA	0.416	BQL	BQL	3	0.139	0.240

BQL = Below quantitation limit (LLOQ = 0.200 µg/mL); BD = Birth Day; NA = Not applicable; Confirmed ADA positive.

Table 1.6: Individual and Summary Infant Female Cynomolgus Monkey Serum LY3074828 Concentrations from Mothers Given Twice Weekly IV Bolus Injection of 300 mg/kg/dose LY3074828 from Gestation Day 21 ± 1 Through Parturition

					Animal									
					2016	2026	2046	2066	2116	2146	2156	N	Mean	SD
TK Sample	Dose (mg/kg)	Gender	Day	Time (hr)	Concentration (µg/mL)									
Infant	300	Female	BD14	NA	4.66	12.3	5.62	2.62	2.16	7.40	6.21	7	5.85	3.39
			BD28	NA	0.547	2.06	0.933	0.683	0.278	1.65	1.19	7	1.05	0.632
			BD56	NA	BQL	BQL+	BQL	BQL	BQL	0.255+	BQL	7	0.0364	0.0964
			BD84	NA	BQL	BQL	BQL	BQL	BQL	BQL	BQL	7	0.00	0.00

BQL = Below quantitation limit (LLOQ = 0.200 µg/mL); BD = Birth Day; NA = Not applicable; + Confirmed ADA positive.

Anti-Drug Antibody (ADA) Assessment: Blood samples were also collected for ADA analyses from adult females and infants according to the schedule shown in the table (from page 1371 of the report).

Text Table 3
Immunogenicity Sample Collection Schedule

Adult Female Sample Collection Time Points		
Group No(s).	**Study Day**	**Time Points (Relative to Dosing)**
1 and 2	GD21 ± 1, GD70, and GD140	Pre
	PPD56 and PPD140	NR
Day of abortion/pregnancy loss confirmation (including stillbirth and any C-sections) and infant losses.	As applicable	NR
Unscheduled necropsy of adult female	As applicable	NR

Pre – Predose; NR = not relevant.

Infant Sample Collection Time Points	
Group No(s).	**Study Day**
1 and 2	BD56 and BD140
Unscheduled necropsy of infant (including rejection or health reasons)	As applicable

At 300 mg/kg/dose, 11 of 15 adult pregnant females were confirmed positive for ADA on GD70. On GD140, 5 of 12 pregnant females were confirmed positive for ADA. On PPD56 and PPD140, 7 of 10 adult females were confirmed positive for ADA. Five of 10 infants that were exposed to the drug in utero were confirmed positive for ADA on BD56, which were from mothers that were also confirmed ADA positive. Three of these 5 infants were also confirmed ADA positive on BD140, though samples were not analyzed for TK on this occasion. Animals that were confirmed ADA positive had similar LY3074828 exposure (C0 and $AUC_{(0-96)}$) on GD70 compared to those that were not ADA positive. The presence of ADA in adult females after repeated dosing of LY3074828 had no apparent impact on LY3074828 serum concentrations during pregnancy or post pregnancy. There was no apparent impact on LY3074828 serum concentrations in ADA positive infants exposed to 300 mg/kg of LY3074828 in utero.

Nonclinical Discussion

In the ePPND study, pregnant cynomolgus monkeys were treated with LY3074828 (Mirikizumab) at 300 mg/kg by twice weekly (600 mg/kg/week) intravenous injection from approximately GD21 until parturition. No reproductive or developmental toxicities of mirikizumab, including no effects on the developing immune system, were identified in the ePPND study at 300 mg/kg twice weekly (600 mg/kg/week) IV dose. Mirikizumab exposure was detected in mothers during pregnancy, and in all infants for at least 28 days after birth, indicating exposure in utero and postpartum exposure. The No Observed Adverse Effect Level (NOAEL) for developmental effects was determined as 300 mg/kg when administered twice weekly (600 mg/kg/week) by IV injection. The NOAEL of 300 mg/kg twice weekly or 600 mg/kg/week dose offers adequate (8-fold based on weekly dose in mg/kg) safety margin for the proposed maximum human dose

of 300 mg/kg IV QW4 (75 mg/kg/week). It is to be mentioned here that the NOAEL of 100 mg/kg (bi-weekly IV dose or 200 mg/kg/week, AUC_{0-96} = 385000 µg.h/mL; monkey AUC_{0-96} value is the average of male and female on Day 176 mean AUC_{0-96} values, multiplied by 7 to align with the 4-week human AUC interval) in the 6-month IV study (Study No. 20119229) in monkeys offers about 28-fold margin of safety (refer to page 19 of the investigator's brochure dated March 13, 2019 submitted under SDN 095 dated 3/19/2019) based on AUC comparison for the maximum proposed human dose of 300 mg Q4W IV ($AUC_{0-672\ h,ss}$ = 13700 µg.h/mL, predicted based on study I6T-MC-AMAA).

(b) (4)

[redacted]

Appendix/Attachments

None

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/s/

TAMAL K CHAKRABORTI
09/18/2019 10:21:34 AM

SUSHANTA K CHAKDER
09/18/2019 12:50:32 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY IND REVIEW AND EVALUATION

Application number:	125444
Supporting document/s:	044
Sponsor's letter date:	September 29, 2017
CDER stamp date:	September 29, 2017
Product:	LY3074828
Indication:	Ulcerative colitis
Sponsor:	Eli Lilly and Company
Review Division:	DGIEP
Reviewer:	Tamal Chakraborti, PhD
Supervisor/Team Leader:	Sushanta Chakder, PhD
Division Director:	Donna Griebel, MD
Project Manager:	Kelly Richards, MSN, RN

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Executive Summary

Introduction

LY3074828 is a humanized immunoglobulin G4 (IgG4) monoclonal antibody that is directed against the p19 subunit of interleukin (IL)-23 and does not bind IL-12. LY3074828 is being developed for the treatment for adult patients with moderately to severely active ulcerative colitis (UC) under this IND.

In this submission, the Sponsor requested a Type C meeting (Written Response Only) and requested Division's concurrence that rodent carcinogenicity studies with LY3074828 are not warranted. The Sponsor has submitted a Carcinogenicity Risk Assessment for LY3074828 to support the waiver of rodent carcinogenicity studies with LY3074828.

Brief Discussion of Nonclinical Findings

No binding was observed for mouse and rat IL-23, indicating that carcinogenicity studies in rodents will not be useful. To assess the nonclinical toxicity of LY3074828, 4-week and 6-month toxicity studies in cynomolgus monkeys were conducted. A tissue cross-reactivity study using normal cynomolgus monkey and human tissues was also performed. No evidence of increased cellular proliferation (hyperplasia or preneoplastic lesions) has been observed in repeat-dose toxicity studies in cynomolgus monkeys. No evidence of effects on cells/organ systems responsible for tumor immunosurveillance (circulating lymphocytes, natural killer cell function, primary immune response, lymphoid organ histopathology) has been observed in repeat-dose toxicity studies in cynomolgus monkeys. In tissue cross-reactivity study, there was no specific staining in any human or monkey tissue.

Recommendations

- The sponsor's request for the waiver of rodent carcinogenicity studies with LY3074828 was communicated to the Executive Carcinogenicity Assessment Committee (ECAC).
- The Exec CAC concurred with the sponsor's justifications for the waiver of rodent carcinogenicity studies with LY3074828.

Relevant INDs, NDAs, BLAs and DMFs

- (b) (4)
-

Previous Reviews Referenced

- Pharmacology review of IND 125444 dated August 21, 2015 by Tamal Chakraborti, PhD

Carcinogenicity

The Sponsor has submitted a Carcinogenicity Risk Assessment for LY3074828 in support of their request for the waiver of rodent carcinogenicity studies. Lilly has conducted a weight-of-evidence analysis including assessment of the data from nonclinical studies with LY3074828 and review of published data on IL-23 and its relationship with tumorigenesis.

- An overview of published literature supports that neutralization of IL-23 would not be expected to increase cancer risk, but rather that IL-23 increases tumor incidence and promotes tumor growth and progression. In general, because IL-23 is considered proinflammatory, enhanced IL-23 expression or activity could be hypothesized to increase tumorigenesis, whereas reduced or absent IL-23 function could be hypothesized to prevent or delay tumor progression. These hypotheses are largely supported by published literature. Literature demonstrates a causal association between treatment with exogenous IL-23, or forced expression of IL-23, and increased tumor development. In animal models (IL-23 knockout mice and mice treated with IL-23 antibodies), elimination or reduction of IL-23 activity caused attenuation of tumor growth, incidence, and progression. These pro-tumor effects of IL-23 are attributable to mechanisms including stimulation of inflammatory cytokines, chemokines and growth factors, evasion of immune surveillance, the promotion of angiogenesis, and increased invasive activity. Literature evidence demonstrates IL-23 expression in several tumor types, and is in many cases associated with a more aggressive phenotype. Overall, these published studies indicate that exogenous IL-23 can encourage tumor progression and metastasis. however, some caution in interpretation is warranted in animal models where IL-23 levels were supra-physiological. It is to be also mentioned here that contrary to the above observations, some publications indicate that increased IL-23 expression can protect against tumorigenesis. For example, in vivo depletion of CD4+ T cells, CD8+ T cells, or NK cells significantly inhibited the antitumor effects of IL-23 expression. Another example of antitumor activity of IL-23 was demonstrated in pediatric B-acute lymphoblastic leukemia (B-ALL) cells. When primary B-ALL patient cell suspensions were cultured in the presence of IL-23, proliferation was significantly inhibited and the percentage of apoptotic cells was significantly increased. However, as noted above, the results of the above studies should be interpreted with caution due to the non-physiologic over-expression of IL-23. Overall, the published nonclinical data on IL-23 and tumor development may be generalized to conclude that in nonclinical models, IL-23 neutralization is more likely to protect against the development of tumors than

to contribute to their growth or progression. While some publications suggesting the contrary exist, IL-23 is considered to increase local inflammation in the tumor microenvironment, leading to suppression of immune surveillance mechanisms, up-regulation of proangiogenic factors, and increased capacity for invasion/metastasis.

Phase 3 clinical studies with two IL-23-neutralzing antibodies that target the p19 subunit demonstrate that therapeutic doses are not associated with an incidence of malignancy higher than that in placebo-controlled or active comparator groups. Long-term safety data with ustekinumab, which targets the IL-23/12 p40 subunit, indicated no increased incidence of malignancy, though prescribing information discloses a potential concern in a high-risk population. Available clinical data suggested that IL-23 neutralization does not significantly increase cancer risk in the studied populations. There is an increased risk of cancer in the intended patient population (UC (b) (4) targeted for the therapy with LY3074828. These diseases may be generally characterized as an autoimmune disorder in which increased inflammatory activity is observed in diseased tissue and sustained inflammation is associated with increased risk for malignancy. Whereas clinical data available to date suggest that IL-23p19 neutralization does not significantly increase cancer risk in the studied populations, this data is limited, and larger and longer clinical evaluations will be needed regarding any potential risks of cancer associated with IL-23 neutralization.

- LY3074828 is selective against IL-23 (Human: K_D = 21 pM; Monkey: K_D = 55 pM), with no evidence of binding to other cytokines (IL-12, IL-27 or IL-35) or cell surface targets in vitro, and no evidence of off-target toxicity observed in toxicology studies. In addition, no binding was detected for mouse and rat IL-23. In tissue cross-reactivity study, there was no specific staining in any human or monkey tissue. LY3074828 is also not expected to induce Fc- or complement-mediated immune activation in vivo as it showed equal binding to Fcγ receptors.

- To assess the nonclinical toxicity of LY3074828, 4-week and 6-month toxicity studies in cynomolgus monkeys were conducted. No evidence of increased cellular proliferation (hyperplasia or preneoplastic lesions) has been observed in repeat-dose toxicity studies in cynomolgus monkeys. No evidence of effects on cells/organ systems responsible for tumor immunosurveillance (circulating lymphocytes, natural killer cell function, primary immune response, lymphoid organ histopathology) has been observed in repeat-dose toxicity studies in cynomolgus monkeys.

Sponsor's Rationale for Not Conducting a Carcinogenicity Study:

- An overview of published literature supports that neutralization of IL-23 would not be expected to increase cancer risk, but rather, that IL-23 increases tumor incidence and promotes tumor growth, and progression.
- LY3074828 does not bind to mouse and rat IL-23.
- The affinity and potency of LSN2479016 (surrogate antibody) for IL-23 are significantly weaker compared to LY3074828, and key differences exist between the epitopes bound by each antibody. Therefore, LSN2479016 would be considered of limited value to assess carcinogenic potential of LY3074828.
- LY3074828 is highly selective against IL-23, with no evidence of binding to other cytokines or cell surface targets in vitro, and no evidence of off-target toxicity observed in toxicity studies.
- No evidence of increased cellular proliferation (hyperplasia or preneoplastic lesions) has been observed in repeat dose toxicity studies in cynomolgus monkeys.
- No evidence of effects on cells/organ systems responsible for facets of tumor immunosurveillance (circulating lymphocytes, natural killer cell function, primary immune response, lymphoid organ histopathology) has been observed in repeat dose toxicity studies in cynomolgus monkeys.

Integrated Summary and Evaluation

The lack of increased cellular proliferation or immunotoxicity in chronic toxicity study in monkeys indicates no increased risk of carcinogenesis. LY3074828 is potent and selective for IL-23, and no off-target toxicities have been observed in animal studies, there appears to be no specific carcinogenicity concerns for LY3074828 beyond those expected due to immunomodulation. Based on the majority of published data on the relationship between IL-23 and tumorigenesis, neutralization of IL-23 would not be expected to increase the risk of cancer in the intended patient population, although there are contradictory reports from the literature concerning the role of IL-23 in cancer. Limited clinical evidence with two antibodies that target IL-23p19 indicates no increased risk of malignancy with these treatments, and because LY3074828 selectively and potently targets the IL-23 p19 subunit, it would be expected to have comparable risk. In addition, no binding was observed for mouse and rat IL-23, indicating that carcinogenicity studies in rodents will not be useful. Overall, based on the above, the Sponsor's justifications for the waiver for rodent carcinogenicity studies with LY3074828 appears reasonable and carcinogenicity studies with LY3074828 may be waived.

The CDER Exec CAC was consulted for their concurrence, and the Committee concurred with the sponsor's justifications for the waiver of rodent carcinogenicity studies with LY3074828.

The Sponsor has asked the following (from page 18 of the Type C briefing document dated 9/29/2017) question in this submission.

- ***Question C2b:*** *Does the FDA agree that the carcinogenicity assessment for LY3074828 is adequate, and does FDA accept Lilly's request to waive additional nonclinical studies to assess carcinogenic potential of LY3074828?*

FDA Response: Yes, we agree that no additional nonclinical studies are needed to assess carcinogenic potential of LY3074828.

Appendix/Attachments

None

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/s/

TAMAL K CHAKRABORTI
11/22/2017

SUSHANTA K CHAKDER
11/22/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY IND REVIEW AND EVALUATION

Application number:	125444
Supporting document/s:	001
Sponsor's letter date:	July 28, 2015
CDER stamp date:	July 28, 2015
Product:	LY3074828
Indication:	Ulcerative colitis
Sponsor:	Eli Lilly and Company
Review Division:	DGIEP
Reviewer:	Tamal Chakraborti, PhD
Supervisor:	Sushanta Chakder, PhD
Division Director:	Donna Griebel, MD
Project Manager:	Kelly Richards, MSN, RN

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1 Executive Summary

1.1 Introduction

LY3074828 is an immunoglobulin G4 (IgG4) monoclonal antibody that neutralizes IL-23. LY3074828 neutralizing activity is directed against the p19 subunit of IL-23. IL-23, a member of the interleukin-12 family of cytokines, is a heterodimeric protein composed of 2 subunits: p40 subunit, which it shares with IL-12, and p19 subunit, considered to be specific to IL-23. IL-23 is produced by antigen-presenting cells (APC) and is critically involved in the maintenance and amplification of T helper 17 cells. This IND was submitted to initiate a Phase 2 study with LY3074828 (anti-interleukin-23 [IL-23] monoclonal antibody) in patients with moderate-to-severe ulcerative colitis (UC).

1.2 Brief Discussion of Nonclinical Findings

LY3074828 was shown to bind to IL-23 and block the interaction of IL-23 binding to its receptor. As LY3074828 does not bind to rodent IL-23, a surrogate mouse antibody (LSN2479016) was developed to neutralize mouse IL-23 for use in preclinical disease models. Neutralization of IL-23 using LSN2479016 demonstrated efficacy in two murine models of inflammatory bowel disease.

Cynomolgus monkey was selected as a species of choice, because LY3074828 binds with high affinity to human and cynomolgus monkey IL-23, but not to other IL-12 family members or rodent IL-23.

In a 4-week intravenous/subcutaneous (IV/SC) toxicity study in cynomolgus monkeys, LY3074828 was administered at 1 (SC), 30 (SC) and 100 mg/kg (IV) once weekly. The no-observed-adverse-effect-level (NOAEL) for each route of administration was the highest dose tested, 30 mg/kg for SC and 100 mg/kg for IV. In a 6-month subcutaneous toxicity study in cynomolgus monkeys, LY3074828 was administered at 10 and 100 mg/kg doses once weekly. The NOAEL was 100 mg/kg. It is to be noted here that two dose levels were used in the 6-month study. At least three dose levels should have been tested. In the above toxicity studies in monkeys, minimal, perivascular mononuclear cell or mononuclear and eosinophil cell infiltrates were observed in the subcutis at the injection sites. There were no significant treatment related microscopic findings at the injection sites in animals administered IV dose of 100 mg/kg. The injection site changes were not considered adverse. In the tissue cross-reactivity study, there was no specific staining in any human or cynomolgus monkey tissues with LY3074828.

1.3 Recommendations

1.3.1 Clinical Study (ies) Safe to Proceed: Yes

1.3.2 If Not Safe to Proceed

Nonclinical deficiencies: N/A

Nonclinical information needed to resolve deficiencies: N/A

1.3.3 Additional Recommendation(s) (Non-hold comments/advice to sponsor) *if any.*

None

2 Drug Information

2.1 Drug

CAS Registry Number (Optional): N/A

Generic Name: N/A

Code Name: LY3074828

Chemical Name: N/A

Molecular Formula: $C_{6380}H_{9842}N_{1686}O_{2004}S_{48}$

Molecular Weight: The average molecular weight of non-glycosylated, disulfide linked LY3074828 was calculated to be 143,768 Da.

Structure or Biochemical Description: LY3074828 is an IgG4 monoclonal antibody consisting of 2 identical light and 2 identical heavy chains. Each light chain is comprised of 214 amino acid residues, and each heavy chain consists of 441 amino acids. The amino acid sequences of the light and heavy chains are shown in the following Figure S.1.2-1 and Figure S.1.2-2, respectively (from page 1 and 2 of Section 3.2.S.1 of the submission).

DIQMTQSPSSLSASVGDRVTITCKASDHILKFLTWYQQKPGKAPKLLIYG	50
ATSLETGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQMYWSTPFTFGG	100
GTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV	150
DNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG	200
LSSPVTKSFNRGEC	214

Figure S.1.2-1 LY3074828 Light Chain Amino Acid Sequence

QVQLVQSGAEVKKPGSSVKVSCKASGYKFTRYVMHWVRQAPGQGLEWMGY	50
INPYNDGTNYNEKFKGRVTITADKSTSTAYMELSSLRSEDTAVYYCARNW	100
DTGLWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPE	150
PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV	200
DHKPSNTKVDKRVESKYGPPCPPCPAPEAAGGPSVFLFPPKPKDTLMISR	250
TPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSV	300
LTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQ	350
EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFF	400
LYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG	441

Figure S.1.2-2 LY3074828 Heavy Chain Amino Acid Sequence

The molecule contains 32 Cys residues, which are involved in 4 inter and 12 intra disulfide bonds. The predominant post-translational modifications included N-linked glycosylation (heavy chain Asn292) and conversion of heavy chain Gln1 to pyroglutamate. The secondary structure of LY3074828 is predominantly β-sheet and the tertiary structure is consistent with a natively folded protein.

Pharmacologic Class: Humanized IgG4 anti-IL23 monoclonal antibody

2.2 Relevant INDs, NDAs, BLAs and DMFs

N/A

2.3 Drug Formulation

[redacted] (b) (4). The drug product (DP) is composed of LY3074828 and the inactive ingredients [redacted] (b) (4) solution is a clear/opalescent, colorless to yellow-

brown solution (b) (4) . The following table (from page 1 of Section 3.2.P.1 of the submission) shows the composition of the drug product (DP).

Table P.1.2-1 Composition of the Drug Product

Ingredient	Quantity[1] (mg/vial)	Function	Reference to Standards
(b) (4)			

2.4 Comments on Novel Excipients

All the excipients are compendial as shown in the table below (from page 1 of Section 3.2.P.4 of the submission).

Compendial Excipients

The excipients comply with the requirements of the following compendia:

Excipient Name	Standard
(b) (4)	

2.5 Comments on Impurities/Degradants of Concern

The impurity profiles of drug substance (DS) batches used in animal toxicology studies are the same or similar to those planned for clinical trials.

Product Related Impurities: (b) (4), a process related impurity, was found in the DS at (b) (4) ppm (quantitation limit, (b) (4) %) in the DS Batch BR127089. The toxicologically acceptable limit for (b) (4) is (b) (4) ppm based on a highest proposed clinical dose of (b) (4) mg. The level of (b) (4) in the DS is well below the qualification threshold of 0.15% per the ICH Q3A(R2) and is qualified.

Process Related Impurities: (b) (4) As a result, a (b) (4) test will not be performed on DS batches made from this process.

2.6 Proposed Clinical Protocol

The Sponsor proposed to conduct a Phase 2, multicenter, randomized, double-blind, parallel, placebo-controlled study (Study I6T-MC-AMAC, [AMAC]) in patients with moderate-to-severe ulcerative colitis (UC). A planned, Phase 1 study (Study I6T-JE-AMAD [AMAD]) will be submitted to the IND in a future IND amendment. The proposed Phase 2 study has three periods (total treatment duration of 52 weeks): induction period (12 weeks), maintenance period (40 weeks) and an extension period. In this study, approximately 240 patients (both sexes, adult) will be enrolled.

Induction Period (12 weeks): In the 12-week induction period, LY3074828 will be administered by intravenous (IV) infusion at Weeks 0, 4, and 8.

Maintenance Period (40 weeks): The maintenance period is designed to examine the safety and durability of clinical responses and remissions to the treatment with 200 mg of LY3074828 administered subcutaneously (SC) every 4 weeks (Q4W) or every 12 weeks (Q12W). Subjects showing clinical responses at Week 12 will continue study participation in the maintenance period up to Week 52. Subjects who do not meet clinical response criteria at Week 12 will have the option to continue in a study extension period or discontinue from the study. Responding subjects who have received LY3074828 in period 1 will be re-randomized to one of two LY3074828 maintenance treatment arms (200 mg Q4W or 200 mg Q12W).

Extension Period: Subjects who complete the study induction period but do not have a clinical response may choose to participate in the study extension period following consultation with, and at the discretion of, the investigator.

Dosage:

Induction Period: 50 mg (0.8 mg/kg), 200 mg (3.3 mg/kg), or 600 mg (10 mg/kg) LY3074828 administered as an IV infusion at Weeks 0, 4, and 8.

Maintenance Period: Responding subjects will be randomized to receive 200 mg (3.3 mg/kg) of LY3074828 administered by SC injection either Q4W or Q12W for up to 52 weeks.

Extension Period: Nonresponding subjects may continue in the study and receive LY3074828 as discussed above.

2.7 Previous Clinical Experience

The Sponsor has conducted a multicenter, single-ascending dose, placebo-controlled, first-in human Phase 1 study in Canada with LY3074828 in healthy volunteers and in subjects with plaque psoriasis (Study AMAA; ongoing). Seven cohorts of subjects with active psoriasis received IV doses of either LY3074828 (33 subjects received a single dose of 5, 20, 60, 120, 200, 350, or 600 mg) or placebo (7 subjects). A single cohort of 5 healthy subjects received a SC injection of LY3074828 (120 mg) for the assessment

of bioavailability. No serious adverse events (SAEs) were reported. Treatment-emergent adverse events (TEAEs) included pruritus, diarrhea, nausea, headache, and injection site pain. All treatment-related AEs were considered by the investigator to be mild in intensity.

2.8 Regulatory Background

N/A

3 Studies Submitted

3.1 Studies Reviewed

The following table shows the list of study reports reviewed.

STUDY TITLE	REPORT NO.	PAGE
PHARMACOLOGY		9
TOXICOLOGY		27
Repeat-Dose		27
Monkey		27
Toxicity and Toxicokinetic Study in Cynomolgus Monkeys Administered LY3074828 by Intravenous or Subcutaneous Injection Once Weekly for 4 Weeks with an 8-Week Recovery	20029153	27
Toxicity and Toxicokinetic Study in Cynomolgus Monkeys Administered LY3074828 by Once Weekly Subcutaneous Injection for 6 Months	20043324	35
SPECIAL TOXICOLOGY		43
Tissue Cross-Reactivity of LY3074828 with Human and Cynomolgus Monkey Tissues Ex Vivo	20029154	43

3.2 Studies Not Reviewed

- (b) (4)
-

3.3 Previous Reviews Referenced

N/A

4 Pharmacology

4.1 Primary Pharmacology

<u>In Vitro</u>

In Vitro Binding Kinetics of LY3074828: Surface Plasmon Resonance Analysis (Report No. (b) (4) 186)

Methods: In this study, antibody affinity (K_D) to human, cynomolgus monkey or rabbit IL-23 were determined using a BIAcore assay. Increasing concentrations of IL-23 were used (0.62 nM to 30 nM for human and monkey IL-23 and 30 nM to 240 nM for rabbit IL-23). Flow cell 1 was used as a control to monitor nonspecific binding of IL-23. The assay was performed 2 times with human, monkey or rabbit IL-23. In addition, LY3074828 was tested 2 times each with mouse IL-23 at 333 nM, rat IL-23 at 200 nM, human IL-12 at 333 nM, human IL-27 at 500 nM or human IL-35 at 833 nM to determine binding of LY3074828 to mouse IL-23, rat IL-23, human IL-12, human IL-27 or human IL-35.

Results: LY3074828 produced a concentration-dependent binding response with human, cynomolgus monkey and rabbit IL-23 in this assay. Saturation of binding of IL-23 was attained at a concentration of 30 nM (human and monkey) and 240 nM (rabbit). Under the conditions of the study, the binding affinity (K_D) of human, monkey or rabbit IL-23 to LY3074828 was 21, 55 or 53,000 pM, respectively as shown in the table (from page 8 of the report). Mouse IL-23, rat IL-23, human IL-12, human IL-27 or human IL-35 did not bind to LY3074828 under these conditions.

Table 1: LSN3074828 binding kinetics and affinity to human, cynomolgus monkey and rabbit IL-23 and family members

Antigen	k_{on} Avg ± SD $M^{-1}s^{-1}$ (10^6)	k_{off} Avg ± SD s^{-1} (10^{-4})	KD Avg ± SD pM
hu IL-12			No binding
hu IL-23	2.43 ± 0.16	0.52 ± 0.21	21 ± 9.9
hu IL-27			No binding
hu IL-35			No binding
monkey IL-23	1.28 ± 0.05	0.7 ± 0.11	55 ± 6.4
rabbit IL-23	0.09 ± 0.001	47.9 ± 0.4	53,000 ± 1131
mouse IL-23			No binding
rat IL-23			No binding

n = 2 for each antigen. IL-12 was tested at a 400x concentration of what is detectable for IL-23. IL-27 and IL-35 were tested at an 800x concentration of what is detectable for IL-23. Mouse and rat IL-23 were tested at 500x and 300x concentrations of what is detectable for human IL-23.

Neutralization of Human or Cynomolgus Monkey IL-23 by LY3074828: In Vitro Study Using Murine Splenocytes (Report No. (b) (4) 187)

Methods: Splenocytes from C57BL/6 mice stimulated with IL-23 and IL-2 has been shown to produce IL-17. In this study, the ability of LY3074828 to inhibit IL-23-induced production of IL-17 was examined using a sub-maximal dose of IL-23. For evaluation of LY3074828, a concentration of human or cynomolgus monkey IL-23 that produced approximately 50% of maximal production of IL-17 was used (16 pM). A dose response ranging from 4.4 pM to 800,000 pM of LY3074828 was evaluated. LY3074828 or LSN2835015 (IgG4 control) and IL-23 were combined in a separate well for 90 minutes at 37^0C before addition to the cells (pre-incubation mix). Mouse splenocytes were resuspended in the assay media (RPMI) containing human IL-2 into a 96-well culture plate. The pre-incubation mix of LY3074828/IL-23 was added to each well and incubated at 37^0C. After 48 hours, culture supernatants were tested for murine IL-17 using enzyme-linked immunosorbent assay (ELISA). The assay was performed twice each for human and cynomolgus monkey IL-23 and IC_{50} values for the inhibition of production of IL-17 were determined.

Results: Mouse splenocytes produced IL-17 in response to human or cynomolgus monkey IL-23. As shown in the following figures (from page 9 of the report) LY3074828

inhibited production of IL-17 from mouse splenocytes stimulated with human IL-23 (Panel A) or cynomolgus monkey IL-23 (Panel B).

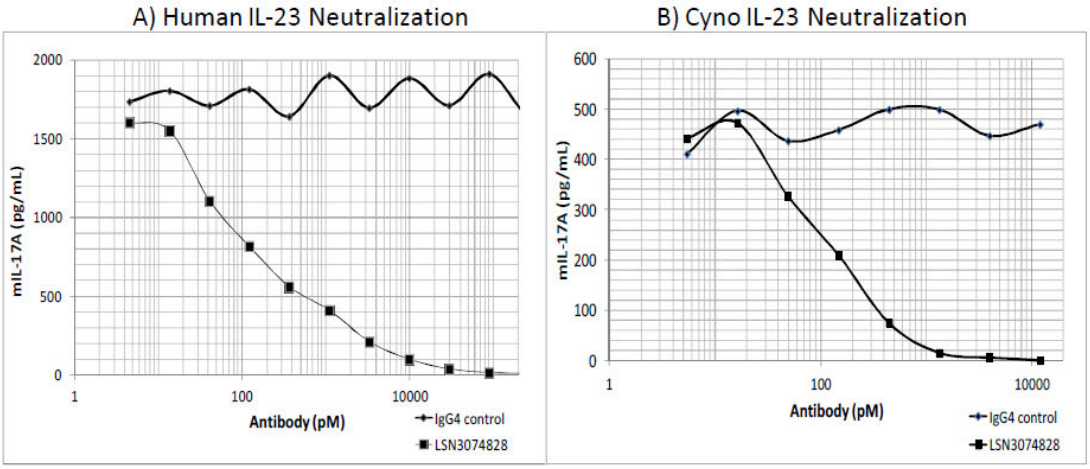

Figure 1: LSN3074828 inhibited production of IL-17 from mouse splenocytes stimulated with human IL-23 (Panel A) or cynomolgus monkey IL-23 (Panel B).

The IC_{50} was determined to be 82 pM for human and 120 pM for cynomolgus monkey IL-23 (n = 2 for each) as shown in the table (from page 9 of the report) below.

Table 1: LSN3074828 Average IC_{50} in the In Vitro Human and Cynomolgus Monkey IL-23 Neutralization Assay

IL-23	IC_{50} (pM) ± SD
Human	82 ± 11
Cynomolgus Monkey	120 ± 14

n = 2 experiments for each antigen

In Vitro Inhibition of IL-23 Binding to IL-23 Receptor by LY3074828: Surface Plasmon Resonance Analysis (b) (4) 188)

Methods: LY3074828 binds specifically to the p19 subunit of human IL-23 and neutralizes human IL-23 in in vitro functional assays. The IL-23 receptor is composed of 2 subunits, the IL-23R and IL-12Rβ1. IL-23R mediates signaling via STAT3 pathway and IL-12Rβ1 stabilizes the interaction through interactions with the p40 subunit of IL-23. In this study, a BIAcore assay was used to demonstrate that LY3074828 could

neutralize IL-23, which mediates its effect through the binding of IL-23 to the IL-23R subunit.

In this study, recombinant human IL-23R/Fc was coupled via free amine groups to carboxyl groups on flow cell 2 of a CM4 biosensor chip using a mixture of N-ethyl-N (dimethylaminopropyl)-carbodiimide (EDC) and N-hydroxysuccinimide (NHS). Recombinant human IgG1 Fc was coupled using the same method to flow cell 1 of the same chip. Mouse anti-6X HIS antibody was coupled using the same method to flow cell 4 of the same chip. Mouse anti-6X HIS was used to pre-capture human IL-12Rβ1/Fc which contains a HIS tag. Recombinant human IL-23 was pre-incubated for 90 minutes with or without the addition of a 16X molar excess of LY3074828. Flow Cell 1 was used as a control to monitor nonspecific binding of IL-23 to the chip. A software program was used to prepare overlays of individual binding sensorgrams. The assay was performed 2 times.

Results: The following figure (from page 8 of the report) shows the BIAcore sensograms showing LY3074828 can inhibit IL-23 binding to IL-23R/Fc but not IL-12Rβ1/Fc.

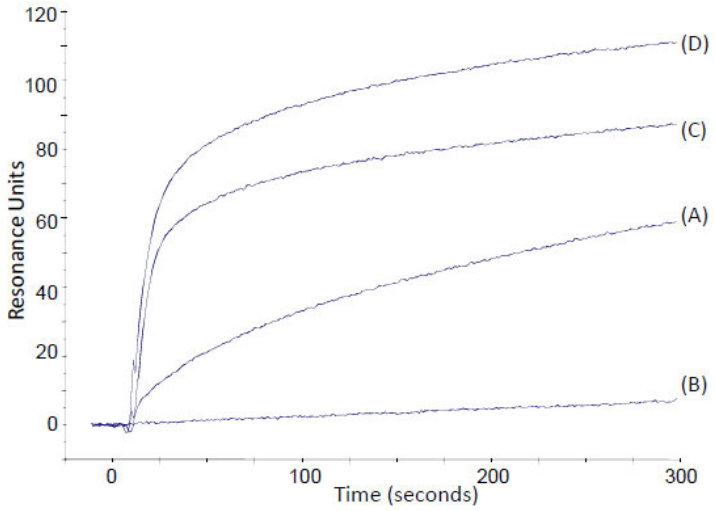

Figure 1: BIAcore sensorgrams showing LY3074828 can inhibit IL-23 binding to IL-23R/Fc but not IL-12Rβ1/Fc.

(A) IL-23 binding to IL-23R/Fc; (B) LY3074828/IL-23 complex does not bind to IL-23R/Fc; (C) IL-23 binding to IL-12Rβ1/Fc; and (D) LY3074828/IL-23 complex binding to IL-12Rβ1/Fc.

The results demonstrated that LY3074828 inhibited binding of IL-23 to IL-23R/Fc. The data are summarized in the following table (from page 9 of the report). Additionally, LY3074828 did not inhibit binding of IL-23 to the IL-12Rβ1 subunit.

Table 1: LY3074828 Prevents IL-23 from Binding IL-23R

Cytokine	Antibody	Binding to IL-23R	Binding to IL-12Rβ1
IL-23	None	YES	YES
IL-23	LY3074828	NO	YES

Epitope Mapping for LY3074828: In Vitro Study Using Hydrogen/Deuterium Exchange Mass Spectrometry ([(b) (4)] 189)

Methods: In Hydrogen/Deuterium exchange (HDX) experiments, amide hydrogen atoms are exchanged with deuterium atoms in a time dependent manner and exchange is measured by differences in mass. To map the binding epitope of an antibody/antigen complex, the immunocomplex is mixed with D_2O to allow for the hydrogen and deuterium atoms to exchange. Where the two proteins bind, deuterium exchange is blocked and the kinetics of this region is different when comparing exchange rates to antigen alone. This process was used to map the binding epitope of LY3074828.

Results: Mature IL-23 p19 subunit peptic peptide 81-88, 81-89, 89-105, and 116-140 showed significant differences in deuterium exchange when compared to LY3074828:IL-23 complex. Peptic peptide 100-114 did not have differences in deuterium uptake at 10 minutes and had minor differences in uptake at 30 minutes, so this region was not included in the epitope mapping. The results of this study helped to narrow the range to 81-99 and 115-140 as being the regions of the human IL-23 p19 subunit containing the binding epitope for LY3074828.

Epitope Mapping for LY3074828: In Vitro Study Using Yeast Display [(b) (4)] 190)

Methods: Epitope mapping studies were performed to determine the specific amino acids in human IL-23 p19 subunit that were required for LY3074828 binding. Epitope mapping of LY3074828 was conducted using alanine scanning with yeast display. Briefly, a panel of alanine mutants for each position of the human IL 23 p19 subunit was created and displayed on the surface of yeast. Binding of LY3074828 was monitored by flow cytometry.

Results: The absence of LY3074828 binding suggested that the amino acid position in question was important for antibody binding. The results of this study demonstrated that amino acid positions 94P, 95S, 97L, 98P, 99D, 123W, 130S, 133P, and 137W of the human IL-23 p19 subunit were important for LY3074828 binding.

In Vitro Analysis of Human Fc Receptor and Complement Binding of the Interleukin 23 Antibody LY3074828 ([(b) (4)] 226)

Methods: LY3074828 is a humanized antibody of the IgG4 isotype with additional mutations to increase stability and further reduce Fcγ receptor binding. The objective of

this study was to examine the ability of LY3074828 to bind human Fcγ receptors I, IIa, and IIIa and to complement component C1q.

CD16a, CD32a, and C1q

In this assay, a 96-well microplate was coated with CD32a with a C-terminal 10-His tag or recombinant human CD16a with a C-terminal 6-His Tag and human C1q (a component of the classical pathway of complement activation). The plate was incubated overnight at 4°C. Following, wash serial dilutions of LY3074828, human IgG1 positive control (LSN2436595), or human IgG4 negative control (LSN2835015) were added to each well and incubated for 2 hours at room temperature (RT) (antibodies were tested with a concentration range of 6.25 to 200µg/mL). Testing was performed in duplicate wells. The plate was then washed before addition of horseradish peroxidase (HRP)-conjugated goat anti-human IgG and incubated for 1 hour at RT. This polyclonal antibody recognizes both human IgG1 and IgG4. The plate was then washed and tetramethylbenzidine (a chromogenic substrate) was added and incubated for 4.5 minutes for CD16a, 9 minutes for CD32a, or 30 minutes for C1q at RT. Optical density was immediately measured using a colorimetric microplate reader set to 450 nm.

Results: The results of the in vitro binding experiments are shown in the following figure (from page 9 of the report).

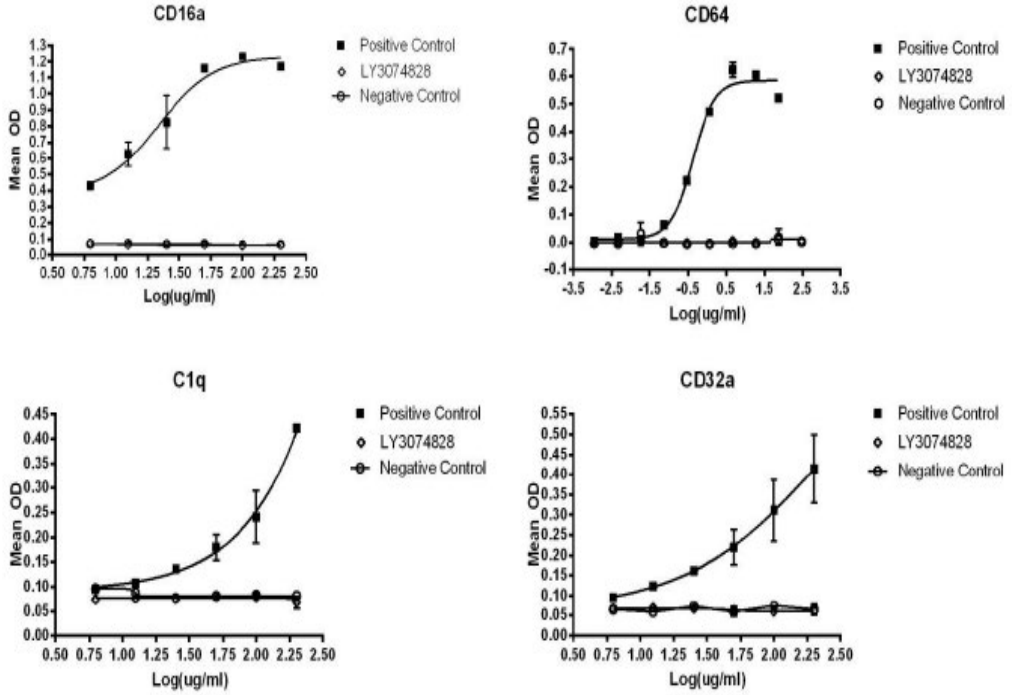

Figure 1: Fcγ receptor and C1q binding results for LY3074828 (open symbols).

Results (mean ± SD) from 1 of 2 experiments performed are shown. Human IgG1 and IgG4 are used as positive and negative controls, respectively.

LY3074828 binding to CD16a, CD32a, CD64, or C1q was equal to that observed with the human IgG4 negative control antibody. The human IgG1 positive control antibody bound to all 4 molecules tested, demonstrating the validity of the assays. These results suggested that it is unlikely that LY3074828 will be able to induce Fc-mediated biological effects in vivo.

LY3074828/IL-23 Complex Does Not Prevent IL-12 Signaling: In Vitro Study Using Human Cell Lines (b) (4) 228)

Methods: The objective of this study was to determine if the LY3074828/IL-23 complex prevented IL-12 signaling in two human T-cell lines, KIT-225 and TALL 104. These two human T cell lines reported to respond to IL-12. The presence of the cytokine receptors IL-12Rβ1, IL-12R-β2, and the IL-23R were verified on each cell line by flow cytometry.

Flasks were seeded with cells in RPMI medium and were incubated for four hours to allow the cells to serum starve. LY3074828 (50 µg/mL) +/- IL-23 (5 µg/mL) were added to RPMI medium. These solutions were incubated at 37^{0}C for 1.5 hours to allow formation of LY3074828/IL-23 complexes. The LY3074828/IL-23 complexes were then

added to the serum-starved cells. The flasks were returned to the incubator for 1.5 hours. IL-12 was added to the flasks and the flasks were incubated for 20 minutes. Following the IL-12 stimulation, cells were centrifuged, pelleted and lysed and lystaes were stored for Western analysis for IL-12 induced phosphorylation of STAT4 in the presence of the LY3074828/IL-23 complex.

Results: In each experiment, STAT4 was only found in the samples that were stimulated with IL-12. Pre-incubation with the LY3074828/IL-23 complex before IL-12 stimulation, did not block phosphorylation of STAT4 in KIT-225 and TALL-104 cell lines indicating that LY3074828/IL-23 complex did not interfere with IL-12 signaling.

Neutralization of Human IL-23 by LY3074828: In Vitro Study Using Human Peripheral Blood Mononuclear Cells ((b) (4) 241)

Methods: In this study, LY3074828 was tested for the inhibition of IL-17 secretion from anti-CD3, anti-CD28, and IL-23 stimulated human peripheral blood mononuclear cells (PBMC). PBMC were isolated from whole blood from 20 donors (Prep 1) or 29 donors (Prep 2) and stored frozen in liquid nitrogen. PBMC were plated on tissue culture plates. LY3074828 (5 µL) was then added to the cells (n = 8) and the plates were pre-incubated for 30 minutes at 37^0C. Following the 30 minute incubation, IL-17 secretion was stimulated by the addition of 30 µL of media containing anti-human CD3, anti-human CD28, and human IL-23 (160 ng/mL, 500 ng/mL, and 5 ng/mL final concentrations, respectively). Following 48-hour incubation, plates were centrifuged and supernatants were analyzed for IL-17 by ELISA.

Results: LY3074828 inhibited IL-23 stimulated IL-17 secretion from human PBMC co-stimulated with anti-CD3/anti-CD28 (shown in the following figure from page 8 of the report). The IC_{50} values were 22 µg/mL for PBMC Prep 1 and 29 µg/mL for PBMC Prep 2 (average = 25 µg/mL). These results demonstrated that LY3074828 could inhibit IL-23-induced IL-17 secretion in vitro in human primary PBMC.

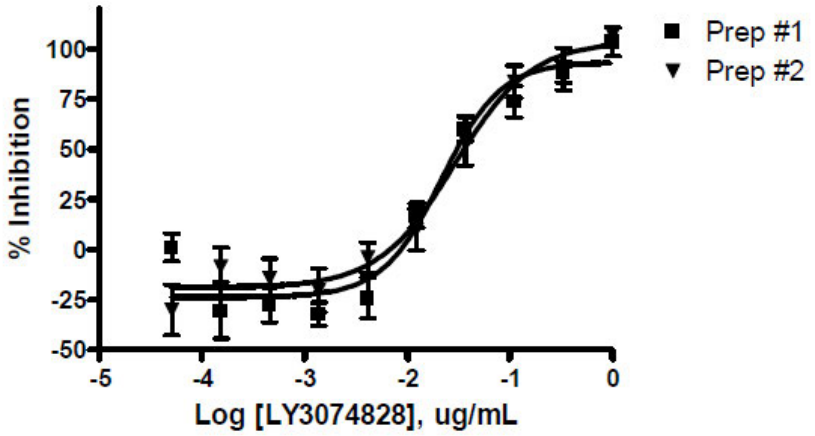

Figure 1: LY3074828 inhibited IL-23 induced secretion of IL-17 from human PBMC.

In Vivo

Neutralization of Human IL-23 by LY3074828: Acute, Systemic In Vivo Mechanism of Action Study ((b) (4) 191)

Methods: LY3074828 is a humanized monoclonal antibody that binds specifically to the IL-23p19 subunit and neutralizes IL-23. LY3074828 does not recognize rodent IL-23 precluding its use in preclinical disease models. To confirm neutralization of IL-23 in vivo, previous studies have determined that intraperitoneal (IP) injection of a combination of human IL-23 and IL-2 was able to prime rodent splenocytes for ex vivo production of IL-17 upon re-stimulation. Using this system, it was determined that concurrent administration of LY3074828 neutralized IL-23 and significantly inhibited production of mouse IL-17 (mIL-17).

In this study, splenocytes were washed in complete RPMI medium and seeded in a 96-well culture plate and stimulated with hamster anti-mouse CD3 and anti-mouse CD28. The plate was then incubated for 48 hours at 37^0C. The amount of IL-17 in each culture supernatant was measured using an ELISA kit for the mouse IL-17. The assay was performed 2 times (4 mice were tested in each antibody group).

Results: As discussed before, when mice are treated with multiple injections of IL-2 and human IL-23 in vivo, their splenocytes are primed to produce significant amounts of IL-17 when re-stimulated with anti-CD3 antibody ex vivo. As shown in the following figure (from page 8 of the report), LY3074828 neutralized human IL-23 in vivo and significantly inhibited production of murine IL-17 upon re-stimulation of cells.

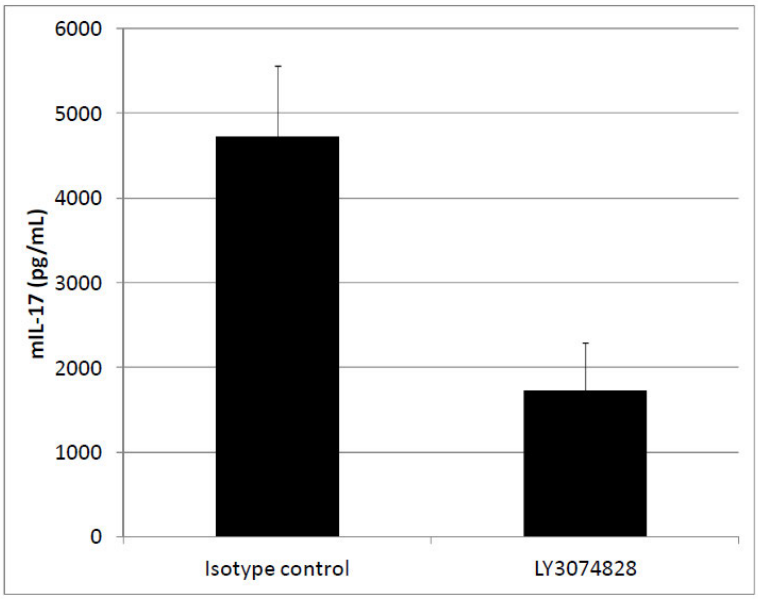

Figure 1: LY3074828 in vivo neutralization of human IL-23-induced murine IL-17 production ($p < 0.01$, t-Test)

Neutralization of Human IL-23 by LY3074828: Acute, Local In Vivo Mechanism of Action Study (b) (4) 192)

Methods: It has been shown that intradermal administration of IL-23 in mouse skin initiates a cascade of events resulting in erythema, mixed dermal infiltrate, epidermal hyperplasia associated with overexpression of keratin-16, and induction of IL-17A and IL-17F mRNA expression. This model was used to determine if systemic administration of LY3074828 was able to neutralize the local response to human IL-23.

Animals (C57BL/6 females, 8 weeks old) were used in this study. Mice (n = 10 per group) received a subcutaneous injection of LY3074828 or an isotype control antibody (LSN2835015, isotype [IgG4]; 0.54 mg per mouse). The following 2 days, mice were injected intradermally with human IL-23 (1 µg in 50 µL saline). Sterile saline was used as a vehicle control. Mice were sacrificed 24 hours after the last IL-23 injection and skin samples were removed from IL-23-injected side and from the sterile saline-injected side. Skin samples were frozen directly in liquid nitrogen for mRNA studies.

Results: Intradermal injection of human IL-23 induced mRNA expression of IL-17A and IL-17F, and this was abrogated by the treatment with LY3074828 but not isotype control antibody. IL-23-driven epidermal thickening was associated with increased mRNA expression of keratin-16 which was significantly inhibited by the administration of LY3074828. The results are shown in the following figure and table (from page 9-10 of the report). Overall, the results demonstrated that LY3074828 inhibited human IL-23-induced murine IL-17A, IL-17F, and keratin16 mRNA expression in this study.

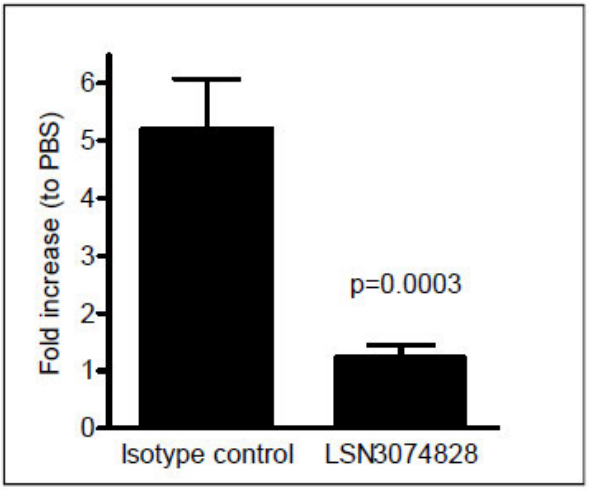

Figure 1: In vivo human IL-23 induction of mouse keratin-16 mRNA expression in the skin is neutralized by LY3074828 (p=0.0003, unpaired t-test).

Table 1: LY3074828 In Vivo Neutralization of Human IL-23 Induced Murine IL-17A and IL-17F mRNA Expression

	Ct Values			
	Saline		IL-23	
	IL17A	IL17F	IL17A	IL17F
Isotype Control	≥40	≥40	35.4	31.6
LY3074828	≥40	≥40	≥40	≥40

4.2 Secondary Pharmacology

In Vitro

In Vitro Binding Kinetics of LSN2479016, mAb for Murine IL-23: Surface Plasmon Resonance Analysis ((b) (4) 34)

Methods: LSN2479016 is a murine monoclonal antibody that binds specifically to the murine IL- 23p19 subunit and neutralizes murine IL-23. LSN2479016 was generated as a surrogate antibody. A BIAcore assay was used to measure the binding affinity of LSN2479016 for murine IL 23 using plasmon resonance analysis. The on-rate, off-rate, K_D and stoichiometry were determined.

Results: LSN2479016 produced a concentration-dependent binding response with murine IL-23. Saturation of binding of IL-23 was attained at a concentration of 70 nM. Under the conditions of the study, the binding affinity (K_D) of murine IL-23 to LSN2479016 was 103 pM (shown in the table below from page 13 of the report).

Table 1: LSN2479016 Versus Murine IL-23: In Vitro Binding Kinetics Determination Using Surface Plasmon Resonance, n = 1

K_a (1/Ms)	K_d (1/s)	K_D (pM)	Stoichiometry*
2.54×10^6	2.61×10^{-4}	103	2.0

*Represents the binding ratio of IL-23 molecules to each molecule of monoclonal antibody (each antibody molecule has 2 binding sites) as determined by the molecular mass of each molecule and the total resonance units for each.

Neutralization of Murine IL-23 by LSN2479016: In Vitro Study Using Murine Splenocytes (b) (4) 35)

Methods: Murine splenocytes produce IL-17 in response to stimulation with IL-23 from multiple species. In this study, the ability of LSN2479016 (mouse surrogate antibody) to inhibit IL-23-induced production of IL-17 was examined using a sub maximal dose of IL-23. A concentration of murine IL-23 that produced approximately 50% of maximal production of IL-17 was used (0.4 ng/mL). A dose response ranging from 50 to 0.025 nM of LSN2479016 was evaluated. Mouse splenocytes were resuspended in assay media into a 96-well culture plate. The pre-incubation mix of LSN2479016/IL-23 was added (in duplicate well), and incubated at 37^0C. Forty-eight hours later, culture supernatants were tested for mIL-17 using an ELISA kit. The IC_{50} was determined.

Results: Mouse splenocytes produced IL-17 in response to murine IL-23. LSN2479016 inhibited the production of IL-17 as shown in the following figure (from page 9 of the report). The IC_{50} for the inhibition of IL-17 was determined to be 400 pM for murine IL-23.

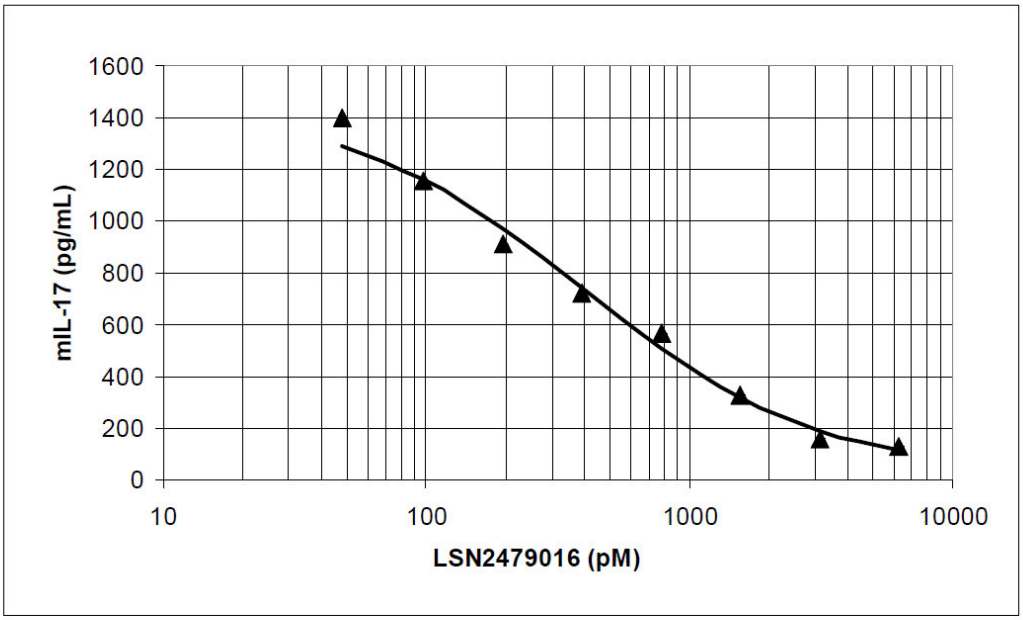

Figure 1: **LSN2479016 neutralization of murine IL-23 shown by inhibition of production of mIL-17 by mouse splenocytes, n = 1. IL-17 was measured using an ELISA kit from R&D Systems.**

In Vivo

Efficacy of Anti-Murine Interleukin-23 (LSN2479016) in an In Vivo Mouse Model of Inflammatory Bowel Disease ((b) (4) 242)

Methods: In this study, a mouse model of inflammatory bowel disease was used to examine the efficacy of LSN2479016 (mouse antibody) when administered in prophylactic or intervention mode. Using mice deficient for IL-23 or the IL-23 receptor, it has been shown that IL-23 is an important cytokine in the pathogenesis of several inflammatory bowel disease models. LSN2479016 is a mouse IgG1 p19 antibody, which selectively neutralizes mouse IL- 23. Female severe combined immunodeficient (SCID) mice (C.B-17/Tac-*Prkdc*^{scid}) and female BALB/cJ mice (age of 6 to 7 weeks) were used in this study.

Induction of Colitis: For induction of colitis, $CD4^+/CD25^-$ cells were transferred from MHC-compatible BALB/c mice into SCID recipients. For the prevention studies, mice were assigned to groups based on body weight (n = 8/group). Mice (n = 8/group) were treated by subcutaneous (SC) injection of test articles (1, 3 and 10 mg/kg). The animals were initially weighed once per week. After onset of disease (about four weeks post transfer), animals were weighed three times per week.

Treatment Study: For the treatment study, mice were tested for peripheral T cells three weeks posttransfer and only mice with $CD4^+$ T cells (indicating a successful

reconstitution) in the periphery were included in the study. On Day 28 post-initial transfer, mice were assigned to groups (n = 8/group). These mice showed significant bowel inflammation by Day 28. Test articles were administered (1, 3 and 10 mg/kg) by SC injection once per week. Disease progression was followed by weighing the animals 3 times per week. Mice that lost more than 20% of their initial body weights were euthanized. Eight to nine weeks post-T cell transfer, mice were euthanized and colons were collected and measured for weight and length. Colon weight/length ratios were calculated and examined for histopathology. Colitis was scored using a 0 to 4 scale.

Results: LSN2479016 treatment significantly reduced the weight/length ratio compared with IgG1 control antibody (shown in table below from page 12 of the report). Histopathological analysis of the colon tissue showed reduced colitis in LSN2479016 treated mice (shown in table below from page 12 of the report). All three dose levels reduced colitis in this model; however, no clear dose response was observed.

LSN2479016 also attenuated colitis. Colon weight/length ratio of the 1 and 3 mg/kg treatment groups as well as the histology scores were significantly different from the isotype control group (shown in table below from page 12 of the report).

Table 1: Effect of anti-IL-23 Treatment on Colon Pathology in the Syngenic T cell Transfer IBD Model when Dosed Prophylactically

			anti IL-23 mAb		
	$CD45RB^{lo}$	IgG Isotype	1 mg/kg	3 mg/kg	10 mg/kg
Colon Weight/Length (mg/cm)	21.9 ± 0.2*	49.6 ± 4.3	32.6 ± 2.0*	nd	31.3 ± 1.9*
Total Colon Histology Score	0.0 ± 0.0	12.6 ± 2.6	6.3 ± 2.4*	nd	6.4 ± 1.8*

Data presented as mean ± sem
* $p \leq 0.05$ vs Isotype
ANOVA with Tukey-Kramer post-hoc test
Abbreviation: nd = not determined

Table 2: Effect of anti-IL-23 Treatment on Colon Pathology in the Syngenic T cell Transfer IBD Model when Dosed Therapeutically

			anti IL-23 mAb		
	$CD45RB^{lo}$	IgG Isotype	1 mg/kg	3 mg/kg	10 mg/kg
Weight/Length (mg/cm)	21.3 ± 0.8*	56.9 ± 6.5	39.9 ± 4.1*	35.3 ± 1.9*	43.4 ± 0.9
Histology Score	0.3 ± 0.7*	11.0 ± 5.0	6.4 ± 3.5*	6.4 ± 2.4*	11.1 ± 1.8

mean ± sem
* $p \leq 0.05$ vs Isotype
ANOVA with Dunnett's post-hoc test

The Effect of Anti-Murine IL-23 (LSN2479016) on In Vivo T Cell-dependent and T Cell-independent Antibody Responses in Mice ([(b) (4)]67)

Methods: The objective of the study was to determine if the in vivo neutralization of IL-23 would affect the ability of a mouse to initiate an immune response to either a T cell-dependent (TD) or T cell-independent (TI) immunogen. Female C57BL/6 mice were treated with anti-IL-23 either prior to immunogen challenge or 5 days after immunogen challenge. The antigen specific immunoglobulin responses were determined for each immunoglobulin isotype. The magnitude of the responses was compared to a control group of animals treated in the same manner with isotype control antibody (LSN2404993 mouse IgG1).

Mouse anti-murine IL-23 (LSN2479016) or isotype control (LSN2404993) was administered subcutaneously at 3 mg/kg. For the studies with pretreated antibody, the antibodies were administered on Day 0, the immunogens were injected on Day 2, and the antibodies were administered again on Day 7. The animals were sacrificed on Day 12 and blood was collected by cardiac puncture.

For the studies with delayed antibody administration, the immunogens were injected on Day 0, the antibodies administered on Day 5 and the animals were sacrificed on Day 10 and blood was collected. The TD study with preadministered antibody utilized 16 mice per group and the TI study with preadministered antibody had 8 mice per group. The TD and TI studies with delayed antibody administration had 8 mice per group. The serum antigen specific immunoglobulin levels were measured by ELISA.

Results:

Preadministration of Anti-Murine IL-23

The T cell-independent, antigen specific immunoglobulin responses were similar when comparing the control and the anti-IL-23 treated groups. There was no significant difference with any of the immunoglobulin isotypes (shown in the table below form 18 of the report).

Table 2: One-way ANOVA Statistical Analysis of Immunoglobulin Responses to a TI Immunogen

	anti-IL-23		control			
Isotype	mean	std. dev.	mean	std. dev.	pvalue	adj. pvalue
IgG1	0.159	0.080	0.175	0.215	0.717	1.000
IgG2a	0.135	0.086	0.113	0.080	0.561	1.000
IgG2b	0.210	0.081	0.246	0.124	0.658	1.000
IgG3	0.182	0.085	0.172	0.074	0.862	1.000
IgM	0.439	0.118	0.378	0.121	0.451	1.000
IgA	0.049	0.009	0.042	0.001	0.081	0.566
IgE	0.043	0.002	0.040	0.002	0.004	0.028

Data from experiment described in Figure 3. Bonferroni approach used to calculate adjusted p values.

Delayed Administration of Anti-Murine IL-23

The antigen specific immunoglobulin response of individual animals for TD and TI immunogens were similar between the anti-IL-23 treated and control groups. The findings showed that the neutralization of IL-23 did not significantly alter the magnitude or immunoglobulin isotype of the immune response to a T cell-dependent or T cell-independent immunogen. The following tables (from page 18 of the report) show the results.

Table 1: One-way ANOVA Statistical Analysis of Immunoglobulin Responses to a TD Immunogen

	anti-IL-23		control			
Isotype	mean	std dev	mean	std dev	pvalue	adj. pvalue
IgG1	0.598	0.263	0.498	0.188	0.334	1.000
IgG2a	0.291	0.176	0.237	0.097	0.505	1.000
IgG2b	0.498	0.231	0.448	0.196	0.534	1.000
IgG3	0.244	0.116	0.246	0.185	0.559	1.000
IgM	0.317	0.102	0.254	0.045	0.054	0.377
IgA	0.068	0.056	0.050	0.020	0.323	1.000
IgE	0.173	0.084	0.148	0.046	0.414	1.000

Data from experiment described in Figure 1. Bonferroni approach used to calculate adjusted p values.

Table 2: One-way ANOVA Statistical Analysis of Immunoglobulin Responses to a TI Immunogen

	anti-IL-23		control			
Isotype	mean	std. dev.	mean	std. dev.	pvalue	adj. pvalue
IgG1	0.159	0.080	0.175	0.215	0.717	1.000
IgG2a	0.135	0.086	0.113	0.080	0.561	1.000
IgG2b	0.210	0.081	0.246	0.124	0.658	1.000
IgG3	0.182	0.085	0.172	0.074	0.862	1.000
IgM	0.439	0.118	0.378	0.121	0.451	1.000
IgA	0.049	0.009	0.042	0.001	0.081	0.566
IgE	0.043	0.002	0.040	0.002	0.004	0.028

Data from experiment described in Figure 3. Bonferroni approach used to calculate adjusted p values.

Table 3: One-way ANOVA Statistical Analysis of Immunoglobulin Responses to a TD Immunogen

	anti-IL-23		control			
Isotype	mean	std dev	mean	std dev	pvalue	adj. pvalue
IgG1	0.447	0.256	0.478	0.149	0.505	1.000
IgG2a	0.228	0.144	0.280	0.113	0.353	1.000
IgG2b	0.365	0.155	0.395	0.086	0.555	1.000
IgG3	0.232	0.135	0.188	0.046	0.753	1.000
IgM	0.296	0.091	0.290	0.039	0.951	1.000
IgA	0.053	0.013	0.047	0.010	0.243	1.000
IgE	0.127	0.060	0.133	0.033	0.715	1.000

Data from experiment described in Figure 5. Bonferroni approach used to calculate adjusted p values.

4.3 Safety Pharmacology

Included in toxicology studies

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Included in toxicology studies

5.2 Toxicokinetics

Included in toxicology studies

6 General Toxicology

6.1 Single-Dose Toxicity

Single dose toxicity studies were not conducted.

6.2 Repeat-Dose Toxicity

Study title: Toxicity and Toxicokinetic Study in Cynomolgus Monkeys Administered LY3074828 by Intravenous or Subcutaneous Injection Once Weekly for 4 Weeks with an 8-Week Recovery

Study no.:	20029153
Study report location:	EDR: 4.2.3.2
Conducting laboratory and location:	(b) (4)
Date of study initiation:	September 17, 2012
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	LY3074828, Lot EL01245-014-API, protein content = 57.3 mg/mL

Key Study Findings:

- In the 4-week IV/SC toxicity study in cynomolgus monkeys, LY3074828 was administered either at 1, 30 mg/kg by SC injection or at 100 mg/kg by IV injection once weekly for 4 consecutive weeks (5 total doses).
- There was no mortality.
- At Day 36, minimal perivascular mononuclear cell or mononuclear and eosinophil cell infiltrates were observed in the subcutis in one or more of the subcutaneous injection sites in animals at ≥ 1 mg/kg (males and females). There were no LY3074828-related microscopic findings in animals treated IV at 100 mg/kg. These findings were not considered adverse in the absence of a clear dose response, minimal severity, were not accompanied by any gross observations and were not seen at 100 mg/kg IV dose.
- The NOAEL for each route of administration was the highest dose tested, 30 mg/kg SC and 100 mg/kg IV.

Methods:

Doses:	1, 30, 100 mg/kg
Frequency of dosing:	Once weekly
Route of administration:	IV (100 mg/kg) and SC (0, 1 and 30 mg/kg)
Dose volume:	4 mL/kg for IV and 1 mL/kg for SC
Formulation/Vehicle:	10 mM sodium citrate, 150 mM NaCl, 0.02%, polysorbate 80, pH 6.0
Species/Strain:	Cynomolgus monkeys (*Macaca fascicularis*)
Number/Sex/Group:	3/sex/group (main study), 2/sex/group (recovery)
Age:	2.3 to 3.8 years
Weight:	2.3 to 3.1 kg
Satellite groups:	Recovery (2/sex/group)
Study design:	Shown below
Deviation from study protocol:	Protocol deviations did not affect the overall integrity of this study or the interpretation of the phase results and conclusions.

The following table (from page of the report) shows the study design.

Group Identification	Dose Level mg/kg [a]	Dose Concentration mg/mL	Animal Numbers			
			Main Study		Recovery	
1 Vehicle Control (SC)	0	0	1001-1003	1501-1503	1004-1005	1504-1505
2 LY3074828 (SC)	1	1	2101, 2002-2003	2501-2503	-	-
3 LY3074828 (SC)	30	30	3001-3003	3601, 3502-3503	-	-
4 LY3074828 (IV)	100	25	4001-4003	4501-4503	4004-4005	4504-4505

[a] Animals from Groups 1, 2, and 3 were dosed via subcutaneous injection. Animals from Group 4 were dosed via intravenous injection. The dose volume was 4 mL/kg for Group 4 and 1 mL/kg for Groups 1, 2, and 3. Concentrations were corrected for lot specific test article content.
SC = subcutaneous; IV = intravenous

Basis of dose selection: The projected dose range for the single ascending dose (SAD) clinical study is 5 to 200 mg SC and 200 to700 mg IV. Based on a 70-kg body weight, doses for this monkey study was expected to provide a 10X dose multiple for the low and high SC doses and a 10X dose multiple for the high dose IV. Additionally, in a 6-week monkey study with the IL-23 Antibody Effort 1 (LY2525623; (b) (4) Study No. 7608-242, report not submitted), IV doses of 10, 30, and 100 mg/kg and a SC dose of 100 mg/kg did not produce any dose limiting toxicity; with a NOAEL in that study of 100 mg/kg.

Observations and Results:

Mortality: Mortality was observed twice daily. There were no mortalities.

Clinical Signs: Clinical signs were observed once daily. Two females at 100 mg/kg had transient slight tremors postdose on Day 29 only. Animal No. 4502 had slight tremors in both legs, while No. 4503 had general slight tremors involving the entire body. Any potential relationship to test article was unknown.

Body Weights: Body weights were measured on a weekly basis. Mean initial (Week -1) and final (Week 5) body weights of control males were 2.58 and 2.70 kg, respectively. Mean initial (Week -1) and final (Week 5) body weights of control females were 2.42 and 2.50 kg, respectively. There were no significant treatment related effects.

Food Consumption: Food consumption was recorded once daily (qualitative). Although several animals had isolated occurrence of low/no food consumption (1 in Group 2, 3 in Group 3, and 2 in Group 4), it was transient, occurred in a control animal (No. 1504), and was not associated with other clinical observations or changes in body weights. Quantitative food consumption data was not provided.

Ophthalmoscopy: Ophthalmoscopy was conducted at the start of the treatment and at the end of recovery. There were no significant treatment related effects.

Safety Pharmacology: Respiratory analysis, neurological examinations with a detailed CNS/behavioral evaluation and body temperatures were recorded. There were no significant treatment related effects on safety pharmacology endpoints.

Respiratory Examinations: Respiratory examinations were performed on unanesthetized animals on Day 1 (predose, and at 1, 12, 24, 48, 96, and 144 hours postdose) and Day 29 (predose, and at 1 and 24 hours postdose), and once toward the end of the recovery phase. There were no significant treatment related effects on respiratory parameters.

Neurologic Examinations: Neurological examinations were performed after respiratory exams on unanesthetized animals on Day 1 (predose, and at 1, 12, 24, 48, 96, and 144 hours postdose) and Day 29 (predose, and at 1 and 24 hours postdose), and once toward the end of the recovery phase. There were no significant treatment related effects.

Electrocardiography (ECG): ECG was recorded once at prestudy and on Days 8 and 22 at predose and at 1, 6, 12, and 20 hours postdose. There were no significant treatment related effects.

Hematology: Blood was collected per the following schedule (from page 23 of the report).

Study Day/Week	Time Point	Sample Type	Total Blood Volume (mL)
Week -2	Prestudy I	Flow/Chem/Hem/Coag/Urin	1/2/1/1.8
Week -1	Prestudy II	Flow/Chem/Hem/Coag/Urin	1/2/1/1.8
Day 1	Predose	TK/ADA	1

Study Day/Week	Time Point	Sample Type	Total Blood Volume (mL)
	1, 4, 8 hrs	TK	1
Day 2	24 hrs	TK	1
Day 3	48 hrs	TK	1
Day4	72 hrs	TK	1
Day5	96 hrs	TK	1
Day 8	168 hrs*	TK	1
Day 15	Predose	Chem/Hem/Coag/Urin	2/1/1.8
Day 15	Predose (all Groups) 1 hr (Group 4 only)	TK	1
Day 16	24 hrs (Groups 1 to 3)	TK	1
Day 29	Predose	TK	1
	1, 4, 8 hrs	TK	1
Day 30	24 hrs	TK	1
Day 31	48 hrs	TK	1
Day 32	72 hrs	TK	1
Day 33	96 hrs	TK	1
Day 36	168 hrs	TK/ADA	1/1
Day 36	Necropsy	Flow Chem/Hem/Coag/Urin	1/2/1/1.8
Day 50	Recovery Week 3	TK	1
Day 64	Recovery Week 5	TK/ADA	1
Day 78	Recovery Week 7	TK	1

* Day 8 blood samples were collected prior to or during telemetry recordings from -3 to -1 hours predose.
ADA = antidrug antibody, Chem = Clinical chemistry, Coag = coagulation, Flow = immunophenotyping, Hem = hematology, TK = Toxicokinetics, Urin = urinalysis

There were no significant treatment related effects on hematology parameters.

Clinical Chemistry: Blood samples were collected as listed in the above table. No significant treatment related effects were observed.

Urinalysis: Urine samples were collected as listed in the above table. There were no significant treatment related effects.

Anti-Drug Antibody (ADA) Analysis: Blood samples were collected as listed in the above table. ADA analysis results were not provided in the report.

Immunophenotyping: Blood samples were collected as listed in the above table. There were no significant treatment related changes in counts of T-lymphocytes, T-cytotoxic lymphocytes, T-helper lymphocytes, B-lymphocytes, NK cells, or in the T-helper:T-cytotoxic lymphocyte ratios.

Gross Pathology: Gross pathology was conducted at necropsy. There were no significant treatment related gross pathology findings.

Organ Weights: The following (from page 28 of the report) organs were weighed.

adrenal glands	pituitary
brain	prostate
epididymis	spleen
heart	thymus
kidneys	testes
liver	thyroid lobes and parathyroid glands

There were no significant treatment related effects on organ weights.

Histopathology: The following tissues (from page 28-29 of the report) were collected for histopathology.

abnormalities	[b]bone (femur)
[a]animal identification	brain (cerebrum, cerebellum, midbrain and medulla oblongata)
adrenals	cecum
aorta (thoracic)	colon
[b]bone and marrow (sternum)	

duodenum
[d]epididymides
esophagus
[f]eyes
gallbladder
heart (including section of aorta)
ileum
injection site(s); test article (IV – most recent; SC – all 4)
jejunum
kidneys
lacrimal glands
liver (sample of 2 lobes)
[d]lungs
lymph nodes (axillary and mesenteric)
mammary gland, thoracic
[f]optic nerves
ovaries
pancreas
pituitary
prostate
[a]rectum
salivary glands (mandibular)
sciatic nerve
seminal vesicles
skeletal muscle (quadriceps femoris)
skin (ventral thoracic)
spinal cord (thoracic)
spleen
stomach
[c]testes
thymus
[e]thyroid lobes (and parathyroids)
tongue
trachea
urinary bladder
uterus (body and cervix)
vagina

a Retained but not processed.
b Bone decalcified prior to sectioning.
c Fixed in Modified Davidson's fluid.
d Infused with neutral buffered 10% formalin.
e At least one parathyroid should be present in a routine section of the thyroid.
f Fixed in Davidson's fluid.

At Day 36, minimal perivascular mononuclear cell or mononuclear and eosinophil cell infiltrates were observed in the subcutis in one or more of the subcutaneous injection sites in animals at ≥ 1 mg/kg (males and females). Generally, these findings were seen mostly at 30 mg/kg, SC; however, the infiltrates were similar in severity (minimal) in both the low and high dose groups. There were no LY3074828-related microscopic findings in animals treated IV at 100 mg/kg LY3074828. These findings were not considered as adverse in the absence of a clear dose response, minimal severity and were not seen at 100 mg/kg IV dose. The following table (from page 339 of the report) shows the injection site findings.

Table 20: Pathology - Intergroup Comparison of Selected Histopathology Observations (Day 36)
Study: 20029153

Observations: Neo-Plastic and Non Neo-Plastic	MALES				FEMALES			
Removal Reasons: All of those SELECTED	0 mg/kg	1 mg/kg	30 mg/kg	100 mg/kg	0 mg/kg	1 mg/kg	30 mg/kg	100 mg/kg
Number of Animals on Study :	3	3	3	3	3	3	3	3
Number of Animals Completed:	(3)	(3)	(3)	(3)	(3)	(3)	(3)	(3)
INJECTION SITE, SUBCUTANEOUS 1;								
Examined	(3)	(3)	(3)	(0)	(3)	(3)	(3)	(0)
Within Normal Limits	2	2	0	0	1	0	2	0
Degeneration/Regeneration, Myocyte; Subcutaneous	(1)	(1)	(0)	(0)	(0)	(0)	(0)	(0)
minimal	1	1	0	0	0	0	0	0
Fibroplasia; Perivascular; Subcutaneous	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)
minimal	0	1	0	0	0	0	0	0
Fibroplasia; Subcutaneous; Skeletal muscle; focal	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
minimal	1	0	0	0	0	0	0	0
Infiltrate, Mononuclear Cell; Perivascular; Subcutaneous	(0)	(0)	(2)	(0)	(0)	(3)	(1)	(0)
minimal	0	0	2	0	0	3	1	0
Infiltrate, Mononuclear Cell; Subcutaneous; Perivascular	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)
minimal	0	0	0	0	1	0	0	0
Infiltrate, Mononuclear Cell; eosinophilic; Perivascular; Subcutaneous	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)
minimal	0	0	1	0	0	0	0	0
Hemorrhage; acute; Subcutaneous	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)
minimal	0	0	0	0	1	0	0	0
INJECTION SITE, SUBCUTANEOUS 2;								
Examined	(3)	(3)	(3)	(0)	(3)	(3)	(3)	(0)
Within Normal Limits	3	2	1	0	3	2	2	0
Infiltrate, Mononuclear Cell; Perivascular; Subcutaneous	(0)	(1)	(2)	(0)	(0)	(1)	(0)	(0)
minimal	0	1	2	0	0	1	0	0
Infiltrate, Mononuclear Cell; Subcutaneous; Skeletal muscle	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(0)
minimal	0	0	0	0	0	0	1	0
IINJECTION SITE, SUBCUTANEOUS 3;								
Examined	(3)	(3)	(3)	(0)	(3)	(3)	(3)	(0)
Within Normal Limits	3	3	0	0	2	1	0	0
Infiltrate, Mononuclear Cell; Perivascular; Subcutaneous	(0)	(0)	(2)	(0)	(0)	(2)	(2)	(0)
minimal	0	0	2	0	0	2	2	0
Infiltrate, Mononuclear Cell; Subcutaneous; Skeletal muscle	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)
minimal	0	0	0	0	1	0	0	0
Infiltrate, Mononuclear Cell; eosinophilic; Perivascular; Subcutaneous	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)
minimal	0	0	1	0	0	0	0	0
Degeneration; Adipose cell; Subcutaneous	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)
minimal	0	0	1	0	0	0	0	0
Degeneration; Skeletal muscle; Subcutaneous	(0)	(0)	(1)	(0)	(0)	(0)	(1)	(0)
minimal	0	0	1	0	0	0	1	0

Table 20: Pathology - Intergroup Comparison of Selected Histopathology Observations (Day 36)
Study: 20029153

Observations: Neo-Plastic and Non Neo-Plastic	MALES				FEMALES			
Removal Reasons: All of those SELECTED	0 mg/kg	1 mg/kg	30 mg/kg	100 mg/kg	0 mg/kg	1 mg/kg	30 mg/kg	100 mg/kg
Number of Animals on Study :	3	3	3	3	3	3	3	3
Number of Animals Completed:	(3)	(3)	(3)	(3)	(3)	(3)	(3)	(3)
IINJECTION SITE, SUBCUTANEOUS 3; (continued)								
Degeneration/Regeneration, Myocyte; Subcutaneous	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)
minimal	0	0	0	0	1	0	0	0
INJECTION SITE, SUBCUTANEOUS 4;								
Examined	(3)	(3)	(3)	(0)	(3)	(3)	(3)	(0)
Within Normal Limits	2	3	0	0	1	2	2	0
Degeneration; Myofiber; Subcutaneous	(1)	(0)	(2)	(0)	(1)	(0)	(0)	(0)
minimal	0	0	1	0	1	0	0	0
mild	1	0	1	0	0	0	0	0
Infiltrate, Mononuclear Cell; Subcutaneous; Skeletal muscle	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)
minimal	0	0	0	0	1	0	0	0
Infiltrate, Mononuclear Cell; Perivascular; Subcutaneous	(0)	(0)	(2)	(0)	(0)	(1)	(1)	(0)
minimal	0	0	2	0	0	1	1	0
Fibroplasia; Subcutaneous	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)
minimal	0	0	0	0	1	0	0	0

Toxicokinetics: Blood samples were collected as listed in the table under “Hematology” above. After SC injection, the C_{max} reached between 8 and 48 hours postdose on Days 1 and 29. Exposure roughly increased in a dose proportional manner between the SC treatment groups. The steady state was reached by Day 15. Mean $T_{1/2}$ ranged from 24.9 to 47.6 hours for the SC route and from 40.1 to 47.8 hours for the IV route. No apparent accumulation of LY3074828 was observed for either route of administration, but the systemic exposure on Day 29 decreased for some animals (2502, 2503, 3502, and 3002) in the SC dose groups while no quantifiable LY3074828 was detected on Day 29 for Animal No 2501. There were no apparent gender differences in systemic exposure for either routes of administration except in the 1 mg/kg SC dose group on Day 29 because of reduced exposure in the females. The absolute bioavailability of

LY3074828 when administered by the SC route ranged from 44 to 61%, except for the females at the 1 mg/kg dose level on Day 29 (F = 24%). During the recovery phase, LY3074828 was not quantifiable in any samples collected from Animal Nos. 4004 and 4005 but remained quantifiable up to 504 hours and 840 hours postdose on Day 29 in samples collected from Animal Nos. 4504 and 4505, respectively. The following table (from page 33-34 of the report) shows the TK data.

Systemic exposure (AUC_{0-168}) to LY3074828, following subcutaneous or intravenous administration.

Parameter	Administered Dose (mg/kg)					
	1 (SC)		30 (SC)		100 (IV)	
Sex	Male	Female	Male	Female	Male	Female
LY3074828						
Day 1						
T_{max} (Hours)	13.3 ± 9.24	13.3 ± 9.24	26.7 ± 20.1	13.3 ± 9.24	N/A	N/A
C_0 (µg/mL)	N/A	N/A	N/A	N/A	2680 ± 235	2420 ± 279
C_{max} (µg/mL)	3.43 ± 1.09	3.90 ± 0.818	147 ± 34.7	135 ± 24.4	2540 ± 191	2320 ± 204
AUC_{0-168} (µg*Hours/mL)	260 ± 104	259 ± 29.3	10,100 ± 2930	8540 ± 3650	59,400 ± 5500	46,500 ± 9650
$T_{1/2}$ (Hours)	40.1 ± 7.78	39.6 ± 15.5	38.1 ± 7.69	41.7 ± 12.7	42.5 ± 6.79	41.4 ± 6.23
Day 29						
T_{max} (Hours)	24.0 ± 0.00	24.0 ± ID	13.3 ± 9.24	21.3 ± 23.1	N/A	N/A
C_0 (µg/mL)	N/A	N/A	N/A	N/A	2530 ± 205	2500 ± 364
C_{max} (µg/mL)	3.46 ± 1.13	2.07 ± ID	126 ± 43.5	126 ± 48.3	2400 ± 186	2370 ± 325
AUC_{0-168} (µg*Hours/mL)	318 ± 142	106 ± ID	8620 ± 994	7490 ± 2920	58,100 ± 10,700	44,000 ± 7380
AUC_{0-t} (µg*Hours/mL)	N/A	N/A	N/A	N/A	63,800 ± ID	49,700 ± ID
AUC_{0-inf} (µg*Hours/mL)	N/A	N/A	N/A	N/A	65,100 ± ID	49,800 ± ID
$T_{1/2}$ (Hours)	47.6 ± 1.73	NC	27.9 ± 21.9	24.9 ± 21.1	47.8 ± 8.45	40.1 ± 16.1

T_{max}	Time of maximum observed concentration.
C_0	Theoretical concentration at time zero.
C_{max}	Maximum observed concentration.
AUC_{0-168}	Area Under the Curve during the dosing interval.
AUC_{0-t}	Area Under the Curve from time zero to the time after dosing at which the last quantifiable concentration of the drug was observed (calculated for recovery animals only).
AUC_{0-inf}	Area Under the Curve from time zero to infinity (calculated for recovery animals only).
$T_{½}$	Terminal elimination half-life.
NC	Not calculated.
ID	Insufficient data.
N/A	Not applicable.

Dosing Solution Analysis: Concentration and stability verification of the dosing solution was determined from Week 1 preparations. Formulations were considered acceptable if results were within ± 10% of the theoretical concentration and the relative standard deviation (RSD) was equal to or less than 6.0%. Mean LY3074828 concentrations for dose formulations sampled and used on Day 1 ranged from 101 to 103% of theoretical values.

Study title: Toxicity and Toxicokinetic Study in Cynomolgus Monkeys Administered LY3074828 by Subcutaneous Injection Once Weekly for 6 Months

Study no.:	20043324
Study report location:	EDR: 4.2.3.2
Conducting laboratory and location:	(b) (4)
Date of study initiation:	November 5, 2013
Date of study completion:	August 29, 2014
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	LY3074828, Lot No. EL01403-007-API, protein content 53.9 mg/mL

Key Study Findings:

- In the 6-month subcutaneous toxicity study in cynomolgus monkeys, LY3074828 was administered at 0, 10 and 100 mg/kg once weekly.
- There was no mortality.
- There were no significant treatment related changes in body weights, food consumption, ophthalmology, clinical pathology, ECG parameters, immunology parameters (peripheral blood immunophenotyping, TDAR, and NK cytotoxicity), organ weights, and macroscopy.
- There were no significant treatment related histopathology findings except at the injection site (minor mixed cell infiltrates at 10 and 100 mg/kg and these changes consisted of minimal to mild perivascular mononuclear and eosinophil cell infiltrates). These changes were not clearly dose related, were seen in control animals and were not accompanied by any gross observations and were not considered adverse.
- The NOAEL was considered as 100 mg/kg.
- It is to be noted here that two dose levels were used in the current study. At least three dose levels should have been tested.

Methods:

Doses:	0, 10, 100 mg/kg
Frequency of dosing:	Once weekly
Route of administration:	Subcutaneous (SC)
Dose volume:	2 mL/kg
Formulation/Vehicle:	10 mM sodium citrate buffer, 150 mM NaCl, 0.02%, polysorbate 80, pH 6.0
Species/Strain:	Cynomolgus monkeys (*Macaca fascicularis*)
Number/Sex/Group:	4/sex/group
Age:	Males: 6.7 to 8.3 years Females: 4.8 to 7.5 years
Weight:	Males: 5.8 - 9.6 kg Females: 2.6 - 3.9 kg
Satellite groups:	None
Study design:	Shown below
Deviation from study protocol:	Protocol deviations did not affect the overall integrity of this study phase or the interpretation of the phase results and conclusions.

The following table (from page 18 of the report) shows the study design.

Animals were randomized into the following groups:

Group Identification	Dose Level mg/kg[a]	Dose Concentration mg/mL	No. Animals	
1 Vehicle Control	0	0	4	4
2 LY3074828	10	5	4	4
3 LY3074828	100	50	4	4

[a] The dose volume was 2 mL/kg. Concentrations were corrected for lot specific test article content.

Basis of dose selection: The high dose (100 mg/kg) is the same high dose used in the previous 4-week toxicity study with LY3074828 (20029153). In the 4 week study, the only findings were changes at the subcutaneous injection sites which consisted of minimal perivascular mononuclear cell or mononuclear and eosinophil cell infiltrates. The changes at the injection sites were not accompanied by any gross observations and were not considered adverse. This dose represents a >10X multiple of the projected maximum clinical dose. The low dose (10 mg/kg) is approximately 1-2X the projected maximum clinical dose. It is to be noted here that two dose levels were used in the current study. At least three dose levels should have been tested.

Observations and Results:

Mortality: Mortality was observed once daily. There were no mortalities.

Clinical Signs: Clinical signs were observed once daily. There were no significant treatment related clinical signs.

Body Weights: Body weights were measured on a weekly basis. Mean initial (Day -1) and final (Day 182) body weights of control males were 7.23 and 8.33 kg, respectively. Mean initial (Day -1) and final (Day 182) body weights of control females were 3.08 and 3.40 kg, respectively. There were no significant treatment related effects.

Food Consumption: Food consumption was recorded once daily (qualitative). There were no significant treatment related effects.

Ophthalmoscopy: Ophthalmoscopy was conducted at the start of the treatment and prior to necropsy. No significant treatment related effects were observed.

Electrocardiography (ECG): ECG was performed once at prestudy and on Days 92 and 169. There were no significant treatment related ECG findings.

Hematology: Blood was collected per the following schedule (from page 24 of the report).

Group No.	Time Point	Hematology	Coagulation	Clinical Chemistry	Urinalysis
All animals	Week -2	X	X	X	X
All animals	Week -1	X	X	X	X
1 to 3	Day 36 (predose)	X	X	X	-
1 to 3	Day 85 (predose)	X	X	X	-
1 to 3	Day 183	X	X	X	X

X = sample collected; - = not applicable

One female (Animal No. 2501) at 10 mg/kg had a transient moderate increase in monocytes (5.18x of Day -5) on Day 36, but this was not observed at subsequent time points. One female (Animal No. 3502) at 100 mg/kg had a moderately increased eosinophil count (1.58 x 10^3/µL; 5.10x) on Day 183 compared to Day -5 that correlated with chronic pancreatitis with a moderate eosinophilic infiltrate observed microscopically. Due to limited exposure to LY3074828 in that animal (undetectable blood levels after Day 85), relationship to the treatment was considered unlikely.

Clinical Chemistry: Blood samples were collected as listed in the table above. On Day 36, one female (Animal No. 2501) at 10 mg/kg exhibited multiple changes in clinical chemistry parameters relative to Day -5 pretreatment values, including a moderate decrease in albumin (0.58x) associated with a minimal increase in globulin (1.27x) and mild decrease in total protein (0.83x), and mild decreases in sodium and chloride (0.93x and 0.87x, respectively). Given a concurrent increase in monocytes, the combined changes in albumin and globulins may indicate an acute phase protein reaction. However, based on the sporadic and transient nature of these findings in addition to the lack of a dose response, these were considered unlikely to be treatment related.

Triglycerides were increased to ≥ 200 mg/dL in one male and one female at 10 mg/kg (Animal Nos. 2002 and 2501, respectively) and in 2 males at 100 mg/kg (Animal Nos. 3001 and 3002) on Day 36 and/or 183. However, based on the sporadic incidence and lack of a dose response, these changes were of uncertain relationship to LY3074828 administration.

Urinalysis: Urine samples were collected as listed in the table above. There were no significant treatment related effects.

Immunogenicity: Blood samples were collected during Week -1, predose on Day 85 and on Day 183. Results were not provided in the report.

Immunophenotyping: Blood was collected during Weeks -2 and -1, and on Days 85 and 183. There were no significant treatment related changes in the lymphocyte subsets evaluated.

Natural-killer (NK) Cell Activity Assay: Blood was collected during Week -2 and on Day 183. No significant treatment related changes were observed.

T-Cell Dependent Antibody Response (TDAR): Blood was collected by femoral venipuncture during Week -1 and on Days 106, 113, 120, 169, 176, and 183. There were no significant treatment related effects.

Gross Pathology: Gross pathology was conducted at necropsy. There were no significant treatment related gross pathology findings.

Organ Weights: The following (from page 31of the report) organs were weighed.

brain	kidney
epididymides	liver
adrenal gland	ovary
pituitary gland	spleen
prostate gland	testis
seminal vesicle gland	thymus
thyroid gland	uterus
heart	

There were no significant treatment related effects on organ weights.

Histopathology: The following tissues (from page 32 of the report) were collected for histopathology.

animal indentification	large intestine, rectum
aorta	liver
bone marrow smear[a]	lung
bone marrow (femur)	lymph node, mesenteric
bone marrow (sternum)	lymph node, axillary
bone (femur)	muscle, skeletal
bone (sternum)	nerve, optic[b]
brain	nerve sciatic
cervix	ovary
epididymides	pancreas
esophagus	site, administration (test article and KLH)
eyes[b]	skin
gallbladder	small intestine, duodenum
adrenal gland	small intestine, ileum
lacrimal gland	small intestine, jejunum
mammary gland	spinal cord (cervical, thoracic, and lumbar)
parathyroid gland	spleen
pituitary gland	stomach
prostate gland	testis[c]
salivary gland	thymus
seminal vesicle gland	tongue
gross lesions/masses	trachea
gut-associated lymphoid tissue	urinary bladder
heart	uterus
kidney	vagina
large intestine, cecum	
large intestine, colon	

[a] Bone marrow smears air dried and not fixed in formalin.
[b] Preserved in Davidson's fixative
[c] Preserved in Modified Davidson's fixative

Minor mixed cell infiltrates at the subcutaneous injection sites were observed at 10 and 100 mg/kg. The changes consisted of minimal to mild perivascular mononuclear and eosinophil cell infiltrates. These changes were not clearly dose related, were seen in control animals and were not accompanied by any gross observations and were not considered adverse.

Female No. 3502 (100 mg/kg) had a chronic pancreatitis characterized by fibrosis, proliferation of ductular elements, and increased eosinophils. Due to limited exposure to LY3074828 in that animal (undetectable blood levels after Day 85); any relationship to the treatment was considered unlikely. It is to be mentioned here, although rare, chronic pancreatitis is seen as a background lesion in Macaque monkeys (Sato J, et al., 2012, Histopathology of Incidental Findings in Cynomolgus Monkeys (*Macaca fascicularis*)

Used in Toxicity Studies, J Toxicol Pathol, 25: 63-101; Tsuchitani M and Narama I, 1988, Chronic Pancreatitis in Macaca Monkeys. Jpn J Vet Sci, 50: 439-444). Special stains to attempt identification of potential pathogenic organisms were negative.

The following tables (from page 580-582 of the report) show histopathology findings.

Table 20: Pathology - Intergroup Comparison of Select Histopathology Observations
Day 183
Study: 20043324

Removal Reason: TERMINAL EUTHANASIA	Male			Female		
	0 mg/kg Group1	10 mg/kg Group 2	100 mg/kg Group 3	0 mg/kg Group1	10 mg/kg Group 2	100 mg/kg Group 3
Number of Animals:	4	4	4	4	4	4
PANCREAS						
Examined	4	4	4	4	4	4
No Visible Lesions	3	4	4	4	4	3
Inflammation, mixed cell; chronic, eosinophilic	0	0	0	0	0	1
.... moderate	0	0	0	0	0	1
Hypertrophy; islet of langerhans	1	0	0	0	0	0
.... mild	1	0	0	0	0	0
Pancreatitis; chronic	0	0	0	0	0	1
.... moderate	0	0	0	0	0	1
SITE, ADMINISTRATION, SC 1						
Examined	4	4	4	4	4	4
No Visible Lesions	2	2	0	3	2	0
Infiltration, mixed cell	1	2	4	1	2	4
.... minimal	1	2	4	1	2	4
Inflammation, granulomatous	1	0	0	0	0	0
.... minimal	1	0	0	0	0	0
SITE, ADMINISTRATION, SC 2						
Examined	4	4	4	4	4	4
No Visible Lesions	2	1	1	3	3	0

Table 20: Pathology - Intergroup Comparison of Select Histopathology Observations
Day 183
Study: 20043324

Removal Reason: TERMINAL EUTHANASIA	Male			Female		
	0 mg/kg Group1	10 mg/kg Group 2	100 mg/kg Group 3	0 mg/kg Group1	10 mg/kg Group 2	100 mg/kg Group 3
Number of Animals:	4	4	4	4	4	4
SITE, ADMINISTRATION, SC 2 (Continued...)						
Infiltration, mixed cell	1	3	3	1	1	4
.... minimal	1	3	3	1	1	2
.... mild	0	0	0	0	0	2
Pigmentation	0	0	0	0	0	1
.... minimal	0	0	0	0	0	1
Inflammation, granulomatous	1	0	0	0	0	0
.... minimal	1	0	0	0	0	0
SITE, ADMINISTRATION, SC 3						
Examined	4	4	4	4	4	4
No Visible Lesions	4	1	1	4	3	0
Infiltration, mixed cell	0	3	3	0	1	4
.... minimal	0	3	3	0	1	2
.... mild	0	0	0	0	0	2
SITE, ADMINISTRATION, SC 4						
Examined	4	4	4	4	4	4
No Visible Lesions	2	2	0	3	3	0
Infiltration, mixed cell	1	2	4	1	1	4
.... minimal	1	2	4	1	1	3

Table 20: Pathology - Intergroup Comparison of Select Histopathology Observations
Day 183
Study: 20043324

Removal Reason: TERMINAL EUTHANASIA	Male			Female		
	0 mg/kg Group1	10 mg/kg Group 2	100 mg/kg Group 3	0 mg/kg Group1	10 mg/kg Group 2	100 mg/kg Group 3
Number of Animals:	4	4	4	4	4	4
SITE, ADMINISTRATION, SC 4 (Continued...)						
.... mild	0	0	0	0	0	1
Inflammation, granulomatous	1	0	0	0	0	0
.... minimal	1	0	0	0	0	0
SITE, ADMINISTRATION, KLH						
Examined	4	4	4	4	4	4
Infiltration, mixed cell	4	4	3	2	3	4
.... minimal	3	3	3	0	2	2
.... mild	1	1	0	2	1	2
Regeneration; myofiber	0	0	1	1	0	0
.... mild	0	0	1	0	0	0
.... moderate	0	0	0	1	0	0
Hemorrhage	0	0	0	0	1	0
.... mild	0	0	0	0	1	0
Inflammation, granulomatous	0	0	1	2	1	0
.... mild	0	0	1	2	1	0

Toxicokinetics: Blood samples were collected per the schedule as listed in the following table (from page 26 of the report).

Group No.	Sample Collection Time Points (Time Postdose) on Days 1 and 176						
	0[a] hr	1 hr	8 hr	24 hr[b]	72 hr[b]	120 hr[b]	168 hr[b]
1	X	X	X	X	X	X	X
2	X	X	X	X	X	X	X
3	X	X	X	X	X	X	X

x = sample collected; hr = hour
[a] Sample was collected before dosing on Day 176 only.
[b] Samples collected at ≥24 hours postdose were collected at ±1 hour of target time.

Systemic exposure (mean C_{max} and $AUC_{0\text{-}168hr}$) increased with increasing dose on Days 1 and 176. The increase in exposure between 10 and 100 mg/kg was roughly dose proportional on Day 1 but not on Day 176 because of suspected ADA at both dose levels. No apparent gender differences in systemic exposure were observed except at 10 mg/kg dose group on Day 176 where exposure was approximately 1.9-fold higher in females compared to males due to the high incidence of suspected ADA in males in this group. Following repeated administration of LY3074828, the individual $AUC_{0\text{-}168hr}$ values on Day 176 were similar compared to Day 1 but were reduced in animals with

suspected ADA, and the accumulation ratios ranged from 0.243 to 1.71. The following table (from page 37 of the report) shows the TK parameters.

Parameter	Administered Dose (mg/kg)			
	10		100	
Sex	Male (n = 4)[a]	Female (n = 4)	Male (n = 4)	Female (n = 4)[b]
LY3074828				
Day 1				
T_{max} (Hours)	16.0 ± 9.24	16.0 ± 9.24	24.0 ± 0.00	20.0 ± 8.00
C_{max} (µg/mL)	35.7 ± 11.8	38.5 ± 8.53	329 ± 96.3	288 ± 103
AUC_{0-168} (µg*Hours/mL)	2420 ± 733	2310 ± 632	21900 ± 1300	16300 ± 6590
$T_{1/2}$ (Hours)	34.6 ± 7.00	30.8 ± 7.19	45.3 ± 12.1	32.6 ± 5.27
Day 176				
T_{max} (Hours)	24.0 ± ID	16.0 ± 9.24	36.0 ± 24.0	24.0 ± 0.00
C_{max} (µg/mL)	23.2 ± ID	43.8 ± 9.78	417 ± 252	287 ± 216
AUC_{0-168} (µg*Hours/mL)	1580 ± ID	2990 ± 744	25000 ± 11500	17900 ± 15200
$T_{1/2}$ (Hours)	30.6 ± ID	32.7 ± 4.22	31.5 ± 10.6	31.6 ± ID

T_{max} Time of maximum observed concentration
C_{max} Maximum observed concentration
AUC_{0-168} Area under the Curve during the dosing interval
$T_{½}$ Terminal elimination half-life
ID Insufficient data

[a] n = 2 on Day 176; TK parameters were not calculated for Animal Nos. 2002 and 2004 because LY3074828 serum concentrations were <LOQ (0.2 µg/mL) at all time points on Day 176.

[b] n = 3 on Day 176; TK parameters were not calculated for Animal No. 3502 because LY3074828 serum concentrations were <LOQ (0.2 µg/mL) at all time points on Day 176.

Dosing Solution Analysis: Concentration analysis was performed on dose formulations prepared for Weeks 1, 9, 18, and 26. Samples were analyzed using a validated UV method for protein content. Formulations were considered acceptable if mean results were within ± 10% of the theoretical concentration and the relative standard deviation (RSD) was equal to or less than 6.0%.

Mean LY3074828 concentrations for dose formulations sampled and used at Weeks 1, 9, 18, and 26 ranged from 98.6% to 102.6% of theoretical values (shown in the table below from page 36 of the report).

Group No.	Week 1		Week 9		Week 18		Week 26	
	Conc. (mg/mL)	RSD (%)	Conc. (mg/mL)	RSD (%)	Conc. (mg/mL)	RSD (%)	Conc. (mg/mL)	RSD (%)
1	0	NA	0	NA	0	NA	0	NA
2	5.13	0.4	5.04	0.1	5.00	0.3	4.93	0.6
3	49.7	0.1	49.5	0.1	49.4	0.1	49.4	0.1

Stability analysis results indicated that the test material was stable over the course of the study (shown in the table below from page 36 of the report).

Parameter	Start of dosing phase	End of dosing phase
Protein content	53.6 mg/mL	53.2 mg/mL
Purity	95.0%	96.9%
pH	5.972	6.506
Appearance	Colorless, clear	Colorless, clear

7 Genetic Toxicology

Genotoxicity studies are not typically appropriate for biotechnology-derived antibody products and were not conducted with LY3074828 [ICH S6(R1)].

8 Carcinogenicity

Carcinogenicity studies have not been conducted. The Sponsor stated that a carcinogenicity assessment will be conducted at the appropriate stage of development per the ICH Guidance.

9 Reproductive and Developmental Toxicology

For the assessment of male and female fertility, sexually mature monkeys were used in the 6-month repeat dose toxicity study (Report 20043324). Sexual maturity was established prior to assignment to study via documentation of menstrual cycling in females and assessment of semen parameters (concentration and motility), testes volume, and serum testosterone levels in males. The fertility assessment was based on the microscopic pathology of reproductive organs and tissues consistent with the ICH S6(R1) guidance. Embryofetal development studies have not been conducted. However, embryofetal development studies will be conducted at the appropriate stage of development per the ICH Guidance.

10 Special Toxicology Studies

Tissue Cross-Reactivity of LY3074828 with Human and Cynomolgus Monkey Tissues Ex Vivo (20029154)

Methods: The objective of this study was to determine the tissue cross-reactivity of LY3074828 with cryosections of human and non-human primate (cynomolgus monkey) tissues. In this study, LY3074828 was applied to cryosections from a full panel of tissues from both species and immunohistochemically detected using a biotinylated mouse anti-human immunoglobulin G4 (IgG4) secondary antibody and visualized with a streptavidin-horseradish peroxidase (HRP) complex and a diaminobenzidine (DAB)

chromogen substrate. LY3074828-binding was evaluated at concentrations of 5 and 25 µg/mL. Chinese hamster ovary (CHO) cells transfected to express IL-23 were used as positive control sample in all experiments. Parental CHO cells were used as negative control.

Results: Specific LY3074828 binding was observed at 5 µg/mL and 25 µg/mL in all positive controls. No specific LY3074828 binding was observed at 5 and 25 µg/mL in any negative control, demonstrating the specificity of the LY3074828 staining.

LY3074828 Binding in Human Tissues:

Questionable LY3074828 staining was observed in multiple human tissues and consisted of minimal to moderate intensity cytoplasmic staining of mucous epithelial cells (colon, small intestine, stomach, parotid gland, and uterus). The most consistent staining was observed in the cytoplasm of mucous epithelial cells in the colon (occasional to frequent in all 3 samples at 5 and/or 25µg/mL concentrations) and small intestine (rare to frequent in all 3 samples at 5 and/or 25 µg/mL concentrations). Inconsistent epithelial cell staining was observed in 2 uterus (cervix) samples (25 µg/mL concentration only) and 1 sample each of parotid salivary gland and stomach (25 µg/mL concentration only). Although similar staining was not observed in isotype controls, per the Sponsor, mucous cells often considered sources of nonspecific staining in immunohistochemistry studies. Because nonspecific staining of mucous cells was observed with LY3074828 in cynomolgus monkey tissues and because staining of mucous cells in some of the human tissues (uterus [cervix], parotid gland, and stomach) was observed only at the high (25 µg/mL) protein concentration, this staining pattern was considered most likely nonspecific in nature.

Minimal to mild intensity rare or occasional staining of hyalinized vessel walls was observed in one fallopian tube sample. Because the intensity and frequency of staining increased with increased protein concentration and because staining was observed in only one sample, this staining was considered likely to be nonspecific. Mild intensity rare staining in dermal keratin in all 3 skin samples (5 and 25 µg/mL concentrations) was also considered likely nonspecific. Although similar staining was not observed in the skin isotype control tissues, similar nonspecific keratin staining was observed in isotype control samples of the thymus.

LY3074828 Binding in Cynomolgus Monkey Tissues:

Specific LY3074828 staining was not observed in cynomolgus monkey tissues. Questionable LY3074828 staining was observed inconsistently in mucous epithelial cells in the colon (1 sample at both protein concentrations), small intestine (2 samples at 25 µg/mL concentration only), and 2 lung samples (25 µg/mL concentration only). Because similar staining was observed in isotype controls for other colon samples, and because the staining was observed only at the high (25 µg/mL) protein concentration in the small intestine and lung, this staining was considered likely nonspecific.

Overall, in this tissue cross-reactivity study, there was no significant specific staining in any human or cynomolgus monkey tissues with LY3074828. Questionable, likely nonspecific, staining was observed in mucous epithelial cells in a variety of human and monkey samples.

11 Integrated Summary and Safety Evaluation

LY3074828 is a humanized anti-interleukin-23 (IL-23) IgG4 monoclonal antibody. This drug is being developed for the treatment of ulcerative colitis (UC). IL-23 is considered to be involved in the pathogenesis of UC. This IND was submitted to initiate a Phase 2 study with LY3074828 in patients with moderate to severe UC.

The Sponsor proposed to conduct a Phase 2, multicenter, randomized, double-blind, parallel, placebo-controlled study (Study I6T-MC-AMAC, [AMAC]) in patients with moderate to severe UC. In the 12-week induction period, LY3074828 will be administered by IV infusion at Weeks 0, 4, and 8 at 50 mg (0.8 mg/kg), 200 mg (3.3 mg/kg), or 600 mg (10 mg/kg). In the maintenance period, patients will be treated at 200 mg dose administered subcutaneously (SC) every 4 weeks (Q4W) or every 12 weeks (Q12W) for 40 weeks (total up to 52 weeks treatment duration).

The Sponsor submitted the following nonclinical studies in this IND: pharmacology, 4-week IV/SC toxicity study and a 6-month SC toxicity study in cynomolgus monkeys and tissue cross reactivity study.

In pharmacology studies, LY3074828 was examined in a variety of in vitro and in vivo assays to determine the binding affinity to IL-23, its ability to block the interaction of IL-23 binding to its receptor, and its interaction with Fcγ receptors. In addition, LY3074828 was evaluated for its ability to block the in vivo human IL23-induced activities using two different in vivo pharmacodynamic assays. LY3074828 binds with high affinity to human and cynomolgus monkey IL-23 but does not bind to other IL-12 family members or rodent IL-23. LY3074828 neutralized human and cynomolgus monkey IL-23-induced activity in in vitro functional assays. In an acute systemic in vivo neutralization assay in mice, LY3074828 inhibited human IL-23-induced IL-17 production. LY3074828 also inhibited human IL-23-induced IL-17A, IL-17F, and keratin-16 mRNA production in an acute local in vivo neutralization assay. LY3074828 inhibited binding of IL-23 to the IL-23 receptor. LY3074828/IL-23 complex did not interfere with IL-12 signaling. LY3074828 also did not interact with Fc receptors or bind C1q; therefore, it is expected to have little or no effector function. As LY3074828 does not bind to rodent IL-23, a mouse surrogate antibody (LSN2479016) was developed to neutralize mouse IL-23 for use in preclinical disease models. Neutralization of IL-23 using LSN2479016 demonstrated efficacy in two murine models of inflammatory bowel disease. No significant treatment related adverse effects on cardiovascular, central nervous, or respiratory system safety pharmacology endpoints were observed at 30 mg/kg SC or 100 mg/kg IV doses.

In a 4-week IV/SC study in cynomolgus monkeys, LY3074828 was administered at 1, 30 and 100 mg/kg (IV) once weekly for 4 consecutive weeks (5 total doses). The NOAEL for each route of administration was the highest dose tested, 30 mg/kg SC and 100 mg/kg IV. In a 6-month subcutaneous toxicity study in cynomolgus monkeys, LY3074828 was administered at 0, 10 and 100 mg/kg once weekly. The NOAEL was considered as 100 mg/kg. It is to be noted here that two dose levels were used in the 6-month study. At least three dose levels should have been tested. In these studies, minimal, perivascular mononuclear cell or mononuclear and eosinophil cell infiltrates were observed in the subcutis in the subcutaneous injection sites in animals given SC doses of 1 mg/kg or greater. There were no LY3074828-related microscopic findings at the injection site in animals administered IV dose of 100 mg/kg. These injection site changes were not considered adverse. In an ex vivo tissue cross-reactivity study, there was no significant specific staining in any human or cynomolgus monkey tissues with LY3074828.

The NOAEL of 100 mg/kg in the 6-month toxicity study in monkeys provide adequate (10-fold) margin of safety for the proposed highest dose of 600 mg (10 mg/kg). Therefore, from a nonclinical perspective, the proposed clinical study appears to be safe to proceed.

12 Appendix/Attachments

None

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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08/21/2015

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