Protocol J1P-MC-KFAH(b)

An Adaptive Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of LY3471851 (NKTR-358) in Patients with Moderately to Severely Active Ulcerative Colitis

NCT04677179

Approval Date: 03-Jun-2021

Title Page

Protocol Title: An Adaptive Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of LY3471851 (NKTR-358) in Patients with Moderately to Severely Active Ulcerative Colitis

Protocol Number: J1P-MC-KFAH

Amendment Number: b

Compound: LY3471851

Study Phase: 2

Acronym: INSTRUCT-UC

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Numbers:

IND: 151216

EudraCT: 2020-003017-35

Approval Date: Protocol Amendment (b) Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 03-Jun-2021 GMT

The medical monitor name and contact information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment (a)	18 November 2020
Original Protocol	03 September 2020

Amendment b
This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The main purpose of this protocol amendment is to modify the study entry criteria and dose preparation for site clarification.

Section Number and Name	Description of Change	Brief Rationale
5.1. Inclusion Criteria	Added Note to clarify Inclusion Criterion 6	For site clarification
5.4.2 Rescreening of Individuals Who Fail Screening	Updated table to reflect Exclusion Criterion 42	For site clarification
6.1 Study Interventions Administered	Dose Preparation	For site clarification

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title: An Adaptive Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of LY3471851 (NKTR-358) in Patients with Moderately to Severely Active Ulcerative Colitis

Rationale

LY3471851 (also known as NKTR-358) is a polyethylene glycol (PEG)-conjugated recombinant human interleukin (IL)-2 (rhIL-2) with the capacity to promote the expansion and activation of regulatory T cells (Tregs) with relatively minimal effect on conventional T cells (Tcons). In preliminary clinical studies, other IL-2 formulations (aldesleukin and ILT-101), which are hypothesized to have a mechanism of action similar to that of LY3471851, were associated with an expansion of peripheral Tregs and biological response in patients with ulcerative colitis (UC).[1,2] As compared to those formulations, PEGylation results in prolonged systemic exposure and improved binding to the high-affinity IL-2 receptor most present on Tregs.

Study J1P-MC-KFAH (KFAH) is a Phase 2 study to evaluate the efficacy and safety of multiple dose levels of LY3471851 in adult patients with moderately to severely active UC who have an inadequate response to, loss of response to, or are intolerant to conventional UC therapy ("conventional-failed") or to advanced UC therapy ("advanced therapy-failed"). For this study, conventional UC therapy is defined as corticosteroids, azathioprine (AZA), or 6-mercaptopurine (6-MP). Results of this study will be used to guide the dose selection for future studies and to further characterize the benefit/risk profile of LY3471851.

Objectives and Endpoints

Objectives	Estimands/Endpoints
Primary	
• To determine whether LY3471851 is superior to placebo in inducing clinical remission in participants with moderately to severely active UC	The study will compare LY3471851 with placebo in participants with moderately to severely active UC. The primary comparison of interest is the difference in the proportion of participants who achieve clinical remission at Week 12. The primary comparison will be assessed using a composite estimand where the intercurrent events that lead to permanent discontinuation of assigned study treatment are part of the response definition.
Secondary	
• To evaluate the efficacy of induction treatment with LY3471851 compared to placebo with respect to clinical, endoscopic, and histologic improvement	Secondary comparisons of interest are the difference between LY3471851 and placebo in the proportion of participants who have not permanently discontinued at Week 12 and have achieved at Week 12: • clinical response • endoscopic remission

Objectives	Estimands/Endpoints
	• endoscopic response • symptomatic remission • symptomatic response • histologic remission • histologic-endoscopic mucosal healing Secondary comparisons with binary endpoints will use a composite estimand as described for the primary comparison.
• To evaluate the efficacy of maintenance treatment with LY3471851 compared to placebo with respect to clinical, endoscopic, and histologic improvement	Secondary comparisons of interest include the difference between LY3471851 and placebo in the proportion of participants who were responders at Week 12 (Week 12 Responders) and have not permanently discontinued at Week 52, who at Week 52 still have • clinical remission • clinical response • endoscopic remission • endoscopic response • symptomatic remission • symptomatic response • histologic remission • histologic-endoscopic mucosal healing Secondary comparisons with binary endpoints will use a composite estimand as described for the primary comparison.
• To evaluate the efficacy of treatment with LY3471851 compared to placebo with respect to patient-reported outcomes and quality of life measures	Comparison of mean changes from baseline to Week 12 and to Week 52 in scores for • IBDQ • Urgency NRS • Abdominal Pain NRS • Nocturnal Stools • Bristol Stool Scale • PGR-S • Fatigue NRS Secondary comparisons with continuous endpoints will use a hypothetical efficacy estimand strategy to address the intercurrent events of early discontinuation to assess the effect of study treatment in a hypothetical trial where all participants have complete data and continue to take study treatment without discontinuing from the study.

Objectives	Estimands/Endpoints
• To evaluate the PK of LY3471851	• Week 12 LY3471851 trough concentrations
CCI	

Abbreviations: CCI IBDQ = Inflammatory Bowel Disease Questionnaire; NRS = numeric rating scale; PGR-S = Patient's Global Rating of Severity; UC = ulcerative colitis; CCI

Overall Design

Study KFAH is an adaptive Phase 2 multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of multiple dose levels of LY3471851 in adult patients with moderately to severely active UC.

The study duration for an individual participant will be approximately 63 weeks.

- Screening: a period lasting up to 5 weeks
- Induction Period: a 12-week double-blind treatment period
- Maintenance Period: a 40-week blinded period for Week 12 Responders

  Note: Week 12 Nonresponders enter an extension, inclusive of extension induction and extension maintenance periods, with treatment for a total of 52 weeks.
- Post-treatment Follow-up: a period lasting approximately 6 weeks

Disclosure Statement: This is a parallel study with an adaptive design involving multiple treatment groups. The study is participant-blinded and investigator-blinded.

Number of Participants: Approximately 200 participants may be randomized across all study stages.

Intervention Groups and Duration

This is an adaptive study with 2 stages. During Stage 1, approximately 100 participants may be enrolled. The intervention groups in Stage 1 are

- CCI µg LY3471851 Q2W SC
- CCI µg LY3471851 Q2W SC, and
- placebo

During Stage 2, approximately 100 additional participants may be enrolled. Based on results of an interim analysis, the intervention groups in Stage 2 may include

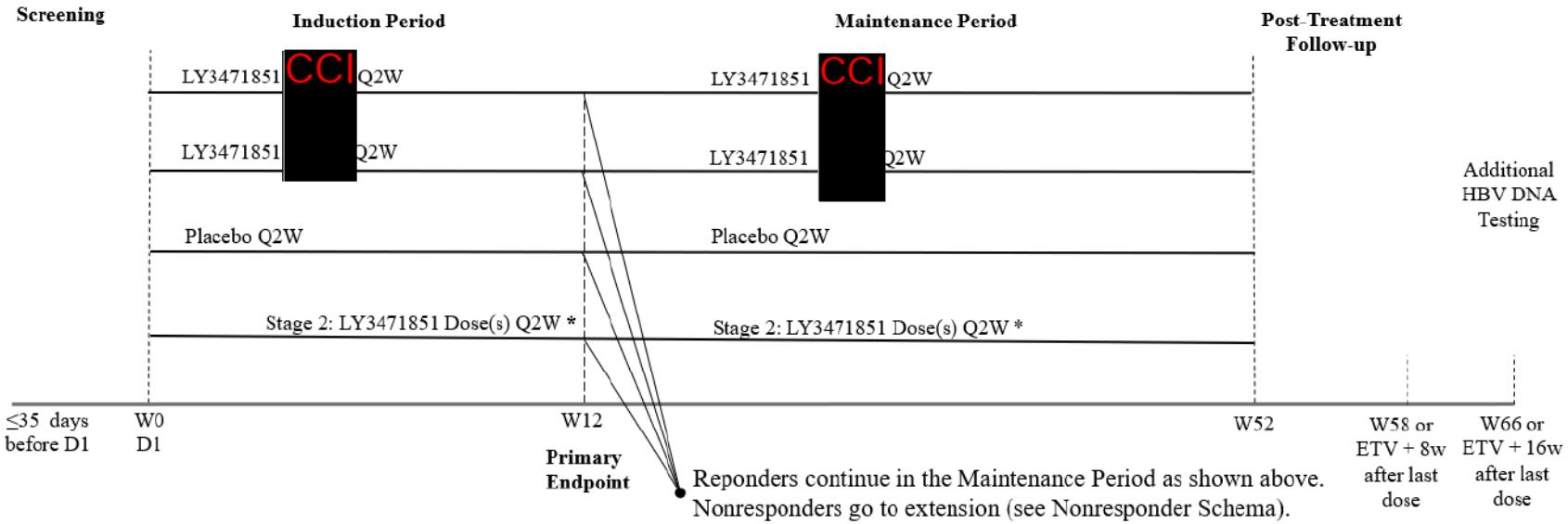
- placebo
- 1, 2, or none of the LY3471851 doses listed for Stage 1, as well as possibly
- 1 or more additional LY3471851 doses, not exceeding CCI µg; also given Q2W SC.

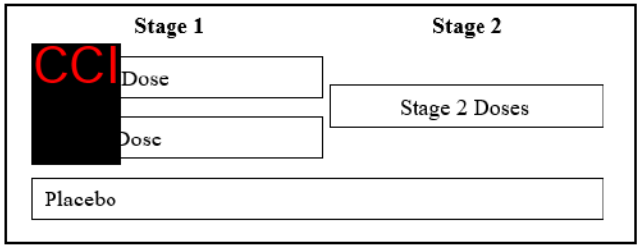
For any individual study participant, the maximum duration of study treatment is 52 weeks.

Data Monitoring Committee: No

1.2. Schema

Trial Schema

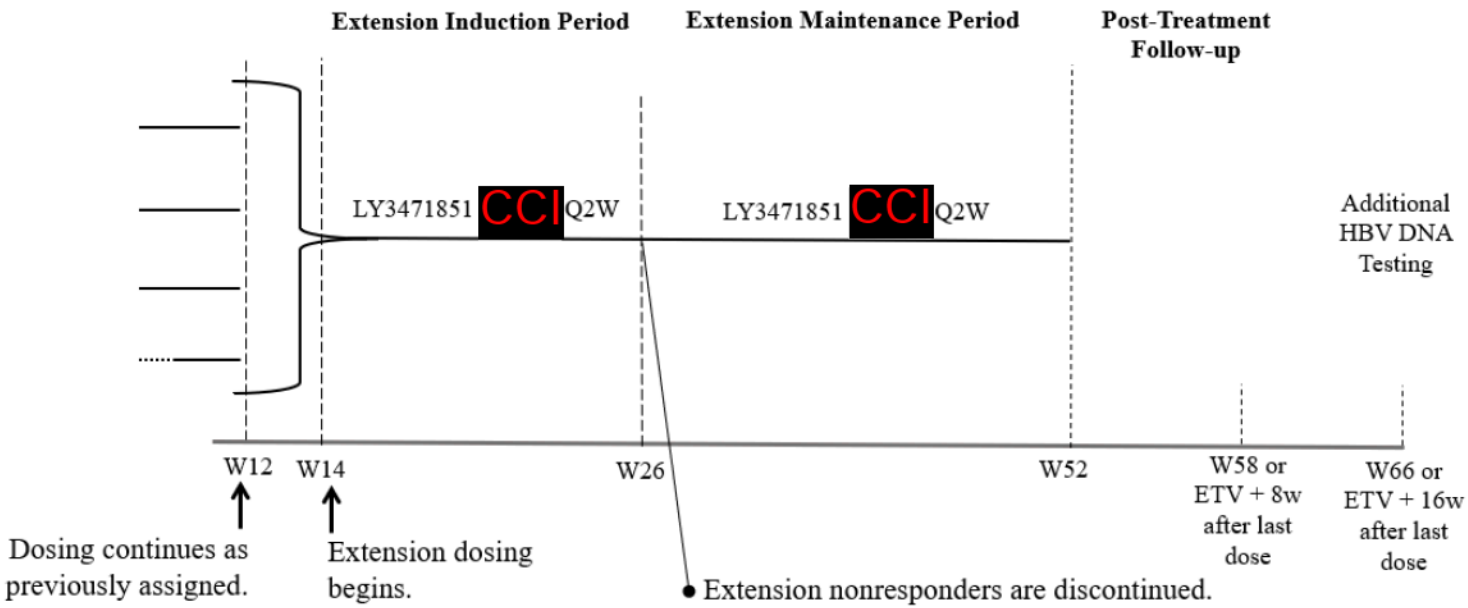




* In Stage 1, two LY doses and placebo are used. In Stage 2, one or more new LY doses may be added via seamless adaptation based on interim analyses; these new doses may be lower than CCI or no greater than CCI

Abbreviations: D = day; DNA = deoxyribonucleic acid; ETV = early termination visit; HBV = hepatitis B virus; LY = LY3471851; Q2W = every 2 weeks; W = Week; w = weeks.

Nonresponder Schema



Abbreviations: DNA = deoxyribonucleic acid; ETV = early termination visit; HBV = hepatitis B virus; Q2W = every 2 weeks; W = Week; w = weeks.

Note: The extension dose could be lower than CCI µg LY3471851, based on interim analyses.

1.3. Schedule of Activities (SoA)

1.3.1. Schedule of Activities for the Screening and Induction Treatment Periods

Table 1. Schedule of Activities for the Screening and Induction Treatment Periods of Study J1P-MC-KFAH

V1 and V9 procedures may be conducted over more than 1 day as long as all activities are completed within the allowable visit tolerance and all scheduled activities are completed prior to dosing.
For procedures at an ETV, see ETV in Table 4.
For procedures at an unscheduled visit, see V997 in Table 4.

Visit number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**Comment**
Weeks from randomization	–5	—	1	2	4	6	8	10	12	
Study day	—	1	8	15	29	43	57	71	85	
Visit interval tolerance (days)	≤35 before V2	—	±3	±3	±3	±3	±3	±3	±3	
Fasting visit		**X**							**X**	
Informed consent	X									
Site staff explains, participant reports remission/normal stool frequency	X									The purpose of UC remission question should be explained before the participant answers the question. Errors in the response cannot be corrected after the participant saves and confirms the response.
Inclusion and exclusion criteria, review and confirm	X	X								
Demographics	X									
Preexisting conditions and medical history	X									Includes relevant surgical history.
Prespecified medical history	X									Indication and history of interest.
Prior treatments for indication	X									Includes all UC-specific therapies since date of diagnosis.
Concomitant medications	X	X	X	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	X	For AESIs, additional data are collected (Section 8.3.6).
Review modified Mayo score (MMS)		X							X	
Tobacco use	X								X	
Alcohol and caffeine use	X									

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Weeks from randomization	–5	—	1	2	4	6	8	10	12	
Study day	—	1	8	15	29	43	57	71	85	
Visit interval tolerance (days)	≤35 before V2	—	±3	±3	±3	±3	±3	±3	±3	
Fasting visit		**X**							**X**	
Physical Evaluation										
Height	X									Participant should remove shoes.
Weight	X								X	
Vital signs	X	X	X	X	X	X	X	X	X	Blood pressure, body temperature, and pulse rate. Vital signs should be measured after participant has been sitting at least 5 minutes.
Physical examination	X									The complete physical exam excludes pelvic, rectal, and breast exams, unless clinically indicated, and includes assessment for signs and symptoms of tuberculosis (TB), including peripheral lymph nodes. See Section 8.2.2.
Symptom-directed physical examination, including assessment for signs and symptoms of tuberculosis (TB), including peripheral lymph nodes		X							X	See Section 8.2.2.
[redacted]	X	X			X		X		X	
12-lead electrocardiogram (ECG)	X								X	Locally performed.

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Weeks from randomization	–5	—	1	2	4	6	8	10	12	
Study day	—	1	8	15	29	43	57	71	85	
Visit interval tolerance (days)	≤35 before V2	—	±3	±3	±3	±3	±3	±3	±3	
Fasting visit		**X**							**X**	
Chest x-ray (posterior-anterior view)	X									Interpreted and reported by radiologist or pulmonologist. Not done at screening if done within 3 months before screening and if qualifying radiographs or equivalent imaging study and/or formal report are available for investigator's review. Lateral view may also be taken. Locally performed.
Patient Diary (Electronic)										
Patient diary dispensed	X									
Diary compliance check		X	X	X	X	X	X	X	X	Check compliance for Stool Frequency Rectal Bleeding Nocturnal Stools Bristol Stool Scale Urgency NRS Abdominal Pain NRS Fatigue NRS, and Patient Global Rating of Severity (PGR-S).
Patient-Reported Outcomes (Electronic)										
Inflammatory Bowel Disease Questionnaire (IBDQ)		X							X	

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Study day	—	1	8	15	29	43	57	71	85	
Visit interval tolerance (days)	≤35 before V2	—	±3	±3	±3	±3	±3	±3	±3	
Fasting visit		**X**							**X**	
Patient Global Impression of Change (PGI-C)									X	
QIDS-SR16		X							X	
Clinician-Administered Questionnaires (Paper)										
Physician's Global Assessment (PGA)	X								X	
C-SSRS Screening/Baseline	X									Adapted for the assessment of ideation and behavior categories only.
Self-Harm Supplement Form	X									
Self-Harm Follow-Up Form	X									Required if triggered by the Self-Harm Supplement Form per instructions.
Laboratory Tests and Sample Collections										
Hematology	X	X	X	X	X	X	X	X	X	
Clinical chemistry	X	X	X	X	X	X	X	X	X	
Lipid panel		X							X	Fasting samples are preferred, but if participant is non fasting at time of collection, this is not a protocol deviation.
Urinalysis		X			X		X		X	
Serum pregnancy	X									Perform only for women of childbearing potential and women with a history of tubal ligation.

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Weeks from randomization	–5	—	1	2	4	6	8	10	12	
Study day	—	1	8	15	29	43	57	71	85	
Visit interval tolerance (days)	≤35 before V2	—	±3	±3	±3	±3	±3	±3	±3	
Fasting visit		**X**							**X**	
Urine pregnancy (local)		X			X		X		X	Perform only for women of childbearing potential and women with a history of tubal ligation. At dosing visits which have pregnancy testing, the pregnancy test result must be confirmed to be negative prior to dosing. Pregnancy testing may be performed more frequently than designated on the SoA, if local laws or regulations require more frequent testing.
Follicle-stimulating hormone (FSH)	X									Optional, perform only for women not of childbearing potential to confirm postmenopausal status.
CCI		X	X	X	X	X	X	X	X	
Tuberculosis (TB) test	X									Patients who had a tuberculin skin test (TST) will return from 48 to 72 hours after placement to have the test result read. Samples may be sent to central or local laboratory based on the type of test. A local laboratory must be qualified by local regulations.
Human immunodeficiency virus (HIV) screening tests	X									
Hepatitis C virus (HCV) screening tests	X									HCV RNA will be measured to confirm positive hepatitis C virus antibody.
Hepatitis B virus (HBV) screening tests	X									Includes testing for HBsAg and anti-HBc.

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For procedures at an unscheduled visit, see V997 in Table 4.

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Weeks from randomization	–5	—	1	2	4	6	8	10	12	
Study day	—	1	8	15	29	43	57	71	85	
Visit interval tolerance (days)	≤35 before V2	—	±3	±3	±3	±3	±3	±3	±3	
Fasting visit		**X**							**X**	
HBV DNA	X								X	Only for participants who are positive for anti-HBc at screening.
Pharmacokinetic (PK) samples		X	X	X	X		X		X	Collect samples before dosing, if dosing is scheduled. Collect additional samples at specified times relative to onset of hypersensitivity events.
CCI		X		X	X		X		X	Collect samples before dosing, if dosing is scheduled. Collect additional samples at specified times relative to onset of hypersensitivity events.
Flow cytometry panel		X		X					X	
Genetics sample		X								Blood sample for DNA pharmacogenetics can be obtained any time at or after V2.
CCI		X			X		X		X	
Endoscopic Procedure										
Endoscopy	X								X	Screening endoscopy must occur ≤14 days prior to randomization. At screening, perform only for participants who are eligible for the study by all other study entry criteria.
Colon biopsy sample collection	X								X	Performed at time of endoscopy. Instructions for collection are provided in the lab manual. Flexible sigmoidoscopy is recommended, except for protocol-specified reasons when a colonoscopy should be performed.

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V1 and V9 procedures may be conducted over more than 1 day as long as all activities are completed within the allowable visit tolerance and all scheduled activities are completed prior to dosing.
For procedures at an ETV, see ETV in Table 4.
For procedures at an unscheduled visit, see V997 in Table 4.

Visit number	V1	V2	V3	V4	V5	V6	V7	V8	V9	Comment
Weeks from randomization	–5	—	1	2	4	6	8	10	12	
Study day	—	1	8	15	29	43	57	71	85	
Visit interval tolerance (days)	≤35 before V2	—	±3	±3	±3	±3	±3	±3	±3	
Fasting visit		**X**							**X**	
Stool Samples										
Stool culture	X									Additional local stool testing (for example, for ova and parasites) is allowed at the investigator's discretion.
C. difficile testing	X									Additional *C. difficile* testing is allowed throughout the study at the investigator's discretion.
CCI		X			X		X		X	
		X			X		X		X	
Randomization and Dosing										
Randomization		X								
Dosing		X		X	X	X	X	X	X	No dosing at V3.

Abbreviations: AESIs = adverse event of special interest; anti-HBc = antibody to hepatitis B core antigen; C-SSRS = Columbia–Suicide Severity Rating Scale; DNA = deoxyribonucleic acid; ETV = early termination visit; NRS = numeric rating scale; HBsAg = hepatitis B surface antigen; QIDS-SR16 = 16-Item Quick Inventory of Depressive Symptomatology–Self Report; RNA = ribonucleic acid; SoA = schedule of activities; UC= ulcerative colitis; V = visit.

1.3.2. Schedule of Activities for the Maintenance Treatment Period

Table 2. Schedule of Activities for the Maintenance Treatment Period of Study J1P-MC-KFAH

This schedule applies to study participants who are **responders** at Week 12.
For procedures at an ETV, see ETV in Table 4.
For procedures at an unscheduled visit, see V997 in Table 4.
Visits 10 through 28 are eligible to be conducted remotely (that is, by telephone, IT-assisted virtual visit, mobile healthcare, or a combination thereof), if written approval is provided by the sponsor and according to the preferences of the participant and the study site. However, no more than 34 days can elapse without an on-site study visit occurring.

Visit number	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**Comment**
Weeks from randomization	14	16	18	20	22	24	26	28	30	32	
Study day	99	113	127	141	155	169	183	197	211	225	
Visit interval tolerance (days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Fasting visit						**X**					
Concomitant medications	X	X	X	X	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	X	X	For AESIs, additional data are collected (Section 8.3.6).
Tobacco use						X					
Physical Evaluation											
Weight						X					
Vital signs	X	X	X	X	X	X	X	X	X	X	Blood pressure, body temperature, and pulse rate. Vital signs should be measured after participant has been sitting for at least 5 minutes.
Symptom-directed physical examination, including assessment for signs and symptoms of tuberculosis (TB), including peripheral lymph nodes						X					See Section 8.2.2.
CCI						X					
12-lead electrocardiogram (ECG)						X					Locally performed.
Patient Diary (Electronic)											

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This schedule applies to study participants who are **responders** at Week 12.
For procedures at an ETV, see ETV in Table 4.
For procedures at an unscheduled visit, see V997 in Table 4.
Visits 10 through 28 are eligible to be conducted remotely (that is, by telephone, IT-assisted virtual visit, mobile healthcare, or a combination thereof), if written approval is provided by the sponsor and according to the preferences of the participant and the study site. However, no more than 34 days can elapse without an on-site study visit occurring.

Visit number	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**Comment**
Weeks from randomization	14	16	18	20	22	24	26	28	30	32	
Study day	99	113	127	141	155	169	183	197	211	225	
Visit interval tolerance (days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Fasting visit						**X**					
Diary compliance check	X	X	X	X	X	X	X	X	X	X	Check compliance for Stool Frequency Rectal Bleeding Nocturnal Stools Bristol Stool Scale Urgency NRS Abdominal Pain NRS Fatigue NRS, and Patient Global Rating of Severity (PGR-S).
Patient-Reported Outcomes (Electronic)											
Inflammatory Bowel Disease Questionnaire (IBDQ)						X					
Patient Global Impression of Change (PGI-C)						X					
QIDS-SR16						X					
Laboratory Tests and Sample Collections											
Hematology		X		X		X		X		X	
Clinical chemistry		X		X		X		X		X	

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For procedures at an unscheduled visit, see V997 in Table 4.
Visits 10 through 28 are eligible to be conducted remotely (that is, by telephone, IT-assisted virtual visit, mobile healthcare, or a combination thereof), if written approval is provided by the sponsor and according to the preferences of the participant and the study site. However, no more than 34 days can elapse without an on-site study visit occurring.

Visit number	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**Comment**
Weeks from randomization	14	16	18	20	22	24	26	28	30	32	
Study day	99	113	127	141	155	169	183	197	211	225	
Visit interval tolerance (days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Fasting visit						**X**					
Lipid panel						X					Fasting samples are preferred, but if participant is nonfasting at time of collection, this is not a protocol deviation.
Urinalysis		X		X		X					
Urine pregnancy (local)		X		X		X		X		X	Perform only for women of childbearing potential and women with a history of tubal ligation. At dosing visits which have pregnancy testing, the pregnancy test result must be confirmed to be negative prior to dosing. Pregnancy testing may be performed more frequently than designated on the SoA, if local laws or regulations require more frequent testing.
CCI						X					
HBV DNA						X					Only for participants who are positive for anti-HBc at screening.
Pharmacokinetic (PK) samples						X					Collect samples before dosing, if dosing is scheduled. Collect additional samples at specified times relative to onset of hypersensitivity events.

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Visit number	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**Comment**
Weeks from randomization	14	16	18	20	22	24	26	28	30	32	
Study day	99	113	127	141	155	169	183	197	211	225	
Visit interval tolerance (days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Fasting visit						**X**					
CCI						X					Collect samples before dosing, if dosing is scheduled. Collect additional samples at specified times relative to onset of hypersensitivity events.
Flow cytometry panel						X					
Genetics sample											Blood sample for DNA pharmacogenetics can be obtained any time at or after V2.
CCI						X					
Endoscopic Procedure											Not applicable for responders during the time period of V10 through V19
Stool Samples											
CCI						X					
						X					
Randomization and Dosing											
Dosing	X	X	X	X	X	X	X	X	X	X	

Table 2 (continued). Schedule of activities for the Maintenance Treatment Period of Study J1P-MC-KFAH

This schedule applies to study participants who are **responders** at Week 12.
For procedures at an early termination visit, see ETV in Table 4.
For procedures at an unscheduled visit, see V997 in Table 4.
Visits 10 through 28 are eligible to be conducted remotely (that is, by telephone, IT-assisted virtual visit, mobile healthcare, or a combination thereof) if written approval is provided by the sponsor and according to the preferences of the participant and the study site. However, no more than 34 days can elapse without an on-site study visit occurring.

Visit number	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	**V27**	**V28**	**V29**	**Comment**
Weeks from randomization	34	36	38	40	42	44	46	48	50	52	
Study day	239	253	267	281	295	309	323	337	351	365	
Visit interval tolerance (days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Fasting visit										**X**	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	X	X	For AESIs, additional data are collected (Section 8.3.6).
Review modified Mayo score (MMS)										X	
Tobacco use										X	
Physical Evaluation											
Weight										X	
Vital signs	X	X	X	X	X	X	X	X	X	X	Blood pressure, body temperature, and pulse rate. Vital signs should be measured after participant has been sitting for at least 5 minutes.
Symptom-directed physical examination, including assessment for signs and symptoms of tuberculosis (TB), including peripheral lymph nodes		X								X	See Section 8.2.2.
CCI		X								X	
12-lead electrocardiogram (ECG)										X	Locally performed.

Table 2 (continued). Schedule of activities for the Maintenance Treatment Period of Study J1P-MC-KFAH

This schedule applies to study participants who are **responders** at Week 12.

For procedures at an early termination visit, see ETV in Table 4.

For procedures at an unscheduled visit, see V997 in Table 4.

Visits 10 through 28 are eligible to be conducted remotely (that is, by telephone, IT-assisted virtual visit, mobile healthcare, or a combination thereof) if written approval is provided by the sponsor and according to the preferences of the participant and the study site. However, no more than 34 days can elapse without an on-site study visit occurring.

Visit number	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	**V27**	**V28**	**V29**	**Comment**
Weeks from randomization	34	36	38	40	42	44	46	48	50	52	
Study day	239	253	267	281	295	309	323	337	351	365	
Visit interval tolerance (days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Fasting visit										**X**	
Patient Diary (Electronic)											
Diary compliance check	X	X	X	X	X	X	X	X	X	X	Check compliance for Stool Frequency Rectal Bleeding Nocturnal Stools Bristol Stool Scale Urgency NRS Abdominal Pain NRS Fatigue NRS, and Patient Global Rating of Severity (PGR-S).
Diary return										X	
Patient-Reported Outcomes (Electronic)											
Inflammatory Bowel Disease Questionnaire (IBDQ)										X	
Patient Global Impression of Change (PGI-C)										X	
QIDS-SR16										X	
Clinician-Administered Questionnaires (Paper)											
Physician's Global Assessment (PGA)										X	

Table 2 (continued). Schedule of activities for the Maintenance Treatment Period of Study J1P-MC-KFAH

This schedule applies to study participants who are **responders** at Week 12.
For procedures at an early termination visit, see ETV in Table 4.
For procedures at an unscheduled visit, see V997 in Table 4.
Visits 10 through 28 are eligible to be conducted remotely (that is, by telephone, IT-assisted virtual visit, mobile healthcare, or a combination thereof) if written approval is provided by the sponsor and according to the preferences of the participant and the study site. However, no more than 34 days can elapse without an on-site study visit occurring.

Visit number	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	**V27**	**V28**	**V29**	**Comment**
Weeks from randomization	34	36	38	40	42	44	46	48	50	52	
Study day	239	253	267	281	295	309	323	337	351	365	
Visit interval tolerance (days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Fasting visit										**X**	
Laboratory Tests and Sample Collections											
Hematology		X		X		X		X		X	
Clinical chemistry		X		X		X		X		X	
Lipid panel										X	Fasting samples are preferred, but if participant is nonfasting at time of collection, this is not a protocol deviation.
Urinalysis										X	
Urine pregnancy (local)		X		X		X		X		X	Perform only for women of childbearing potential and women with a history of tubal ligation. At dosing visits which have pregnancy testing, the pregnancy test result must be confirmed to be negative prior to dosing. Pregnancy testing may be performed more frequently than designated on the SoA, if local laws or regulations require more frequent testing.
CCI										X	
HBV DNA		X						X			Only for participants who are positive for anti-HBc at screening.

Table 2 (continued). Schedule of activities for the Maintenance Treatment Period of Study J1P-MC-KFAH

This schedule applies to study participants who are **responders** at Week 12.

For procedures at an early termination visit, see ETV in Table 4.

For procedures at an unscheduled visit, see V997 in Table 4.

Visits 10 through 28 are eligible to be conducted remotely (that is, by telephone, IT-assisted virtual visit, mobile healthcare, or a combination thereof) if written approval is provided by the sponsor and according to the preferences of the participant and the study site. However, no more than 34 days can elapse without an on-site study visit occurring.

Visit number	V20	V21	V22	V23	V24	V25	V26	V27	V28	V29	Comment
Weeks from randomization	34	36	38	40	42	44	46	48	50	52	
Study day	239	253	267	281	295	309	323	337	351	365	
Visit interval tolerance (days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Fasting visit										**X**	
Pharmacokinetic (PK) samples		X								X	Collect samples before dosing, if dosing is scheduled. Collect additional samples at specified times relative to onset of hypersensitivity events.
CCI		X								X	Collect samples before dosing, if dosing is scheduled. Collect additional samples at specified times relative to onset of hypersensitivity events.
Flow cytometry panel										X	
Genetics sample											Blood sample for DNA pharmacogenetics can be obtained any time at or after V2.
CCI		X								X	
Endoscopic Procedure											
Endoscopy										X	
Colon biopsy sample collection										X	Performed at time of endoscopy. Instructions for collection are provided in the lab manual. Flexible sigmoidoscopy is recommended, except for protocol-specified reasons when a colonoscopy should be performed.
Stool Samples											
CCI		X								X	
		X								X	

Table 2 (continued). Schedule of activities for the Maintenance Treatment Period of Study J1P-MC-KFAH

This schedule applies to study participants who are **responders** at Week 12.

For procedures at an early termination visit, see ETV in Table 4.

For procedures at an unscheduled visit, see V997 in Table 4.

Visits 10 through 28 are eligible to be conducted remotely (that is, by telephone, IT-assisted virtual visit, mobile healthcare, or a combination thereof) if written approval is provided by the sponsor and according to the preferences of the participant and the study site. However, no more than 34 days can elapse without an on-site study visit occurring.

Visit number	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	**V27**	**V28**	**V29**	**Comment**
Weeks from randomization	34	36	38	40	42	44	46	48	50	52	
Study day	239	253	267	281	295	309	323	337	351	365	
Visit interval tolerance (days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Fasting visit										**X**	
Randomization and Dosing											
Dosing	X	X	X	X	X	X	X	X	X		No dosing at V29.

Abbreviations: AESIs = adverse event of special interest; anti-HBc = antibody to hepatitis B core antigen; DNA = deoxyribonucleic acid; ETV = early termination visit; HBV = hepatitis B virus; IT = information technology; NRS = numeric rating scale; QIDS-SR16 = 16-Item Quick Inventory of Depressive Symptomatology–Self Report; SoA = schedule of activities; V = visit.

1.3.3. Schedule of Activities for the Extension Induction and Extension Maintenance Periods

Table 3. Schedule of Activities for the Extension Induction and Extension Maintenance Treatment Periods of Study J1P-MC-KFAH

This schedule applies to study participants who are **nonresponders** at Week 12.

V16 procedures may be conducted over more than 1 day as long as all activities are completed within the allowable visit tolerance and all scheduled activities are completed prior to dosing

For procedures at an ETV, see ETV in Table 4.

For procedures at an unscheduled visit, see V997 in Table 4.

Visits 17 through 28 are eligible to be conducted remotely (that is, by telephone, IT-assisted virtual visit, mobile healthcare, or a combination thereof) if written approval is provided by the sponsor and according to the preferences of the participant and the study site. However, no more than 34 days can elapse without an on-site study visit occurring.

Visit number	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**Comment**
Weeks from randomization	14	16	18	20	22	24	26	28	30	32	
Study day	99	113	127	141	155	169	183	197	211	225	
Visit interval tolerance (days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Fasting visit							**X**				
Concomitant medications	X	X	X	X	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	X	X	For AESIs, additional data are collected (Section 8.3.6).
Review modified Mayo score (MMS)							X				
Tobacco use							X				
Physical Evaluation											
Weight	X						X				
Vital signs	X	X	X	X	X	X	X	X	X	X	Blood pressure, body temperature, and pulse rate. Vital signs should be measured after participant has been sitting for at least 5 minutes.
Symptom-directed physical examination, including assessment for signs and symptoms of tuberculosis (TB), including peripheral lymph nodes	X						X				See Section 8.2.2.
[redacted]	X		X		X		X				
12-lead electrocardiogram (ECG)	X						X				Locally performed.
Patient Diary (Electronic)											

Table 3. Schedule of Activities for the Extension Induction and Extension Maintenance Treatment Periods of Study J1P-MC-KFAH

This schedule applies to study participants who are **nonresponders** at Week 12.

V16 procedures may be conducted over more than 1 day as long as all activities are completed within the allowable visit tolerance and all scheduled activities are completed prior to dosing

For procedures at an ETV, see ETV in Table 4.

For procedures at an unscheduled visit, see V997 in Table 4.

Visits 17 through 28 are eligible to be conducted remotely (that is, by telephone, IT-assisted virtual visit, mobile healthcare, or a combination thereof) if written approval is provided by the sponsor and according to the preferences of the participant and the study site. However, no more than 34 days can elapse without an on-site study visit occurring.

Visit number	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**Comment**
Weeks from randomization	14	16	18	20	22	24	26	28	30	32	
Study day	99	113	127	141	155	169	183	197	211	225	
Visit interval tolerance (days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Fasting visit							**X**				
Diary compliance check	X	X	X	X	X	X	X	X	X	X	Check compliance for Stool Frequency Rectal Bleeding Nocturnal Stools Bristol Stool Scale Urgency NRS Abdominal Pain NRS Fatigue NRS, and Patient Global Rating of Severity (PGR-S).
Patient-Reported Outcomes (Electronic)											
Inflammatory Bowel Disease Questionnaire (IBDQ)							X				
Patient Global Impression of Change (PGI-C)							X				
QIDS-SR16							X				
Clinician-Administered Questionnaires (Paper)											
Physician's Global Assessment (PGA)							X				

Table 3. Schedule of Activities for the Extension Induction and Extension Maintenance Treatment Periods of Study J1P-MC-KFAH

This schedule applies to study participants who are **nonresponders** at Week 12.

V16 procedures may be conducted over more than 1 day as long as all activities are completed within the allowable visit tolerance and all scheduled activities are completed prior to dosing

For procedures at an ETV, see ETV in Table 4.

For procedures at an unscheduled visit, see V997 in Table 4.

Visits 17 through 28 are eligible to be conducted remotely (that is, by telephone, IT-assisted virtual visit, mobile healthcare, or a combination thereof) if written approval is provided by the sponsor and according to the preferences of the participant and the study site. However, no more than 34 days can elapse without an on-site study visit occurring.

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Weeks from randomization	14	16	18	20	22	24	26	28	30	32	
Study day	99	113	127	141	155	169	183	197	211	225	
Visit interval tolerance (days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Fasting visit							**X**				
Laboratory Tests and Sample Collections											
Hematology	X	X	X	X	X	X	X	X		X	
Clinical chemistry	X	X	X	X	X	X	X	X		X	
Lipid panel							X				Fasting samples are preferred, but if participant is nonfasting at time of collection, this is not a protocol deviation.
Urinalysis	X	X	X	X	X		X				
Urine pregnancy (local)		X		X		X		X		X	Perform only for women of childbearing potential and women with a history of tubal ligation. At dosing visits which have pregnancy testing, the pregnancy test result must be confirmed to be negative prior to dosing. Pregnancy testing may be performed more frequently than designated on the SoA if local laws or regulations require more frequent testing.
CCI	X		X		X		X				

Table 3. Schedule of Activities for the Extension Induction and Extension Maintenance Treatment Periods of Study J1P-MC-KFAH

This schedule applies to study participants who are **nonresponders** at Week 12.

V16 procedures may be conducted over more than 1 day as long as all activities are completed within the allowable visit tolerance and all scheduled activities are completed prior to dosing

For procedures at an ETV, see ETV in Table 4.

For procedures at an unscheduled visit, see V997 in Table 4.

Visits 17 through 28 are eligible to be conducted remotely (that is, by telephone, IT-assisted virtual visit, mobile healthcare, or a combination thereof) if written approval is provided by the sponsor and according to the preferences of the participant and the study site. However, no more than 34 days can elapse without an on-site study visit occurring.

Visit number	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**Comment**
Weeks from randomization	14	16	18	20	22	24	26	28	30	32	
Study day	99	113	127	141	155	169	183	197	211	225	
Visit interval tolerance (days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Fasting visit							**X**				
HBV DNA							X				Only for participants who are positive for anti-HBc at screening.
Pharmacokinetic (PK) samples							X				Collect samples before dosing, if dosing is scheduled. Collect additional samples at specified times relative to onset of hypersensitivity events.
CCI [redacted]							X				Collect samples before dosing, if dosing is scheduled. Collect additional samples at specified times relative to onset of hypersensitivity events.
Flow cytometry panel							X				
Genetics sample											Blood sample for DNA pharmacogenetics can be obtained any time at or after V2.
CCI [redacted]			X				X				
Endoscopic Procedure											
Endoscopy							X				

Table 3. Schedule of Activities for the Extension Induction and Extension Maintenance Treatment Periods of Study J1P-MC-KFAH

This schedule applies to study participants who are **nonresponders** at Week 12.

V16 procedures may be conducted over more than 1 day as long as all activities are completed within the allowable visit tolerance and all scheduled activities are completed prior to dosing

For procedures at an ETV, see ETV in Table 4.

For procedures at an unscheduled visit, see V997 in Table 4.

Visits 17 through 28 are eligible to be conducted remotely (that is, by telephone, IT-assisted virtual visit, mobile healthcare, or a combination thereof) if written approval is provided by the sponsor and according to the preferences of the participant and the study site. However, no more than 34 days can elapse without an on-site study visit occurring.

Visit number	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**Comment**
Weeks from randomization	14	16	18	20	22	24	26	28	30	32	
Study day	99	113	127	141	155	169	183	197	211	225	
Visit interval tolerance (days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Fasting visit							**X**				
Colon biopsy sample collection							X				Performed at time of endoscopy. Instructions for collection are provided in the lab manual. Flexible sigmoidoscopy is recommended, except for protocol-specified reasons when a colonoscopy should be performed.
Stool Samples											
CCI			X				X				
			X				X				
Randomization and Dosing											
Dosing	X	X	X	X	X	X	X	X	X	X	

Table 3 (continued). Schedule of activities for the Extension Induction and Extension Maintenance Treatment Periods of Study J1P-MC-KFAH

This schedule applies to study participants who are **nonresponders** at Week 12.
For procedures at an ETV, see ETV in Table 4.
For procedures at an unscheduled visit, see V997 in Table 4.
Visits 17 through 28 are eligible to be conducted remotely (that is, by telephone, IT-assisted virtual visit, mobile healthcare, or a combination thereof) if written approval is provided by the sponsor and according to the preferences of the participant and the study site. However, no more than 34 days can elapse without an on-site study visit occurring

Visit number	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	**V27**	**V28**	**V29**	**Comment**
Weeks from randomization	34	36	38	40	42	44	46	48	50	52	
Study day	239	253	267	281	295	309	323	337	351	365	
Visit interval tolerance (days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Fasting visit										**X**	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	X	X	For AESIs, additional data are collected (Section 8.3.6).
Review modified Mayo score (MMS)										X	
Tobacco use										X	
Physical Evaluation											
Weight			X							X	
Vital signs	X	X	X	X	X	X	X	X	X	X	Blood pressure, body temperature, and pulse rate. Vital signs should be measured after participant has been sitting for at least 5 minutes.
Symptom-directed physical examination, including assessment for signs and symptoms of tuberculosis (TB), including peripheral lymph nodes			X							X	See Section 8.2.2.
CCI			X							X	
12-lead electrocardiogram (ECG)			X							X	Locally performed.

Table 3 (continued). Schedule of activities for the Extension Induction and Extension Maintenance Treatment Periods of Study J1P-MC-KFAH

This schedule applies to study participants who are **nonresponders** at Week 12.
For procedures at an ETV, see ETV in Table 4.
For procedures at an unscheduled visit, see V997 in Table 4.
Visits 17 through 28 are eligible to be conducted remotely (that is, by telephone, IT-assisted virtual visit, mobile healthcare, or a combination thereof) if written approval is provided by the sponsor and according to the preferences of the participant and the study site. However, no more than 34 days can elapse without an on-site study visit occurring

Visit number	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	**V27**	**V28**	**V29**	**Comment**
Weeks from randomization	34	36	38	40	42	44	46	48	50	52	
Study day	239	253	267	281	295	309	323	337	351	365	
Visit interval tolerance (days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Fasting visit										**X**	
Patient Diary (Electronic)											
Diary compliance check	X	X	X	X	X	X	X	X	X	X	Check compliance for Stool Frequency Rectal Bleeding Nocturnal Stools Bristol Stool Scale Urgency NRS Abdominal Pain NRS Fatigue NRS, and Patient Global Rating of Severity (PGR-S).
Diary return										X	
Patient-Reported Outcomes (Electronic)											
Inflammatory Bowel Disease Questionnaire (IBDQ)										X	
Patient Global Impression of Change (PGI-C)										X	
QIDS-SR16										X	
Clinician-Administered Questionnaires (Paper)											
Physician's Global Assessment (PGA)										X	

Table 3 (continued). Schedule of activities for the Extension Induction and Extension Maintenance Treatment Periods of Study J1P-MC-KFAH

This schedule applies to study participants who are **nonresponders** at Week 12.

For procedures at an ETV, see ETV in Table 4.

For procedures at an unscheduled visit, see V997 in Table 4.

Visits 17 through 28 are eligible to be conducted remotely (that is, by telephone, IT-assisted virtual visit, mobile healthcare, or a combination thereof) if written approval is provided by the sponsor and according to the preferences of the participant and the study site. However, no more than 34 days can elapse without an on-site study visit occurring

Visit number	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	**V27**	**V28**	**V29**	**Comment**
Weeks from randomization	34	36	38	40	42	44	46	48	50	52	
Study day	239	253	267	281	295	309	323	337	351	365	
Visit interval tolerance (days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Fasting visit										**X**	
Laboratory Tests and Sample Collections											
Hematology		X	X	X		X		X		X	
Clinical chemistry		X	X	X		X		X		X	
Lipid panel										X	Fasting samples are preferred, but if participant is nonfasting at time of collection, this is not a protocol deviation.
Urinalysis										X	
Urine pregnancy (local)		X		X		X		X		X	Perform only for women of childbearing potential and women with a history of tubal ligation. At dosing visits which have pregnancy testing, the pregnancy test result must be confirmed to be negative prior to dosing. Pregnancy testing may be performed more frequently than designated on the SoA if local laws or regulations require more frequent testing.
CCI			X							X	
HBV DNA			X					X			Only for participants who are positive for anti-HBc at screening.

Table 3 (continued). Schedule of activities for the Extension Induction and Extension Maintenance Treatment Periods of Study J1P-MC-KFAH

This schedule applies to study participants who are **nonresponders** at Week 12.

For procedures at an ETV, see ETV in Table 4.

For procedures at an unscheduled visit, see V997 in Table 4.

Visits 17 through 28 are eligible to be conducted remotely (that is, by telephone, IT-assisted virtual visit, mobile healthcare, or a combination thereof) if written approval is provided by the sponsor and according to the preferences of the participant and the study site. However, no more than 34 days can elapse without an on-site study visit occurring

Visit number	V20	V21	V22	V23	V24	V25	V26	V27	V28	V29	Comment
Weeks from randomization	34	36	38	40	42	44	46	48	50	52	
Study day	239	253	267	281	295	309	323	337	351	365	
Visit interval tolerance (days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Fasting visit										**X**	
Pharmacokinetic (PK) samples			X							X	Collect samples before dosing, if dosing is scheduled. Collect additional samples at specified times relative to onset of hypersensitivity events.
CCI [redacted]			X							X	Collect samples before dosing, if dosing is scheduled. Collect additional samples at specified times relative to onset of hypersensitivity events.
Flow cytometry panel										X	
Genetics sample											Blood sample for DNA pharmacogenetics can be obtained any time at or after V2.
CCI [redacted]										X	
Endoscopic Procedure											
Endoscopy										X	
Colon biopsy sample collection										X	Performed at time of endoscopy. Instructions for collection are provided in the lab manual. Flexible sigmoidoscopy is recommended, except for protocol-specified reasons when a colonoscopy should be performed.
Stool Samples											
CCI [redacted]			X							X	
			X							X	

Table 3 (continued). Schedule of activities for the Extension Induction and Extension Maintenance Treatment Periods of Study J1P-MC-KFAH

This schedule applies to study participants who are **nonresponders** at Week 12.

For procedures at an ETV, see ETV in Table 4.

For procedures at an unscheduled visit, see V997 in Table 4.

Visits 17 through 28 are eligible to be conducted remotely (that is, by telephone, IT-assisted virtual visit, mobile healthcare, or a combination thereof) if written approval is provided by the sponsor and according to the preferences of the participant and the study site. However, no more than 34 days can elapse without an on-site study visit occurring

Visit number	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	**V27**	**V28**	**V29**	**Comment**
Weeks from randomization	34	36	38	40	42	44	46	48	50	52	
Study day	239	253	267	281	295	309	323	337	351	365	
Visit interval tolerance (days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Fasting visit										**X**	
Randomization and Dosing											
Dosing	X	X	X	X	X	X	X	X	X		No dosing at V29.

Abbreviations: AESIs = adverse event of special interest; anti-HBc = antibody to hepatitis B core antigen; DNA = deoxyribonucleic acid; ETV = early termination visit; HBV = hepatitis B virus; IT = information technology; NRS = numeric rating scale; QIDS-SR16 = 16-Item Quick Inventory of Depressive Symptomatology–Self Report; SoA = schedule of activities; V = visit.

1.3.4. Schedule of activities for ETV, unscheduled visits, and Post-Treatment Follow-Up Period

Table 4. Schedule of Activities for Early Termination, Unscheduled Visits, and Post-Treatment Follow-Up Period

V802 is only for randomized participants who were positive for anti-HBc at screening. All other participants will have their final visit at V801 or ETV.
V997: Additional study procedures can be performed at the discretion of the investigator.

Visit number	ETV	V997	V801	V802	Comment
Weeks from randomization	—	—	58 or ETV + 8 weeks after last dose	66 or ETV + 16 weeks after last dose	The intervals between ETV and the post-treatment follow-up visit(s) should be adequate to ensure that V801 occurs at least 8 weeks since last dose and V802 (if applicable) occurs at least 16 weeks since last dose.
Study day	—	—	—	—	
Visit interval tolerance (days)	—	—	±7	±7	
Fasting visit					**No fasting in this period**
Concomitant medications	X	X	X	X	
Adverse events	X	X	X	X	For AESIs, additional data are collected (Section 8.3.6).
Review modified Mayo score (MMS)	X				
Tobacco use	X				
Physical Evaluation					
Weight	X		X		
Vital signs	X	X	X	X	Blood pressure, body temperature, and pulse rate. Vital signs should be measured after participant has been sitting for at least 5 minutes. V997: Vital signs collection is optional.
Symptom-directed physical examination, including assessment for signs and symptoms of tuberculosis (TB), including peripheral lymph nodes	X		X	X	See Section 8.2.2.
CCI	X		X	X	
12-lead electrocardiogram (ECG)	X				Locally performed.
Patient Diary (Electronic)					
Diary return	X				
Patient-Reported Outcomes (Electronic)					
Inflammatory Bowel Disease Questionnaire (IBDQ)	X				
Patient Global Impression of Change (PGI-C)	X				

Table 4. Schedule of Activities for Early Termination, Unscheduled Visits, and Post-Treatment Follow-Up Period

V802 is only for randomized participants who were positive for anti-HBc at screening. All other participants will have their final visit at V801 or ETV.
V997: Additional study procedures can be performed at the discretion of the investigator.

Visit number	ETV	V997	V801	V802	Comment
Weeks from randomization	—	—	58 or ETV + 8 weeks after last dose	66 or ETV + 16 weeks after last dose	The intervals between ETV and the post-treatment follow-up visit(s) should be adequate to ensure that V801 occurs at least 8 weeks since last dose and V802 (if applicable) occurs at least 16 weeks since last dose.
Study day	—	—	—	—	
Visit interval tolerance (days)	—	—	±7	±7	
Fasting visit					**No fasting in this period**
QIDS-SR16	X				
Clinician-Administered Questionnaires (Paper)					
Physician's Global Assessment (PGA)	X				
Laboratory Tests and Sample Collections					
Hematology	X		X	X	
Clinical chemistry	X		X	X	
Lipid panel	X				Fasting is not required for the lipid panel at ETV.
Urinalysis	X		X	X	
Urine pregnancy (local)	X		X	X	Perform only for women of childbearing potential and women with a history of tubal ligation. At dosing visits which have pregnancy testing, the pregnancy test result must be confirmed to be negative prior to dosing. Pregnancy testing may be performed more frequently than designated on the SoA if local laws or regulations require more frequent testing.
CCI	X				
HBV DNA	X			X	Only for participants who are positive for anti-HBc at screening.
Pharmacokinetic (PK) samples	X		X		Collect samples before dosing, if dosing is scheduled. Collect additional samples at specified times relative to onset of hypersensitivity events.

Table 4. Schedule of Activities for Early Termination, Unscheduled Visits, and Post-Treatment Follow-Up Period

V802 is only for randomized participants who were positive for anti-HBc at screening. All other participants will have their final visit at V801 or ETV.
V997: Additional study procedures can be performed at the discretion of the investigator.

Visit number	ETV	V997	V801	V802	Comment
Weeks from randomization	—	—	58 or ETV + 8 weeks after last dose	66 or ETV + 16 weeks after last dose	The intervals between ETV and the post-treatment follow-up visit(s) should be adequate to ensure that V801 occurs at least 8 weeks since last dose and V802 (if applicable) occurs at least 16 weeks since last dose.
Study day	—	—	—	—	
Visit interval tolerance (days)	—	—	±7	±7	
Fasting visit					**No fasting in this period**
CCI [redacted]	X		X		Collect samples before dosing, if dosing is scheduled. Collect additional samples at specified times relative to onset of hypersensitivity events.
Flow cytometry panel	X				
Genetics sample					Blood sample for DNA pharmacogenetics can be obtained any time at or after V2.
CCI [redacted]	X				
Endoscopic Procedure					
Endoscopy	X				Recommended at ETV based on judgment of the investigator and after discussion with the sponsor's medical monitor. If not performed at ETV, this will not be considered a protocol deviation.
Colon biopsy sample collection	X				Recommended at ETV based on judgment of the investigator and after discussion with the sponsor's medical monitor. Instructions for collection are provided in the lab manual. Flexible sigmoidoscopy is recommended, except for protocol-specified reasons when a colonoscopy should be performed. If not performed at ETV, this will not be considered a protocol deviation.
Stool Samples					
CCI [redacted]	X				
	X				

Table 4. Schedule of Activities for Early Termination, Unscheduled Visits, and Post-Treatment Follow-Up Period

V802 is only for randomized participants who were positive for anti-HBc at screening. All other participants will have their final visit at V801 or ETV.
V997: Additional study procedures can be performed at the discretion of the investigator.

Visit number	ETV	V997	V801	V802	Comment
Weeks from randomization	—	—	58 or ETV + 8 weeks after last dose	66 or ETV + 16 weeks after last dose	The intervals between ETV and the post-treatment follow-up visit(s) should be adequate to ensure that V801 occurs at least 8 weeks since last dose and V802 (if applicable) occurs at least 16 weeks since last dose.
Study day	—	—	—	—	
Visit interval tolerance (days)	—	—	±7	±7	
Fasting visit					**No fasting in this period**
Randomization and Dosing					
Dosing					No dosing at ETV, V997, or post-treatment follow-up visits.

Abbreviations: AESIs = adverse event of special interest; anti-HBc = antibody to hepatitis B core antigen; DNA = deoxyribonucleic acid; ETV = early termination visit; HBV = hepatitis B virus; QIDS-SR16 = 16-Item Quick Inventory of Depressive Symptomatology–Self Report; SoA = schedule of activities; V = visit.

2. Introduction

2.1. Study Rationale

LY3471851 (also known as NKTR-358) is a polyethylene glycol (PEG)-conjugated recombinant human interleukin (IL)-2 (rhIL-2) with the capacity to promote the expansion and activation of regulatory T cells (Tregs) with relatively minimal effect on conventional T cells (Tcons). In preliminary clinical studies, other IL-2 formulations (aldesleukin and ILT-101), which are hypothesized to have a mechanism of action similar to that of LY3471851, were associated with an expansion of peripheral Tregs and biological response in patients with UC.[1,2] As compared to those formulations, PEGylation results in prolonged systemic exposure and improved binding to the high-affinity IL-2 receptor most present on Tregs.

Study KFAH is a Phase 2 study to evaluate the efficacy and safety of multiple dose levels of LY3471851 in adult patients with moderately to severely active UC who have an inadequate response to, loss of response to, or are intolerant to conventional UC therapy ("conventional-failed") or to advanced UC therapy ("advanced therapy-failed"). For this study, conventional UC therapy is defined as corticosteroids, AZA, or 6-MP. Results of this study will be used to guide the dose selection for future studies and to further characterize the benefit/risk profile of LY3471851.

2.2. Background

Ulcerative colitis is a chronic disease characterized by inflammation of the rectum and colon. Symptoms include diarrhea, rectal bleeding (RB), urgency, and a feeling of incomplete evacuation of the rectum after defecation (tenesmus). Ulcerative colitis has a relapsing–remitting course, meaning that many patients have intermittent disease flares that are interspersed with periods of remission. Treatment goals in UC include induction of remission, typically within a 6 to 12-week time frame, and maintenance of remission in the longer term, which may be over 52 weeks of continuous treatment in clinical trials. In both clinical practice and in clinical trials, clinical response and clinical remission are assessed by a combination of endoscopy (improvement in the endoscopic appearance of the mucosa and healing of ulcers) and by patient-reported outcomes, including reduced stool frequency (SF) and resolved RB.[3] Control of intestinal inflammation in UC is associated with a reduction in the risk of hospitalization and colectomy, and in the longer term, reduction in the risk of UC-associated dysplasia and colorectal cancer.

Medications used for the treatment of UC include 5-ASA–containing medications (sulfasalazine, mesalazine, balsalazide, and olsalazine), corticosteroids, immunomodulators such as AZA and 6-MP, biologic medications, and JAK inhibitor medications. A significant proportion of patients with moderately to severely active UC may

- have an inadequate response to medicines such as 5-ASAs or corticosteroids
- be unable to maintain a clinical response to 5-ASAs or AZA, or
- be unable to discontinue corticosteroids without a relapse in disease activity.[4]

Many of these patients require additional treatment with the next line of therapy, which could include medical treatment with a biologic or JAK inhibitor medication or surgical treatment with a colectomy.

Advanced therapies, including anti-TNF antibodies (for example, infliximab, adalimumab, and golimumab), IL-12/23 antibodies (for example, ustekinumab), and anti-integrin antibodies (for example, vedolizumab), as well as tofacitinib, a JAK inhibitor, are indicated for the treatment of moderately to severely active UC in individuals who fail to respond to, have an inadequate response to, or are intolerant to 5-ASAs and immunomodulators. The key registration trials for the above advanced therapies show that although many participants benefitted, many also failed to achieve the treatment goals of clinical remission[5,6]. Long-term (52 weeks) clinical remission was achieved in less than 50% of participants.[7-9,28-30.] These results show that, despite an improving treatment landscape, a sizable proportion of individuals do not respond to available treatments, underscoring the need for new therapeutic options for individuals with moderately to severely active UC.

Dysfunction in Treg cell biology has been proposed as a factor in the pathophysiology of UC.[10,11] The goal of LY3471851 therapy is to increase Treg number and function, with a minimal effect on Tcons and NK cells.

2.3. Benefit/Risk Assessment

The Investigator's Brochure (IB) designates local injection site reactions as an identified risk of LY3471851, based on reports of primarily low-grade injection site reactions in the Phase 1 studies. Reports of cytokine release syndrome and clinical symptom complex attributed to elevated cytokine levels were of Grade 1 severity. Eosinophilia without evidence of target organ damage was observed in some participants in the Phase 1 study involving patients with systemic lupus erythematosus (SLE). The safety findings from Phase 1 studies showed no evidence of AEs characteristic of capillary leak syndrome, increased risk of infection, worsening or new onset autoimmune disease, cardiac disorders (cardiac rhythm disturbances, angina, or myocardial infarction), pulmonary disorders, central nervous system effects, or severe anemia/thrombocytopenia known to be associated with high-dose IL 2 (aldesleukin).

To minimize risks to participants in Study KFAH, enrolled participants will have appropriate predose safety assessments and post-dose monitoring. The routine safety assessments include physical examinations, clinical safety laboratory tests (including hematology and chemistry), suicidality/self-harm and depression evaluations, and collection of vital signs and spontaneously reported AEs. The study design includes a post-treatment follow-up period with at least one visit for safety assessments.

Systemic allergic/hypersensitivity reactions, which include anaphylaxis[12] and other immediate allergic type reactions, such as non-antibody mediated systemic reactions (for example, cytokine release syndrome [CRS]), are among the study's AESIs (see Section 8.3.6.1). These reactions, if they occur, will prompt additional testing and data collection, and are among the reasons that a participant might be discontinued from study drug (Section 7.1.1). Other AESIs, for example, infections, are likewise addressed by special data collection and other considerations of this protocol (Section 8.3.6.2).

In addition, based on observations of treatment-related biliary hyperplasia noted in nonclinical studies, as described in the IB, investigators should be aware of the possible occurrence of treatment-related hepatobiliary changes that could possibly include cholestasis. The protocol includes hepatic-related laboratory testing to support intensive monitoring for symptoms and physical signs suggestive of liver or biliary toxicity, including jaundice, scleral icterus, and pruritis (see Section 8.2.9).

Ongoing study-level monitoring of safety data will be performed, as described in Section 8.2. Interim analyses to review unblinded safety data will also be conducted, as described in Section 9.5 and Section 10.1.5.

The efficacy of LY3471851 in UC has not been established. Participants may benefit by receiving personal health information from the physical examinations and from other routine safety assessments performed in this study.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of LY3471851 may be found in the IB.

3. Objectives and Endpoints

This table shows the objectives, endpoints, and estimands of the study. Primary and secondary efficacy endpoint definitions appear in Section 8.1.

Objectives	Estimands/Endpoints
Primary	
• To determine whether LY3471851 is superior to placebo in inducing clinical remission in participants with moderately to severely active UC	The study will compare LY3471851 with placebo in participants with moderately to severely active UC. The primary comparison of interest is the difference in the proportion of participants who achieve clinical remission at Week 12. The primary comparison will be assessed using a composite estimand where the intercurrent events that lead to permanent discontinuation of assigned study treatment are part of the response definition.
Secondary	
• To evaluate the efficacy of induction treatment with LY3471851 compared to placebo with respect to clinical, endoscopic, and histologic improvement	Secondary comparisons of interest are the difference between LY3471851 and placebo in the proportion of participants who have not permanently discontinued at Week 12 and have achieved at Week 12: • clinical response • endoscopic remission • endoscopic response • symptomatic remission • symptomatic response • histologic remission • histologic-endoscopic mucosal healing Secondary comparisons with binary endpoints will use a composite estimand as described for the primary comparison.

Objectives	Estimands/Endpoints
• To evaluate the efficacy of maintenance treatment with LY3471851 compared to placebo with respect to clinical, endoscopic, and histologic improvement	Secondary comparisons of interest include the difference between LY3471851 and placebo in the proportion of participants who were responders at Week 12 (Week 12 Responders) and have not permanently discontinued at Week 52, who at Week 52 still have • clinical remission • clinical response • endoscopic remission • endoscopic response • symptomatic remission • symptomatic response • histologic remission • histologic-endoscopic mucosal healing Secondary comparisons with binary endpoints will use a composite estimand as described for the primary comparison.
• To evaluate the efficacy of treatment with LY3471851 compared to placebo with respect to patient-reported outcomes and quality of life measures	Comparison of mean changes from baseline to Week 12 and to Week 52 in scores for • IBDQ • Urgency NRS • Abdominal Pain NRS • Nocturnal Stools • Bristol Stool Scale • PGR-S • Fatigue NRS Secondary comparisons with continuous endpoints will use a hypothetical efficacy estimand strategy to address the intercurrent events of early discontinuation to assess the effect of study treatment in a hypothetical trial where all participants have complete data and continue to take study treatment without discontinuing from the study.
• To evaluate the PK of LY3471851	• Week 12 LY3471851 trough concentrations
CCI	

Objectives	Estimands/Endpoints
CCI	

Abbreviations: CCI IBDQ = Inflammatory Bowel Disease Questionnaire; NRS = numeric rating scale; PGR-S = Patient's Global Rating of Severity; PK = pharmacokinetics; UC – ulcerative colitis; CCI

Additional details will be provided in the SAP.

4. Study Design

4.1. Overall Design

Study KFAH is an adaptive Phase 2 multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of multiple dose levels of LY3471851 in adult patients with moderately to severely active UC. Enrolled study participants will have either

- an inadequate response to, loss of response to, or be intolerant to corticosteroid or immunomodulator therapy for UC (termed "conventional-failed" in this protocol), or
- an inadequate response to, loss of response to, or are intolerant to biologic or JAK inhibitor therapy for UC (termed "advanced therapy-failed" in this protocol).

For complete definitions of the terms "conventional-failed" and "advanced therapy-failed," see the study entry criteria listed in Section 5.1.

Study Stages

This adaptive study has two stages, as shown in the lower left of the first schema in Section 1.2.

Stage 1: A prespecified number of study participants will be randomly assigned to one of three treatment groups, including placebo. Interim analyses will be conducted for safety, dosing tolerability, and efficacy. These interim analyses will determine the doses to be used in Stage 2.

Note: Participants enrolled during Stage 1 of the study will remain on their randomly assigned Stage 1 doses. Their doses will be changed only if necessary due to safety reasons or due to their clinical response status.

Stage 2: A prespecified number of additional study participants will be enrolled and randomly assigned to study treatment groups as well as placebo. The treatment doses used in Stage 2 may include any of the doses used in Stage 1 (or none), as well as one or more additional LY3471851 doses, not exceeding1800 µg. The Stage 2 LY3471851 treatment doses will be determined by the sponsor based on results of the Stage 1 interim analyses and recommendations of the sponsor's IAC. For example, a small group of sponsor personnel having pre-identified roles and no contact with investigative sites may review the IAC recommendation and may also review unblinded data in order to further assess the recommendation. Details regarding the process for internal decision-making and action plan will be provided in a separate document.

Thus, whereas Stage 1 will have three treatment groups (including placebo), Stage 2 could have more treatment groups or fewer.

The sponsor intends for the transition from Stage 1 to Stage 2 to be seamless, with participant screening and enrollment activities occurring continuously in the transition period. The study IWRS will allocate newly enrolling participants to groups according to the Stage 1 randomization ratio until the Stage 2 groups have been decided upon and implemented. The randomization ratios are described in Section 9.2.

Study Periods

This study has multiple periods, as shown the schema in Section 1.2.

Screening period

This period begins with Visit 1, which occurs 5 weeks (or less) before the planned randomization visit. A participant's screening evaluations must be completed and reviewed to confirm the participant's eligibility before randomization and dosing occurs at Visit 2.

Blinded induction and blinded maintenance periods

The double-blind, placebo-controlled, 12-week induction treatment period begins at Visit 2. Dosing, sample collection, and assessments continue Q2W, as shown in the SOA. Between Week 12 and Week 14, based on samples and assessments collected at Week 12, participants will be classified as either "Week 12 Responders" or "Week 12 Nonresponders" based on the "clinical response" criteria defined in Section 8.1.

- "Week 12 Responders" will continue to receive their same randomly assigned treatment throughout the blinded 40-week Maintenance Period, with the final dose occurring at Week 50 and the last maintenance assessments and sample collections at Week 52.
- "Week 12 Nonresponders" will enter the Extension Induction and Extension Maintenance Periods.

Extension induction and maintenance periods

Beginning at Week 14, participants who were classified as Week 12 Nonresponders will receive the high dose (CCI µg) of LY3471851 Q2W, unless a lower dose is selected for Stage 2 based on interim analyses.

Between Week 26 and Week 28, based on samples and assessments collected at Week 26, these participants will again be classified according to their response status (responder or nonresponder).

- Participants who are classified as responders based on the samples and assessments at Week 26 will continue to receive LY3471851 Q2W as maintenance through the remainder of the study. These participants have their final dose at Week 50 and their last maintenance assessments and sample collections at Week 52.
- Participants who are classified as nonresponders based on the Week 26 samples and assessments will be permanently discontinued from study drug when his/her status as a nonresponder has been determined; such participants will enter the post-treatment follow-up period (Section 7.1.1).

Post-treatment follow-up period

All participants will have a post-treatment follow-up visit (Visit 801) for safety assessments. Visit 801 occurs approximately 6 weeks after the Week 52 visit. The last dose of study drug is given at Week 50. Thus, participants will have been withdrawn from study drug for approximately 8 weeks at Visit 801. Participants who were positive for anti-HBc at screening will have one additional post-treatment follow-up visit (Visit 802).

Early discontinuation

Participants who permanently discontinue the study drug early or withdraw from the study (Section 7) will undergo early termination procedures, including an ETV and the post-treatment follow-up visits specified in the SoA.

4.2. Scientific Rationale for Study Design

Primary endpoint definition

The primary endpoint for this study tests the superiority of treatment with LY3471851 versus placebo for clinical remission at Week 12. The endpoint of the MMS was chosen based on available regulatory guidance from the 2016 FDA "Guidance for industry. Ulcerative colitis: clinical trial endpoints" and the 2018 EMA "Guideline on the development of new medicinal products for the treatment of UC." [14,31] Both recommend a composite endpoint for both symptomatic and endoscopic remission. The timing of the primary endpoint was based on the PK/PD results of LY3471851 in the Phase 1 single- and multiple-ascending dose studies.

Duration of treatment periods and post-treatment follow-up

The 52-week total duration of treatment was chosen based on the 2018 EMA guideline[14], which recommends at least 12 months for the assessment of long-term efficacy of maintenance of remission.

The post-treatment follow-up period allows for continued safety monitoring after the last dose. A period of 6 weeks for the post-treatment follow-up is considered sufficient to wash out study drug based on the mean half-life, which has been estimated as between 8 to 13 days in the Phase 1 studies.

The inclusion of an extension period for participants who were not clinical responders after the first 12 weeks of treatment is intended to provide additional time for participants on the highest dose to receive potential benefit and respond, and also for participants receiving the lower doses and placebo the opportunity to receive potential benefit and respond to the highest dose.

Choice of control and number of treatment groups

The double-blind, placebo-controlled design of this study limits potential bias in investigator assessments and enables a clearer interpretation of the effects of active drug compared to placebo (background therapy). Nonbiologic background therapy, such as 5-ASA, corticosteroids, AZA, or 6-MP, is allowed in this study with limitations as described in the dose stabilization criteria and listing of allowed concomitant medications. The selection of placebo as a comparator for this study is warranted because study participants will be permitted to use these medications as background therapy.[13,14]

The use of multiple active dose levels in this study will allow for an evaluation of safety and efficacy across a broad dose range and so provide information to guide dose selection for future studies.

Demographics collection

In this study, collection of demographic information includes race and ethnicity. The scientific rationale is based on the possible need to assess variable response in safety and/or efficacy based on race or ethnicity. Such a need can be addressed only if all the relevant data are collected.

Exclusion of certain study candidates

Male and female participants from 18 to 75 years of age, inclusive, at screening will be included in this study. Elderly patients are at increased risk of ischemic colitis and segmental colitis associated with diverticula, which may confound efficacy assessment. Elderly patients are also at increased risk of hospitalization and poorer outcomes following hospitalization for UC, which include an increased risk of venous thromboembolism and mortality. Elderly patients who require surgery for UC also have increased rates of postoperative complications and increased length of hospital stay compared with younger patients.[15]

4.2.1. Participant Input into Design

The sponsor has involved investigative sites and patients in events soliciting input on the study design and implementation of prior UC clinical development programs. The study implementation insights gained from those events were considered in the design of this study.

4.3. Justification for Dose

CCI

4.4. End of Study Definition

A participant is considered to have completed the study if he or she has completed all required periods of the study, including the last visit or the last scheduled procedure shown in the SoA.

The "end of the study" is defined as the date of the last visit or last scheduled procedure shown in the SoA for the last participant in the study globally.

5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria.

The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

For rescreening and retesting activities within the screening period, see Section 5.4.

5.1. Inclusion Criteria

Patients with UC will be included in the study only if they meet all of the following inclusion criteria.

Informed Consent

1. Are capable of giving informed consent as described in Appendix 1, Section 10.1.3, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol, including the contraception requirements.

   Note: For the contraception requirements of this protocol, see Appendix 4. Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Patient Characteristics

2. Are male or female patients from 18 to 75 years of age, inclusive, at the time of initial screening (Visit 1).

   Note: Women of child-bearing potential (WOCBP) must test negative for pregnancy as indicated by a negative serum pregnancy test at the screening visit followed by a negative urine pregnancy test within 24 hours prior to first exposure to study drug.

3. Have venous access sufficient to allow the protocol-required blood sampling.

4. Are willing and able to complete the scheduled study assessments, including endoscopies and daily diary entries.

Disease-Specific Characteristics

5. Have had an established diagnosis of UC of ≥3 months in duration before baseline (Visit 2), which includes endoscopic evidence of UC and a histopathology report that supports a diagnosis of UC (see Section 8.1.1.3). Supportive endoscopy and histopathology reports must be available in the source documents.

6. Have moderately to severely active UC as defined by a modified Mayo score (MMS) of 4 to 9 with an endoscopic subscore (ES) ≥2, with endoscopy performed within 14 days before baseline.

   Note: The MMS requires accurate documentation of the stool frequency (i.e. baseline prior to onset of UC signs/symptoms OR stool frequency when in remission) as well as

3 days of diary data (of stool frequency and rectal bleeding) in the 7 days preceding the first date of bowel prep, if no bowel prep, day of endoscopy).

Note: The Mayo ES, as determined by the Image Review charter, will be provided to the site prior to randomization to enable determination of the MMS for eligibility.

7. Have evidence of UC extending proximal to the rectum (with ≥15 cm of involved colon).

8. Have documentation of

8a. a surveillance colonoscopy (performed according to local standard) within 12 months before baseline for

- patients with pancolitis of greater than 8 years' duration, or
- patients with left-sided colitis of greater than 12 years' duration, or
- patients with primary sclerosing cholangitis.

OR

8b. in patients for whom Inclusion Criterion 8a does not apply, up-to-date colorectal cancer surveillance (performed according to local standard).

Note: At the discretion of the investigator, a colonoscopy instead of a flexible sigmoidoscopy can be performed as the screening endoscopy for this study. Patients who do not have a colonoscopy report available in source documentation will have a colonoscopy at screening.

Prior Medication Failure

9. Have an inadequate response to, loss of response to, or intolerance to at least 1 of the medications described in Inclusion Criteria 9a OR 9b. Documentation of dose, frequency, route of administration, and duration of the prior failed treatment is required.

9a. **Conventional-failed patients**: Patients who have an inadequate response to, loss of response to, or are intolerant to at least 1 of the following medications:

- corticosteroids
    - corticosteroid-refractory colitis, defined as signs and/or symptoms of active UC despite oral prednisone (or equivalent oral corticosteroid) at doses of at least 30 mg/day for a minimum of 2 weeks; or
    - corticosteroid-dependent colitis, defined as:
        - an inability to reduce corticosteroids below the equivalent of prednisone 10 mg/day within 3 months of starting corticosteroids without a return of signs and/or symptoms of active UC; or
        - a relapse within 3 months of completing a course of corticosteroids; or

  - history of intolerance of corticosteroids (including, but not limited to, Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, or neuropsychiatric side-effects, including insomnia, associated with corticosteroid treatment).

- immunomodulators

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

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

  - history of intolerance to at least 1 immunomodulator; intolerance includes, but not limited to, nausea/vomiting, abdominal pain, pancreatitis, liver function test abnormalities, and lymphopenia

AND

- have neither failed nor demonstrated an intolerance to an advanced therapy (biologic medication such as anti-TNF, anti-IL12p40 or anti-integrin antibody or a JAK inhibitor) indicated for the treatment of UC

  - Participants without any prior exposure to these treatments would meet this part of this criterion.
  - Participants with prior exposure to these treatments could meet part of this criterion if the treatment duration was 1 year or less and the treatment was discontinued for reasons other than loss of response, inadequate response, or intolerance (for example, change of insurance or well-controlled disease).

9b. **Advanced therapy-failed patients**: Patients who have an inadequate response to, loss of response to, or are intolerant to advanced therapy for UC, defined as anti-TNF antibodies, anti-IL12p40 antibodies or anti-integrin antibodies, or JAK inhibitors, such as tofacitinib. The medication used to qualify the patient for entry into this category must be approved for the treatment of UC in the United States, European Union, or Japan. Investigators must be able to document an adequate clinical trial of the medication. Patients should fulfill 1 of the following criteria:

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

- Loss of response: Recurrence of signs and symptoms of active disease during approved maintenance dosing following prior clinical benefit (discontinuation despite clinical benefit does not qualify as having failed or being intolerant to UC advanced therapy), or
- Intolerance: History of intolerance to infliximab, adalimumab, golimumab, ustekinumab, vedolizumab, tofacitinib, or other approved biologics or JAK inhibitors including, but not limited to, infusion-related event, demyelination, congestive heart failure, or any other drug-related AE that led to a reduction in dose or discontinuation of the medication.

Patients previously exposed to advanced therapy who do not meet Inclusion Criterion 9b must still meet Inclusion Criterion 9a in order to be eligible to participate in the study.

Patients previously exposed to investigational therapies for the treatment of UC must still meet Inclusion Criteria 9a OR 9b.

Patients who meet both Inclusion Criteria 9a and 9b will be considered to be "advanced therapy-failed" for the purpose of this study.

Ulcerative Colitis Medication Dose Stabilization

10. Are on a stable dose, defined as listed here, if using these medications:

10a. oral 5-ASA therapy: The prescribed dose has been stable for at least 2 weeks prior to the screening endoscopy.

10b. oral corticosteroid therapy (prednisone ≤20 mg/day or equivalent, or budesonide extended release tablets 9 mg/day [budesonide MMX]): The prescribed dose has been stable for at least 2 weeks before the screening endoscopy.

10c. AZA, 6-MP, and methotrexate: The prescribed dose has been stable for at least 8 weeks before the screening endoscopy.

Diagnostic Assessments

11. Have clinically acceptable central laboratory test results at screening (retesting is allowed for hematology and chemistry), as assessed by the investigator, including

11a. hematology

- absolute neutrophil count ≥1.5 times (x) 10^9/L (≥1.5x10^3/μL or ≥1.5 GI/L)
- platelet count ≥100x10^9/L (≥100x10^3/μL or ≥100 GI/L)
- hemoglobin ≥8.5 g/dL (≥85 g/L) for males and >8.0 g/dL (>80 g/L) for females
- lymphocyte count ≥500 cells/μL (>0.50x103/μL or >0.50 GI/L), and
- total white blood cell count ≥3.0x10^9/L (≥3.0x10^3/μL or ≥3.0 GI/L)

11b. chemistry

- serum creatinine ≤1 times upper limit of normal (ULN)

- estimated glomerular filtration rate (eGFR) (Modification of Diet in Renal Disease [MDRD]) ≥60 mL/min/1.73 m^2 [36]
- total bilirubin level (TBL) ≤1 times ULN
- alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤1 times ULN
- alkaline phosphatase (ALP) ≤1 times ULN

Note: Patients with an established diagnosis of Gilbert's syndrome (requires source documentation showing unconjugated hyperbilirubinemia, with no evidence of hemolysis) can be included with bilirubin levels ≤3 times ULN.

5.2. Exclusion Criteria

Patients will be excluded from study enrollment if they meet any of the following criteria within the screening period, which is 35 days or less prior to the start of study treatment, unless specifically defined otherwise.

Gastrointestinal

12. Have a current diagnosis of Crohn's disease, inflammatory bowel disease unclassified (IBD-U) (formerly known as indeterminate colitis), or UC proctitis (disease limited to the rectum, that is, distal to the recto-sigmoid junction, which lies approximately 15 cm from anal margin).
13. Have an inherited immunodeficiency syndrome or a known monogenic cause of UC-like colonic inflammation.
14. Have had or will need abdominal surgery, specifically:

14a. Have had bowel resection or intestinal or intra-abdominal surgery:

- Extensive colonic surgery for UC (for example, subtotal colectomy)
- Have had any small bowel or colonic surgery within 6 months prior to baseline (Visit 2).
- Have had any nonintestinal intra-abdominal surgery within 3 months of baseline.

14b. Are likely to require surgery for the treatment of UC during the study.

Note: Patients who have had limited surgery for UC (for example, segmental colonic resection) may be allowed in the study, if this does not affect the assessment of efficacy. Discussion with the sponsor should occur prior to screening of such patients.

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

Adenoma, Dysplasia, Gastrointestinal Cancer

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

17. Have any current sporadic adenoma without dysplasia (adenomatous polyps occurring proximal to known areas of colitis) that has not been removed.

    Note: Once the sporadic adenoma without dysplasia is completely removed, the patient may be eligible for the study, provided all other study eligibility criteria are met.

18. Have dysplasia occurring in flat mucosa, sporadic adenomas containing dysplasia, and dysplasia-associated lesions or masses (DALMs) as follows:

18a. Any history or current evidence of high-grade dysplasia is exclusionary.

18b. Any history or current evidence of dysplasia occurring in flat mucosa is exclusionary. This includes histopathology reporting "indefinite for dysplasia," low-grade dysplasia, and high-grade dysplasia.

18c. Any history or current evidence of a nonadenoma-like DALM, with or without evidence of dysplasia, is exclusionary.

18d. Any current sporadic adenoma containing dysplasia or any current adenoma-like DALM that has not been removed is exclusionary.

    Note: Once the sporadic adenoma containing dysplasia or adenoma-like DALM is completely removed, the patient may be eligible for the study, provided all other study eligibility criteria are met.

Prior or Current Medications

19. Have received any of the following for treatment of UC within the time frames listed here:

19a. Rectally administered topical corticosteroid therapies (for example, enemas, suppositories, foam applications), or a course of IV corticosteroids within 2 weeks prior to screening endoscopy.

    Note: Patients requiring systemic corticosteroids for non-UC conditions (except corticosteroids to treat adrenal insufficiency) are excluded.

19b. 5-ASA enemas or 5-ASA suppositories within 2 weeks prior to screening endoscopy.

19c. Immunomodulatory medications, including oral cyclosporine, IV cyclosporine, tacrolimus, mycophenolate mofetil, thalidomide or JAK inhibitors (for example, tofacitinib) within 2 weeks prior to the screening endoscopy.

    Note: AZA, 6-MP, and methotrexate are allowed (see Inclusion Criterion 10c). Other immunomodulatory medications should be discussed with the sponsor prior to screening.

19d. Anti-TNF antibodies (for example, infliximab, adalimumab, or golimumab) within 4 weeks prior to screening endoscopy.

19e. Anti-integrin antibodies (for example, vedolizumab) within 12 weeks prior to screening endoscopy.

Note: This exclusion does not apply if the participant has a result from a validated drug-level test demonstrating no drug concentration in the period between last dose and the screening visit.

19f. Anti-IL12p40 antibodies (for example, ustekinumab [Stelara®]) or anti-IL-23p19 antibodies (for example, mirikizumab [LY3074828], risankizumab [BI-655066], brazikumab [MEDI-2070], guselkumab [CNTO1959], or tildrakizumab [MK-3222]) within 4 weeks prior to screening endoscopy.

19g. Agents that deplete B or T cells (for example, rituximab, alemtuzumab, or visilizumab) within 12 months of baseline. Patients remain excluded if there is evidence of persistent targeted lymphocyte depletion at the time of screening endoscopy.

19h. Any investigational nonbiologic therapy within 4 weeks prior to the screening endoscopy or within 5 half-lives prior to the screening endoscopy, whichever is longer.

19i. Any investigational biologic therapy, not otherwise mentioned, within 8 weeks prior to the screening endoscopy or within 5 half-lives prior to the screening endoscopy, whichever is longer.

19j. Leukocyte apheresis (leukapheresis, for example, Adacolumn®) within 3 weeks prior to screening endoscopy.

19k. Interferon therapy within 8 weeks prior to screening endoscopy.

20. Have failed 3 or more classes of advanced therapies approved for treatment of UC.

Infections and Infectious Disease

21. Have or have had active tuberculosis (TB) or latent tuberculosis infection (LTBI):

21a. Have current active TB or past history of active TB (see Section 8.2.6).

21b. Have LTBI, or have had LTBI that has not been treated with a complete course of appropriate therapy as defined by the WHO and/or the United States Centers for Disease Control and Prevention (see Section 8.2.6).

Note: Patients who have a documented history of completing an appropriate TB prophylaxis regimen with no history of risk of re-exposure since completing their treatments and with no evidence of active TB may be eligible to participate in the study, provided all other study eligibility criteria are met.

22. Have HIV infection, or AIDS, or test positive for HIV antibodies at screening.

23. Have a current infection with hepatitis B virus (that is, positive for hepatitis B surface antigen [HBsAg] and/or PCR positive for HBV DNA) (Section 8.2.7).

24. Have a current infection with hepatitis C virus (that is, positive for HCV RNA) (Section 8.2.8).

25. Have *C. difficile* or other intestinal infection within 30 days of screening endoscopy, or test positive at screening for *C. difficile* toxin or for other intestinal pathogens.

26. Have a confirmed diagnosis of cytomegalovirus-associated colitis.

Note: Patients may be eligible if they have had adequate treatment of this condition and have resolution of symptoms at least 3 months prior to screening endoscopy, provided all other study eligibility criteria are met.

27. Have serious, opportunistic, or chronic or recurring extraintestinal infections that are not adequately treated or that require antibiotics during the period from 30 days prior to screening until baseline (Visit 2). Such infections include, but are not limited to, the following:

27a. Serious (requiring hospitalization, and/or IV or equivalent oral antibiotic treatment).

27b. Opportunistic (as defined in Winthrop et al.[16])

Note: Active and ongoing Herpes zoster within 8 weeks prior to screening is exclusionary. Herpes zoster is considered active and ongoing until all vesicles are dry and crusted over.

27c. Chronic or recurrent infections (duration of symptoms, signs, and/or treatment of 6 weeks or longer)

27d. Recurring (including, but not limited to, herpes simplex, herpes zoster, recurring cellulitis, chronic osteomyelitis).

Note: Patients with only recurrent, mild and uncomplicated orolabial, and/or genital herpes may be considered for enrollment if discussed with the sponsor's designated medical monitor and if other study eligibility criteria are met. Patients with other opportunistic infection or chronic, recurrent extraintestinal infections within 60 days before baseline should be discussed on a case-by-case basis with the sponsor's designated medical monitor.

28. Have a nonserious extraintestinal infection that is not adequately treated prior to screening and randomization. A patient who develops an extraintestinal infection during the screening period must be adequately treated before receiving study drug.

Other Medical Conditions

29. Have had extra-abdominal surgery and have not recovered fully following surgery, including complete wound healing, before screening.

30. Have a solid organ transplant or hematopoietic stem cell transplantation.

31. Have a diagnosis or history of malignant disease within 5 years prior to baseline

Exceptions:

- Participants with cervical carcinoma in situ that has been resected with no evidence of recurrence or metastatic disease for at least 3 years prior to baseline may participate in the study, if all other study eligibility criteria are met.
- Participants with basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for at least 3 years may participate in the study, if all other study eligibility criteria are met.

32. Have an unstable or uncontrolled illness, including but not limited to cerebrocardiovascular, respiratory, gastrointestinal (excluding UC), hepatic, renal, endocrine, hematologic, neurological disorder, or significant uncontrolled neuropsychiatric disorder that would potentially affect a patient's safety within the study or else confound efficacy assessments.
33. Have experienced any of the following within 12 months before screening: myocardial infarction, unstable ischemic heart disease, stroke, or New York Heart Association Stage IV heart failure.
34. Have any of the following:

    - are, in the judgment of the investigator, actively suicidal and therefore deemed to be at significant risk for suicide
    - have answered "yes" to either Question 4 or Question 5 on the "Suicidal Ideation" portion of the C-SSRS **or** have answered "yes" to any of the suicide-related behaviors on the "suicidal behavior" portion of the C-SSRS, **and** the ideation or behavior occurred within the past month.

35. Have experienced a thrombotic event within 24 weeks before baseline, or are on anticoagulants, and in the opinion of the investigator are not well-controlled regarding management of hypercoagulable risk.
36. Have a known allergy or hypersensitivity to LY3471851 or any of its excipients, or clinically significant multiple or severe drug allergies, or history of severe post-treatment hypersensitivity reactions, including, but not limited to, erythema multiforme major, linear IgA dermatosis, toxic epidermal necrolysis, or exfoliative dermatitis.
37. Have abnormal laboratory values or ECG abnormalities at screening that, in the opinion of the investigator, indicate unacceptable risk for the participant's safety in the study.
38. Have a history of chronic alcohol abuse, IV drug abuse, or other illicit drug abuse within 1 year before screening.

    Note: Marijuana is considered an illicit drug for the purposes of this study, regardless of local laws. Cannabidiol products may be used during the study, if they are derived exclusively from hemp. Participants who use hemp-based cannabidiol (CBD) products must be on a stable dose for at least 10 days prior to randomization, and participants must remain on that stable dose during the study.
39. Have received a Bacillus Calmette-Guerin (BCG) vaccination or treatment within 12 months before baseline, or have received a live attenuated vaccine within 3 months before baseline, or intend to receive such during the study or within 20 weeks after the last dose of study drug.

Previous or Concurrent Clinical Trial Participation

40. Are currently enrolled in any other clinical study involving an IP or any other type of medical research judged not to be scientifically or medically compatible with this study.

41. Have previously been randomized in this study or have received LY3471851 in any previous study.

    Note: This criterion does not apply to potential participants who are undergoing rescreening procedures.

Other Exclusions

42. Are unsuitable for inclusion in the study in the opinion of the investigator or sponsor for any reason that may compromise the participant's safety or confound data interpretation.
43. Are unwilling or unable to comply with the use of a data collection device to directly record data from the patient daily for the duration of the study, or are unable or unwilling to make themselves available for the required number of study visits, or are unwilling to complete study procedures and follow the restrictions of the study.
44. Are women who are currently pregnant or breastfeeding, or who intend to become pregnant or to breastfeed at any time during the study or within 20 weeks after receiving the last dose of study drug.
45. Are investigative site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
46. Are employees of Eli Lilly and Company (Lilly) or are employees of a third-party organization involved in the study which requires exclusion of their employees.

5.3. Lifestyle Considerations

Study participants should be instructed not to donate blood or blood products during the study and for 20 weeks following their last dose.

To participate in the study, patients must agree to the contraception, reproduction, and breastfeeding criteria detailed in Section 5.1, Section 5.2, and Appendix 4.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

5.4.1. Allowed Retesting of Screening Investigations

Retesting of screening investigations (without a requirement for screen failure and rescreening) is allowed at the discretion of the sponsor's designated medical monitor. The screening investigations specified here may be retested **1 time** at the discretion of the investigator:

- **Screening hematology and chemistry blood tests:** where results are outside the acceptable range for inclusion in the study but may be within the acceptable range for inclusion on retesting, due to test-retest variability

- **Stool testing:** if there is a technical difficulty in performing or reporting the *C. difficile* or stool culture assays

- **Retesting or confirmatory testing with an IGRA:** for example, QuantiFERON®-TB Gold or T-SPOT® assay (see Section 8.2.6 for details)

- **Endoscopy:** where the endoscopist is unable to adequately visualize the mucosa (for example, due to poor bowel preparation or technical issues with equipment) or where the central reader is unable to determine the centrally read Mayo ES (for example, failure of the recording equipment).

Retesting of all other screening investigations should be discussed with the medical monitor prior to retesting.

5.4.2. Rescreening of Individuals Who Fail Screening

Informed consent for rescreenings

Each time an allowed rescreening is performed, the individual must sign a new ICF and will be assigned a new identification number (Section 10.1.3).

Procedures not required to be repeated during rescreening

Individuals in rescreening who have already completed the protocol-required screening CXR or TB tests are not required to repeat these procedures if they were performed within 90 days before the date of signing the rescreening ICF. However, these procedures can be repeated at the discretion of the investigator.

Rescreening after failure to meet study entry criteria

The following table describes conditions under which a potential study participant may be rescreened. If a participant's reason for screen failure is not listed in the table, the participant may not be rescreened.

The interval between the allowed rescreenings should be at least 4 weeks, unless a shorter interval has been agreed with the study's designated medical monitor. The investigator should confirm that the patient has a negative *C. difficile* stool toxin/stool culture/stool ova parasite (as applicable) before performing additional rescreening investigations.

If a participant is not eligible because of this entry criterion...	then the participant...	Frequency of allowed rescreening for the specified criterion
4, 5, 6, 7, 8, 9, 10, 11, 14, 19, 27, 28, 29, 31, 32, 38, 39, 40, 42, or 44	may be rescreened when the reason for the screen failure has resolved.	up to 2 times, for a maximum total of 3 screenings
17	may be rescreened when the polyps have been removed.	up to 2 times, for a maximum total of 3 screenings
18d	may be rescreened when all of the following have been removed: sporadic adenomas containing dysplasia, or adenoma like-DALMs containing an area diagnosed as “indefinite for dysplasia” or low grade dysplasia.	up to 2 times, for a maximum total of 3 screenings
21b	if completely treated for LTBI.	up to 2 times, for a maximum total of 3 screenings
26	may be rescreened when the reason for the screen failure has resolved.	1 time

6. Study Intervention

Study intervention is defined as any investigational intervention, marketed product, placebo, or medical device intended to be administered to or used by a study participant according to the study protocol.

6.1. Study Interventions Administered

Study interventions

In Stage 1, this study involves 2 dose levels of LY3471851, as well as placebo. Depending on the interim analyses and seamless adaptation described in Section 4.1, the study may involve these and/or other dose levels of LY3471851, as well as placebo, in Stage 2.

Treatment Name:	LY3471851	Placebo
Dosage Formulation:	0.6-mL vial delivers 0.9 mg LY3471851	0.9% sodium chloride
Dosage Levels:	CCI µg CCI µg new doses[a]	not applicable
Routes of Administration:	subcutaneous injection	subcutaneous injection
Dosing Instructions:	dosing Q2W	dosing Q2W

[a] New doses added in Stage 2 may be lower than CCI µg or greater but will not exceed CCI µg.

LY3471851 drug product will be provided as a sterile solution in a single-use vial for SC injection. The drug product vials will be supplied in cartons with the appropriate quantity specific to the planned dispensing schedule. An unblinded pharmacist or other unblinded qualified individual will prepare the study intervention for SC dosing (see Section 6.3). When prepared for dosing according to the detailed instructions provided by the sponsor, it will not be possible to distinguish LY3471851 from placebo.

Monitoring after dose administration

All participants should be monitored for 30 minutes or longer after dosing, according to investigator practice or local standard of care.

Packaging and labeling

LY3471851 will be supplied by the sponsor or its designee in accordance with current Good Manufacturing Practice. Clinical trial materials will be labeled according to the country's regulatory requirements. All IPs will be stored, inventoried, reconciled, and destroyed according to applicable regulations.

6.2. Preparation/Handling/Storage/Accountability

The Pharmacy Preparation Instructions and Pharmacy Manual provide instructions for the preparation, handling, and storage of LY3471851 drug product and placebo, and describes site responsibility and accountability for the administered products.

Investigators and authorized site personnel should consult the information provided in the Pharmacy Preparation Instructions, Pharmacy Manual, or the label for specific preparation and administration information, including warnings, precautions, contraindications, adverse reactions, and dose modifications.

Preparation

The IPs will be prepared by an unblinded pharmacist (or other unblinded qualified individual) who is not involved in any other study-related procedures.

Handling and storage

Follow the storage and handling instructions for the IP, as noted in the IP packaging.

Site responsibilities and accountability

The following are responsibilities of the investigator or his or her designee:

- The investigator or designee must confirm appropriate storage conditions have been maintained during transit for all study intervention received and that any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention. Only authorized study personnel may supply, prepare, or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- The investigator or authorized study personnel is responsible for study intervention accountability, reconciliation, and record maintenance (that is, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

The investigator or designee is also responsible for

- explaining the correct use of the study interventions
- verifying that instructions are followed properly
- maintaining accurate records of IP dispensing and collection, and
- returning all unused medication to Lilly or its designee at the end of the study.

Note: In some cases, sites may destroy the material if, during the investigative site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose of clinical materials.

6.3. Measures to Minimize Bias: Randomization and Blinding

Blinding will be maintained throughout the conduct of the study, as described in the separate Unblinding Plan.

Method of treatment assignment

Assignment to treatment groups will be determined by a computer-generated random sequence using the IWRS.

The randomization ratios for Stage 1 and Stage 2 are described in Section 9.2.

The randomization will be stratified based on the following factors:

- previous advanced therapy failure status (yes/no)
- baseline corticosteroid use (yes/no), and
- baseline disease activity (MMS: [4 to 6] or [7 to 9]).

Unblinded pharmacist or other qualified individual

Investigators and all individuals involved in administering the blinded treatment or performing assessments will remain blinded to each participant's assigned study intervention throughout the course of the study. To maintain this blind, an otherwise uninvolved party (unblinded pharmacist or other unblinded qualified individual) will be responsible for the preparation and dispensation of all study intervention. Blinded site personnel or blinded designee will administer the study intervention to the participant.

Independent evaluation for potential injection site reactions (ISRs)

If a participant spontaneously reports symptoms of an injection site reaction, an authorized member of the site staff who, in the opinion of the investigator, is qualified to assess reports of potential ISRs and who is not involved with any other study procedure will evaluate the participant's report. If signs or symptoms of an injection site reaction are indeed present and further evaluation is warranted, this authorized evaluator will contact the investigator's designee or the investigator for further evaluation of the participant's report. See additional instructions provided in Section 8.3.6.3.

Emergency unblinding

Emergency unblinding for AEs may be performed through the IWRS. This option may be used ONLY if the participant's well-being requires knowledge of the participant's treatment assignment. All actions resulting in an unblinding event are recorded and reported by the IWRS.

If, because of emergency unblinding, a participant's study treatment assignment is unblinded to the participant or to blinded site personnel who are performing study assessments, including the investigator, the participant must be discontinued from study drug (Section 7.1.1). In cases where there are ethical reasons to have the participant remain in the study, the investigator must obtain specific approval from the sponsor's clinical research physician for the participant to continue in the study.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is

warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify the sponsor as soon as possible.

6.4. Study Intervention Compliance

The date and time of each dose administered will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed prior to the time of dosing. Deviations from the prescribed dosage regimen are identifiable via the eCRF.

6.5. Concomitant Therapy

Participants should be instructed to consult authorized site personnel before taking any new medications or supplements during the study. Authorized site personnel should consult the sponsor's medical monitor if there are any questions about concomitant therapies during the study.

Recording of concomitant therapy

Any medication or vaccine (including over-the-counter, bowel preparations or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded in the Concomitant Medication eCRF along with

- reason for use
- route of administration, and
- dates of administration, including start and end dates.

Dosage information including dose level and frequency may also be collected when applicable.

Allowed concomitant therapy

Participants are encouraged to maintain their usual medication regimens for concurrent conditions or diseases throughout the study treatment periods, unless those medications are specifically excluded (see Appendix 7). Participants taking permitted UC concomitant medications are to keep doses stable unless modifications are needed due to AEs, and are to follow the instructions regarding dose stabilization in Appendix 8.

Administration of prohibited UC medications, approved or investigational, constitutes treatment failure. Use of such medications should not be withheld if, in the opinion of the investigator, failure to prescribe them would compromise participant safety. Participants who require a prohibited medication to treat their UC must be discontinued from study drug (Section 7.1.1).

If a concomitant medication is needed to treat an AE or for appropriate medical management, the investigator should base decisions on the participant and clinical factors, considering prohibited medications. A participant who initiates a prohibited medication for a non-UC indication may either discontinue the study drug or discontinue the prohibited medication.

Vaccinations

See Appendix 7 and Appendix 8 for requirements on the timing of vaccinations.

Use of prohibited medications after discontinuation of study drug

At discretion of the investigator, medications listed in Appendix 7 are allowed after a patient discontinues study drug and completes the ETV.

Rescue therapy

This study does not include rescue therapy. Participants who are nonresponders at Week 12 will be assigned to the highest dose of LY3471851 (CCI µg), as described in Section 4.1. If these participants remain nonresponders at Week 26, they will be discontinued from study drug and enter post-treatment follow-up period (Section 7.1.1).

Corticosteroid tapering

Participants who enter the study on oral corticosteroid therapy for treatment of their UC should maintain the stable dose of corticosteroid during the entire 12-week induction period. Participants who achieve clinical response at Week 12 will initiate corticosteroid tapering, as described below. For participants who cannot tolerate the corticosteroid taper without recurrence of clinical symptoms, corticosteroid taper may be paused and/or corticosteroid dose may be increased up to the original dose at induction baseline (should not exceed induction baseline dose). In such cases, attempts to reinitiate corticosteroid tapering should be made within 2 weeks of interruption of taper, with a goal to complete tapering no later than Week 26.

Week 12 clinical nonresponders who undergo extended induction with the high dose of LY3471851 will begin corticosteroid tapering if clinical response is achieved at Week 26. For participants who cannot tolerate the corticosteroid taper without recurrence of clinical symptoms, corticosteroid taper may be paused and/or corticosteroid dose may be increased up to the original dose at induction baseline (should not exceed induction baseline dose). In such cases, attempts to reinitiate corticosteroid tapering should be made within 2 weeks of interruption of taper, with a goal to complete tapering no later than Week 40.

The recommended tapering schedule for oral corticosteroids (other than budesonide extended release tablets [budesonide MMX] or beclomethasone dipropionate [gastro-resistant prolonged release tablet]) is as follows.

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

The recommended tapering schedule for participants receiving oral budesonide MMX 9 mg/day is to reduce tablets to 9 mg every other day for 2 weeks, followed by 9 mg every third day for 2 weeks, and then discontinue.

The recommended tapering schedule for participants receiving oral beclomethasone dipropionate (gastro-resistant prolonged-release tablet) 5 mg/day is to reduce tablets to 5 mg every other day for 4 weeks, and then discontinue.

6.6. Dose Modification

The adaptive design of this study allows the introduction of new dose levels of LY3471851 after the interim analyses for Stage 1, as described in Section 4.1 and Section 6.1. In all stages and study periods, the maximum dose will not exceed CCI µg.

No other dose modifications are permitted, except for reasons of immediate participant safety.

6.7. Intervention after the End of the Study

LY3471851 will not be available to participants following completion of the study.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

These sections describe reasons for a participant's

- permanent or temporary discontinuation of study drug (Section 7.1), or
- discontinuation (withdrawal) from the study (Section 7.2).

Discontinuation of specific sites or the trial as a whole ("stopping rules") are handled as part of regulatory, ethical, and trial oversight considerations in Section 10.1.9.

7.1. Discontinuation of Study Intervention

Study drug may be permanently discontinued or temporarily withheld during the study.

Participants who permanently discontinue study drug early will undergo early termination procedures, which include

- an ETV, **and**
- post-treatment follow-up visits, as shown in the SoA.

7.1.1. Criteria for Permanent Discontinuation of Study Drug

Data collection and safety follow-up when study drug is permanently discontinued

In rare instances, it may be necessary for a participant to permanently discontinue (definitively discontinue) study intervention.

If study intervention is permanently discontinued, the participant will remain in the study to be evaluated at the ETV and post-treatment follow-up visits.

See the SoA for data to be collected at the time of discontinuation and follow-up and for any further evaluations that need to be completed. Safety follow-up is as outlined in the SoA, Section 8.2, and Section 8.3.

Criteria for permanent discontinuation of study drug

Possible reasons for permanent discontinuation of study drug include, but are not limited to, the following:

Participant decision

- The participant requests to discontinue the study drug.

Pregnancy

- The participant becomes pregnant during the study (see Section 8.2.5.1). Pregnant patients **will not** undergo an endoscopy at the ETV.

Safety considerations

- The participant develops any of the following conditions during the study:

  - malignancy (except for successfully treated basal or squamous cell skin carcinoma)
  - dysplasia occurring in flat mucosa
  - dysplasia-associated lesion or mass (DALM)
  - HIV infection/acquired immune deficiency syndrome (AIDS)
  - active TB infection or untreated LTBI (Section 7.1.2; Section 8.2.6)
  - HCV RNA positive (Section 8.2.8)
  - HBV DNA positive and clinical assessment consistent with HBV reactivation
    - **Note**: The HBV DNA result is to be confirmed if initial positive test result is positive but below the level of quantification (Section 7.1.2; Section 8.2.7). The participant is to be referred to, evaluated, and managed by a specialist physician with expertise in evaluation and management of viral hepatitis prior to discontinuation of any immunomodulatory and/or immunosuppressive therapy, including study drug. Timing of discontinuation from study drug relative to the initiation of any antiviral treatment for hepatitis is to be based on the recommendation of the consulting specialist physician, in conjunction with the investigator, and aligned with medical guidelines and standard of care.

- The participant requires a colectomy, proctocolectomy, or partial colectomy during the study.
- The investigator, after consultation with the sponsor's designated medical monitor, determines that a systemic hypersensitivity reaction has occurred and is related to study drug administration.
- The participant has any of the following results on 2 consecutive samples taken at least 48 hours, but no more than 1 week, apart:
  - Total WBC <1000 cells/µL
  - ANC <500 cells/µL
  - ALC <200 cells/µL
  - Hemoglobin <6.5 g/dL
- The participant develops CRS. In consultation with the Lilly medical monitor, if an AE is deemed possibly or probably due to CRS based on the details and severity of clinical signs and symptoms, time course of symptom onset relative to study drug administration, and if possible, a cytokine panel from a blood sample obtained at the time of the event,

the participant will be discontinued from study treatment, and will continue safety follow-up.

- The participant develops hypereosinophilia.
    - Participants with absolute eosinophil counts >1500 cells/µL and signs and/or symptoms of target organ involvement that is not consistent with UC and/or with the participant's UC and medical history will be discontinued from study drug in consultation with the medical monitor. Participants will undergo appropriate medical evaluation, which should take into account the participant's known UC and past medical history according to the participant's history and medical records, including previous imaging, biopsies and laboratory findings. Evaluation of target organ involvement will involve additional diagnostic tests as appropriate, including laboratory tests, imaging (for example, echocardiogram, chest x-ray, CT scan), and biopsies. New onset cardiac, pulmonary, and skin findings in the setting of peripheral eosinophilia will be considered as target organ involvement, unless attributable to other causes.
    - Asymptomatic participants with an absolute eosinophil count >5000 cells/µL should have a repeat measurement to confirm the count. If the count is confirmed, the participant will be permanently discontinued from study drug and undergo appropriate medical evaluation.
- The participant has an AE, SAE, or a clinically significant change in a laboratory value that, in the opinion of the investigator, merits the discontinuation of the study drug and appropriate measures being taken.

Hepatic event or liver test abnormality

- Participants who are discontinued from study drug because of a hepatic event or liver test abnormality should have additional hepatic safety data collected via the hepatic eCRF packet. Discontinuation of study drug because of abnormal liver tests should be considered by the investigator when a participant meets 1 of the following conditions after consultation with the sponsor's designated medical monitor (see Section 8.2.9):
    - ALT or AST >8 times ULN
    - ALT or AST >5 times ULN sustained for more than 2 weeks
    - ALT or AST >3 times ULN and TBL >2 times ULN or INR >1.5
    - ALT or AST >3 times ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
    - ALP >3 times ULN
    - ALP >2.5 times ULN and TBL >2 times ULN, or

- ALP >2.5 times ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

Other reasons for permanent discontinuation of study drug

- The participant
  - scores a 3 for Item 12 (Thoughts of Death or Suicide) on the QIDS-SR16 at any time in the study, or
  - reports suicidal ideation or suicidal behaviors during the study.

    Note: A psychiatrist or appropriately trained professional may assist in the decision to discontinue the participant from study drug.

- The participant requires treatment for exacerbation of UC and the treatment involves 1 or more medications at doses higher than those specified in the "dose stabilization" inclusion criterion; for example, the participant requires prednisone >20 mg/day) (see Appendix 8).

- The participant requires treatment with prohibited medications specified in the "prohibited medications" exclusion criterion, for example, a course of IV corticosteroids or a single dose of infliximab or IV cyclosporine (see Appendix 7).

- The participant was nonresponder at Week 12 and remains a treatment nonresponder at Week 26.

- Unblinding: If an investigator, blinded site personnel or blinded designees who are performing assessments, or the participant is unblinded to a participant's treatment assignment because of an emergency unblinding as described in Section 6.3, the participant must be discontinued from the study drug and continue to post-treatment follow-up. In cases where there are ethical reasons to have the participant continue on study drug, the investigator must obtain specific approval from the sponsor's designated medical monitor for the participant to continue.

  Note: The presence or absence of an ISR will not be considered an unblinding event; participants with an ISR may remain in the study and continue to receive study drug, and this will not be considered a protocol deviation.

7.1.2. Criteria for Temporary Interruption (Withholding) of Study Drug

7.1.2.1. Infection-Related Criteria for Temporary Interruption of Study Drug

Temporary withholding of study drug is required for the development of any of the following infection-related criteria during the study:

- Serious or opportunistic infections, as defined in Section 5.2. Study drug is to be withheld until resolution of all acute clinical signs and symptoms, and completion of all appropriate anti-infective treatment (exception for LTBI).
- Participants diagnosed with LTBI during the study are to be permanently discontinued from study drug unless the participant is a candidate for LTBI treatment, and is treated for LTBI as follows:
    - Study drug is temporarily withheld for at least the first 4 weeks of LTBI treatment.
    - After receiving at least 4 weeks of appropriate LTBI therapy (as per WHO and/or the United States Centers for Disease Control guidelines), if there is no evidence of hepatotoxicity (ALT/AST must remain ≤2 times ULN) or other treatment intolerance, study drug may be resumed.
    - The participant must complete appropriate LTBI therapy to remain eligible to receive study drug.
- HBV DNA results that are reported as positive, or as detecting HBV DNA, but HBV DNA is below the level of quantification. The sponsor's designated medical monitor should be contacted regarding study status of the participant. HBV DNA testing is to be repeated as soon as is feasible. If HBV DNA is confirmed as positive, the participant must be permanently discontinued from study drug (Section 7.1).

7.1.2.2. Other Criteria for Temporary Interruption of Study Drug

This table lists criteria for interrupting study drug administration and conditions.

Interrupt study drug if the participant...	Resume study drug administration after...
requires major surgery.	adequate wound healing has occurred.
has AEs or abnormal laboratory values which, in the opinion of the investigator, have an unclear relationship to study drug.	consultation with the sponsor's designated medical monitor, when investigator and the medical monitor agree that resumption of study drug is appropriate for the participant.

Except in an emergency, the investigator should consult with sponsor's designated medical monitor whenever possible before temporarily interrupted study drug, or for resuming temporarily interrupted study drug, for any reasons not specified in this protocol.

7.2. Participant Discontinuation/Withdrawal from the Study

Participant discontinuation (withdrawal from the study) is expected to be uncommon.

A participant may withdraw from the study in the following circumstances:

- at any time at his or her own request, or at the request of his or her designee (for example, parents or legal guardian)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons

- if the participant enrolls in any other clinical study involving an IP or enrolls in any other type of medical research judged not to be scientifically or medically compatible with this study, or
- if the participant, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurs prior to introduction of the new agent.

Data collection and follow-up for participants who discontinue the study

At the time of discontinuing from the study, an ETV should be conducted, if possible, as shown in the SoA. See the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The participant will be permanently discontinued both from the study drug and from the study at that time.

No follow-up procedures will be performed for a participant who withdraws informed consent, unless he or she has explicitly provided permission and consent.

Withdrawal of consent for disclosure

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, he or she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.2.1. Discontinuation of Inadvertently Enrolled Participants

If the sponsor or investigator identify a participant who did not meet enrollment criteria and was inadvertently enrolled, then the participant should be discontinued from study treatment, unless there are extenuating circumstances that make it medically necessary for the participant to continue on study treatment. If the investigator and the sponsor's clinical research physician agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor clinical research physician to allow the inadvertently enrolled participant to continue in the study with or without treatment with IP. Safety follow up is as outlined in the SoA, Section 8.2, and Section 8.3.

7.3. Lost to Follow up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel or designee are expected to make diligent attempts to contact participants who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All blinded assessments and sample collections should be completed before a dose is administered at the dosing visits.

8.1. Efficacy Assessments

This study uses components and permutations of the Mayo score[17] to assess UC disease activity for the primary and several secondary endpoints, as defined in the table below.

Complete and accurate daily recording of the Mayo SF and RB subscores by participants in their daily eDiary is necessary for the success of the study. Adequate bowel preparation and an endoscopy with adequate visualization of the mucosa will enable calculation of the Mayo ES.

Endpoint	Definition
Clinical remission	SF subscore = 0, or SF = 1 with a decrease of ≥1 point from baseline, and RB subscore = 0, and ES = 0 or 1, excluding friability
Clinical response	A decrease in the MMS of ≥2 points and ≥30% decrease from baseline, and A decrease of ≥1 point in the RB subscore from baseline or a RB score of 0 or 1
Endoscopic remission	Mayo ES = 0 or 1, excluding friability
Endoscopic response	A decrease in the Mayo ES of ≥1 point compared to baseline
Symptomatic remission	SF = 0, or SF = 1 with a decrease of ≥1 point from baseline, and RB = 0
Symptomatic response	≥30% decrease from baseline in the composite clinical endpoint of the sum of SF and RB subscores
Histologic remission	Geboes score <2 or Geboes subscores = 0 for Grade 2a, 2b, 3, 4, and 5 (equivalent definitions)
Histologic-endoscopic mucosal healing	Geboes score <2 AND endoscopic remission

Abbreviations: ES = endoscopic subscore; MMS = modified Mayo score; RB = rectal bleeding; SF = stool frequency.

8.1.1. Primary Efficacy Assessment

8.1.1.1. Primary Endpoint

The primary endpoint is clinical remission at Week 12. Clinical remission is based on the MMS and is defined in Section 8.1.

8.1.1.2. Mayo Score

The Mayo score is a composite instrument comprised of the following subscores:

Stool Frequency: The SF subscore is a participant-reported measure. This item reports the number of stools in a 24-hour period, relative to the normal number of stools for that participant in the same period, on a 4-point scale. A stool is defined as a trip to the toilet when the participant has either a bowel movement, or passes blood alone, blood and mucus, or mucus only. The total number of stools passed in a 24-hour period will be recorded by the participant in a daily eDiary. The reference "normal" SF for that participant will be recorded electronically at the screening visit. Study software will use the participant-reported daily SF and the reference normal SF to automatically calculate the Mayo SF subscore. The participant will record this in an electronic diary. Further details on the analysis of daily diary items are contained in the SAP.

The Normal SF is a participant-reported measure. This item reports the number of stools in a 24-hour period when the participant was in remission or, if the participant has never achieved remission, the reported SF before initial onset of signs and symptoms of UC. Remission refers to a period of time since being diagnosed with UC when the participant is not experiencing any signs or symptoms relating to UC. This period of time may last a few weeks or a few months, or may even last several years. The participant will record this electronically as source data at the screening study visit.

> **Note:** The "Remission/Normal Stool Frequency (SF)" question should be explained to the participant before the participant answers the question to ensure accurate participant understanding and data capture. Errors made by the participant cannot be corrected once the response is saved and confirmed.

Rectal Bleeding: The RB subscore is a participant-reported measure. This item reports the most severe amount of blood passed *per rectum* for a given day, on a 4-point scale. The participant will record this in a daily electronic diary.

Endoscopic Subscore: The ES is a physician-reported measure that reports the worst appearance of the mucosa on flexible sigmoidoscopy or colonoscopy, on a 4-point scale. Determination of the ES is further detailed in Section 8.1.1.3. Consistent with current clinical practice and regulatory advice, this study excludes friability from the definition of an ES of 1.

Physician's Global Assessment: The PGA is a physician-reported measure that summarizes the investigator's assessment of the participant's UC disease activity on a 4-point scale. Assessment of the PGA score will be collected by the investigator or designee at appropriate study visits and entered into the eCRF. Consistent with regulatory guidance, the PGA will not be used as an efficacy assessment in this study.

Each subscore is scored on a 4-point scale, ranging from 0 to 3, to give a maximum Mayo score of 12. The MMS is a sum of the Mayo SF, RB, and ES, giving a maximum MMS of 9. Additional scorings involving the Mayo score (for example, CCI have been described and may be used in analyzing data from this study.

See Appendix 9 for more information about the Mayo score.

See Appendix 11 for more information about the daily electronic diary.

8.1.1.3. Endoscopy

Endoscopy will be used to determine the Mayo ES at screening and at other visits, as noted on the SoA. The Mayo ES will be determined by

- blinded readings performed by site personnel or their designees, and
- blinded central readers.

  Note: Disagreement between the site reader and central reader will be adjudicated by an additional blinded central reader, as detailed in the Image Review charter.

A flexible sigmoidoscopy or colonoscopy will be performed on all participants during screening, within 14 days prior to randomization. The endoscopy report and histopathology report (if biopsies are sent to the local histopathology laboratory) must be available in the source documents. Prior to performing the screening endoscopy, investigators or designees should ensure that participants have clinically acceptable central laboratory test results, including stool tests that are "negative" for *C. difficile* and other intestinal pathogens (see Section 5).

Flexible sigmoidoscopy is recommended for all participants, except the following participants for whom colonoscopy is the required endoscopic procedure at screening:

1. Participants who require surveillance for UC-associated dysplasia and malignancy, who have not had a surveillance colonoscopy, including random and targeted biopsies, within 12 months of baseline. These include

   participants with pancolitis of greater than 8 years' duration

   participants with left-sided colitis of greater than 12 years' duration, or

   participants with primary sclerosing cholangitis.

   In these participants, the investigator or designee can obtain additional biopsies to surveille for dysplasia at the screening colonoscopy. This screening colonoscopy will be performed according to local guidelines, and biopsies will be sent to the local histopathology laboratory. Chromoendoscopy may be an acceptable method of targeting biopsies, if allowed according to local guidelines.
2. Participants who require screening for colorectal cancer, who do not have a current screening colonoscopy according to local guidelines. These may include

   - participants with family history of colorectal cancer

- personal history indicating increased colorectal cancer risk, for example, previous adenomatous polyps, or
- participants 50 years or older, or with other known risk factor.

3. Participants who do not have the report of a completed, full colonoscopy available in source documents to establish extent of the disease. Participants with rectal sparing on baseline endoscopy must have documentation of rectal involvement on a prior endoscopy.
4. Participants for whom, in the opinion of the investigator, a colonoscopy is indicated at screening, for example, to confirm that a recent removal of an adenomatous polyp is complete prior to randomization.

If a participant already has up-to-date surveillance for dysplasia and/or up-to-date screening for colorectal cancer, the endoscopy report and histopathology report (if applicable) used to support this must be available in the source documents, in order to satisfy study entry criteria (Section 5).

Participants who undergo colonoscopy at screening do not require a separate flexible sigmoidoscopy in the same screening period.

At Week 12 (or ETV), a flexible sigmoidoscopy is recommended for all participants. Colonoscopy can be performed instead of flexible sigmoidoscopy at Week 12 for clinically indicated reasons in the judgement of the investigator and after discussion with the sponsor-designated medical monitor, as appropriate. The endoscopy report and histopathology report (if biopsies are sent to the local histopathology laboratory) must be available in the source documents. Participants who undergo a flexible sigmoidoscopy at an ETV will not undergo additional endoscopies within the study. Participants who discontinue the study drug because of pregnancy **will not** undergo a flexible sigmoidoscopy at their ETV.

If a participant undergoes early termination soon after screening endoscopy, the need for ETV endoscopy should be discussed with the sponsor's designated medical monitor. There is no need for an ETV endoscopy if fewer than 16 weeks have elapsed since a prior endoscopy.

The endoscopist will be a licensed physician, who is qualified by education, training, and experience to perform colonoscopies. Investigators may delegate endoscopy to other authorized site personnel. However, authorized site personnel performing endoscopy must receive training from the sponsor or designee in the determination and calculation of the Mayo ES. The endoscopist will determine the site-read Mayo ES at each endoscopy, and site personnel or their designee will record this in the eCRF.

All endoscopic procedures will be video recorded using a storage medium provided by the sponsor or designee. The video images will be sent for independent central reading. A detailed Image Review charter from the central reading laboratory will outline the standard study procedures used to capture and transmit video recordings of endoscopic procedures throughout the study, and will outline the qualifications required of the central reader. Recorded endoscopy procedures (without participant identifying information) will be used for research purposes.

The central reader will determine the centrally-read Mayo ES at each colonoscopy in a blinded manner, as detailed in the Image Review charter.

The adjudicated Mayo ES will be provided to the site prior to randomization to enable determination of the MMS for eligibility. An endoscopic Mayo score, as determined by the Image Review charter, will be used for endpoint determination and clinical responder status.

8.1.2. Secondary Efficacy Assessments

Secondary efficacy endpoints are based on

- scores derived from the Mayo score tool described in Section 8.1.1.2,
- scores from the Geboes score for the assessment of histological activity, or
- patient-reported outcome instruments.

8.1.2.1. Endoscopic Biopsies

A histopathology report supporting the diagnosis of UC must be available in the source documents prior to randomization, in order to satisfy study entry criteria (Section 5). If a histopathology report is not available, the investigator or designee can obtain additional biopsies for this purpose at the screening endoscopy (sent to the local histopathology laboratory).

Biopsies will be obtained at each endoscopy to support assessment of the histopathology endpoints in this study and, where permitted, for further research purposes (without participant identifying information), including the assessment of CCI These will be sent to the central study laboratory for processing. Histopathologic scoring of these biopsies will be performed by a blinded central reader. A detailed histopathology charter will outline the procedures to be used for secure specimen transfer, processing, slide preparation, and digitization of slides for histopathologic scoring. These results will not be made available to study sites.

8.1.2.2. Geboes Score

The Geboes scale is based on a comprehensive grading system that evaluates aspects of mucosal injury seen in UC, including crypt architecture, lamina propria chronic inflammation, lamina propria eosinophils, lamina propria neutrophils, intraepithelial neutrophils, crypt destruction, and surface epithelial injury. For each of the histological features assessed, the highest grade in which there is evidence of disease is assigned. The Geboes scale is further described in Appendix 10.

8.1.2.3. Patient-Reported Outcome Instruments

The following are patient-reported outcome instruments collected using a participant eDiary:

- Rectal Bleeding
- Stool Frequency
- Nocturnal Stool
- Bristol Stool Scale
- Urgency NRS

- Abdominal Pain NRS
- Fatigue NRS, and
- PGR-S

The following are patient-reported outcome instruments collected electronically:

- PGI-C and
- IBDQ

Appendix 11 contains descriptions of these patient-reported outcome instruments.

8.1.3. Exploratory Efficacy Assessments

8.2. Safety Assessments

Visits and order of safety assessments

Safety assessments occur as specified in the SoA.

If multiple safety assessments are scheduled for the same visit, the preferred order of completion is

1. ECG and then vital signs
2. other safety assessments, including physical examinations and nonleading (spontaneous) AE collection, followed by C-SSRS (Section 8.2.10), and finally
3. blood sample collection for clinical laboratory, PK, PD, pharmacogenetic, biomarker, and CCI testing.

Data collection and reporting

The AE data collection and reporting requirements are described in Section 8.3 and Appendix 3. Additional requirements regarding (AESIs are described in Section 8.3.6.

Any clinically significant findings that result in a diagnosis and that occur after the participant receives the first dose of study drug should be reported to Lilly or its designee as an AE via eCRF.

Safety monitoring

The principle investigator will monitor the safety data throughout the study. Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue the study intervention.

The sponsor will monitor the safety data, including AEs, SAEs, discontinuations, vital signs, and clinical laboratory results by means of blinded reviews performed at least quarterly and by other appropriate methods. These methods include reviews by a functionally independent safety physician and/or clinical research scientist who regularly reviews SAE reports in real time and across studies, and who reviews applicable clinical safety and epidemiological publications from the literature. If this safety monitoring uncovers an issue that needs to be addressed by unblinding at the individual or group level, additional analyses of the safety data can be performed by the sponsor's independent internal safety review committee.

Appropriateness of safety assessments

The safety assessments used in this study are routine elements of clinical health assessment and Phase 2 drug development.

8.2.1. Vital Signs

Vital signs (blood pressure, body temperature, and pulse rate) will be measured when specified in the SoA and as clinically indicated. Additional vital signs may be measured during study visits if warranted, as determined by the investigator.

Blood pressure and pulse rate should be measured after the participant has been sitting for at least 5 minutes.

Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. If the participant feels unable to stand, sitting or supine vital signs will be recorded.

8.2.2. Physical Examinations

Physical examinations will be performed when specified in the SoA. Physical examinations may also be performed as clinically indicated at other visits, at the discretion of the investigator.

Physical examination at screening

At screening, the complete physical examination should include the following regions and body systems:

- general appearance
- skin
- head, ears, eyes, nose, throat
- lymph nodes
- cardiovascular
- respiratory
- abdominal
- extremities, and
- neurologic.

Pelvic, rectal, and breast exams are not required unless clinically indicated.

The screening physical examination should include an assessment of TB risk factors and symptoms or signs of TB, including an assessment of peripheral lymph nodes.

Height (without shoes) and weight will also be measured and recorded.

Symptom-directed physical examinations after screening

After screening, physical examinations should include a symptom-directed evaluation, as well as examination of eyes, heart, lungs, abdomen, and visual examination of the skin (other than area covered by clothing or other material). At approximately every third to fourth month after screening, the physical examination should also include an assessment of TB risk factors and symptoms or signs of TB, including an assessment of peripheral lymph nodes (Section 8.2.6).

8.2.3. Electrocardiograms

For each participant, 12-lead ECGs will be collected when specified in the SoA. The ECGs should be recorded before collecting any blood for safety or PK tests. Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine, but awake, during ECG collection.

ECGs may be obtained at additional times, when deemed clinically necessary. Collection of additional ECGs at a particular time point is allowed to ensure high quality records.

ECGs will be interpreted by a qualified physician (the investigator or qualified designee) as soon after the time of ECG collection as possible, and ideally while the participant is still present, to determine whether the participant meets the study entry criteria and for immediate participant management, should any clinically relevant findings be identified.

If a clinically significant finding is identified (including, but not limited to changes from baseline in QT/QTc interval) after enrollment, the investigator or qualified designee, in conjunction with the sponsor's medical monitor, will determine whether the participant can continue in the study and if any change in participant management is needed.

The review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

8.2.4. Chest Radiography

A posterior–anterior CXR, interpreted and reported by a radiologist or pulmonologist, will be obtained when specified in the SoA.

A lateral CXR can also be obtained if, in the opinion of the investigator, a lateral view is indicated.

Note: Participants do not need to have a CXR at screening if, based on the judgment of the investigator, both of the following 2 conditions are met:

- the CXR was performed within 3 months before initial screening, and
- documentation of the CXR, read by a qualified radiologist or pulmonologist, is sufficient for TB evaluation according to local standard of care.

For each participant, the CXR films, images, or a radiology report must be available to the investigator for review before the participant is randomized. Certain findings from the CXR may be consistent with a condition that excludes a participant from the study (see Section 5.2).

Note: Results of a chest CT scan or other imaging study similar to a CXR may be substituted in place of the CXR as described above, in consultation with the sponsor's medical monitor.

8.2.5. Laboratory Tests

Appendix 2 lists the clinical laboratory tests to be performed, and the SoA specifies when samples are routinely collected for clinical laboratory tests. Samples for laboratory testing will be obtained in the event of anaphylaxis or generalized urticaria, as described in Section 8.3.6.1 and

Appendix 2, Section 10.2.2. Additional tests may be performed at any time during the study, as determined necessary by the investigator or as required by local regulations.

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the SoA, standard collection requirements, and laboratory manual.

If laboratory values from nonprotocol specified laboratory assessments performed at an investigator-designated local laboratory require a change in participant management or are considered clinically significant by the investigator (for example, SAE, AE, or dose modification), then report the information as an AE.

Reviewing and recording test results

The investigator must review the laboratory results, document this review, and report any clinically relevant changes occurring during the study as an AE. The laboratory results must be retained with source documents, unless a Source Document Agreement or comparable document cites an electronic location that accommodates the expected retention duration.

Repeat testing after clinically significant abnormal findings

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 8 weeks after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or the medical monitor. If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

Blinding of laboratory test results

Laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel.

Sample retention

Unless otherwise specified in the subsections of Section 8 or in Appendix 1, Section 10.1.12, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

8.2.5.1. Pregnancy Testing

Pregnancy testing is to be performed on WOCBP and women with a history of tubal ligation. Participants who are pregnant will be discontinued from the study (Section 7).

Pregnancy testing visits and times

Serum pregnancy test will be done at screening only, and results will be confirmed by the central laboratory.

Urine pregnancy testing will be performed locally when specified in the SoA. If the specified visit includes study drug administration, the urine pregnancy test must be “negative” within 24 hours before the study drug is administered.

Urine pregnancy testing may be performed at additional time points during the study treatment period and/or follow-up period, at the discretion of the investigator or if this is required by local regulations.

If a urine pregnancy test is not available, a local serum pregnancy test is an acceptable alternative.

Optional FSH testing

The participant's FSH level can be obtained during screening at the discretion of the investigator to assist in determining whether a woman meets the definition of "postmenopausal." The FSH level can also be optionally obtained during the study to determine the participant's postmenopausal status (see the SoA and Appendix 4).

8.2.6.Tuberculosis Testing and Monitoring

Tuberculosis testing

During screening, all participants are to be assessed for risk factors, symptoms, and signs of TB with all of the following:

- Thorough history to determine the lifetime risk factors for
    - TB infection
    - TB progression, and
    - symptoms and/or signs of active TB, and
- Signs of previous or active TB by means of
    - thorough physical examination for signs of active TB, including
        - measurement of body temperature (Section 8.2.1), and
        - assessment of peripheral lymph nodes (Section 8.2.2), and
    - posterior-anterior CXR interpreted and reported by radiologist or pulmonologist (Section 8.2.4).

All participants with no history of LTBI or active TB, and no history of positive Mantoux TST using PPD or positive *Mycobacterium tuberculosis* IGRA must have 1 of the following:

- PPD TST
    - The TST is performed by injecting 0.1 mL of tuberculin PPD into the inner surface of the forearm. The injection should be made with a tuberculin syringe, with the needle bevel facing upward. The TST is an intradermal injection. When placed correctly, the injection should produce a pale elevation of the skin (a wheal) 6 to 10 mm in diameter. Measure induration at site of intradermal

injection 48 to 72 hours after intradermal injection. The test must be read during this window of time. The reaction should be measured in millimeters of induration (palpable, raised, hardened area, or swelling). The reader should not measure erythema (redness). The diameter of the indurated area should be measured across the forearm (perpendicular to the long axis).

- An induration of 5 or more millimeters is considered positive.
- Two-step testing (repeat TST from 1 to 3 weeks after the first TST) is recommended for certain participant groups, based on investigator judgment, including
  - persons receiving immunosuppressant treatment
  - persons with a history of temporally remote increased risk of TB infection, and
  - persons for whom the first test is negative, as per local public health and/or professional medical society recommendations.

- IGRA for *Mycobacterium tuberculosis*. Ensure that specimen handling, transport, timing, and laboratory procedures meet all requirements per package insert.

Retesting

One retest is allowed for participants with an "indeterminate" QuantiFERON-TB Gold assay or "borderline" T-SPOT.TB assay. Participants with 2 indeterminate QuantiFERON-TB Gold assays or 2 borderline T-SPOT.TB assays will be excluded.

Diagnosed LTBI

Participants diagnosed with LTBI, or have had LTBI that has not been treated with a complete course of appropriate therapy as defined by the WHO and/or the United States Centers for Disease Control and Prevention, are excluded (Section 5.2).

Monitoring during the study

For all participants, monitoring for TB is to be continuous throughout the study. At a minimum, each participant is to have the following documented at least approximately every 3 to 4 months:

- thorough history to determine any risk factors for TB infection and for TB progression, symptoms or signs of active TB, and
- physical examination that includes assessment for signs of active TB, including measurement of body temperature and assessment of peripheral lymph nodes (Section 8.2.2).

8.2.7. Hepatitis B Testing and Monitoring

Initial testing for HBV infection includes hepatitis B surface antigen (HBsAg) and antibody to hepatitis B core antigen (anti-HBc).

- If HBsAg is positive, the participant is excluded.
- If HBsAg is negative and anti-HBc is negative, the participant is not excluded.
- If HBsAg is negative and anti-HBc is positive, further testing for HBV DNA is required.
    - If the screening HBV DNA is positive, the participant is excluded.
    - If the screening HBV DNA is negative, the participant is not excluded. Repeat testing for HBV DNA is required at least approximately every 8 to 14 weeks during the study (see the timing in the SoA), with temporary withholding or permanent discontinuation of study intervention if HBV DNA is positive, as described in Section 7.

Management of enrolled participants with detectable HBV DNA during the study

If HBV DNA is detected during the study, the study drug will be temporarily withheld or discontinued and participants should receive appropriate follow-up medical care as described in Section 7.

8.2.8. Hepatitis C Testing and Monitoring

Initial testing for HCV infection includes testing for antibodies to HCV.

- If anti-HCV is positive, a serum test for circulating HCV RNA is required.
- If HCV RNA test is negative, the participant is not excluded.
- If HCV RNA test is positive, the participant is excluded (see Section 5.2).

Participants who have had HCV infection and been successfully treated, defined as a sustained virologic response (HCV RNA by PCR negative for at least 24 weeks following treatment completion) are not excluded on the basis of HCV, as long as HCV RNA test is negative at screening.

If HCV RNA is detected during the study, the study drug will be discontinued (see Section 7), and the participant should receive appropriate follow-up medical care.

8.2.9. Hepatic Safety Monitoring

Close hepatic monitoring

The laboratory tests listed in Appendix 5, including ALT, AST, ALP, TBL, direct bilirubin, GGT, and CK, should be repeated within 48 to 72 hours to confirm the abnormality and to determine whether it is increasing or decreasing, if any of the conditions listed in this table occur.

If a participant has the following elevations:
ALT or AST ≥3 times ULN
ALP ≥2 times ULN
TBL ≥2 times ULN (except for patients with Gilbert's syndrome)

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin level; ULN = upper limit of normal.

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for the possible causes of the abnormal liver tests should be initiated by the investigator in consultation with the sponsor's designated medical monitor. At a minimum, this evaluation should include a physical examination and a thorough medical history, including symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), recent travel, history of concomitant medications (including over-the-counter), herbal and dietary supplements, history of alcohol drinking, and other substance abuse.

Initially, monitoring of symptoms and hepatic biochemical tests should be done at a frequency of 1 to 3 times weekly, based on the participant's clinical condition and hepatic biochemical tests. Subsequently, the frequency of monitoring may be lowered to once every 1 to 2 weeks, if the participant's clinical condition and lab results stabilize. Monitoring of ALT, AST, ALP, and TBL should continue until levels normalize or return to approximate baseline levels.

Comprehensive hepatic evaluation

A comprehensive evaluation should be performed to search for possible causes of liver injury, if 1 or more of the conditions listed in this table occur:

If a participant has the following elevations:
ALT or AST ≥3 times ULN with hepatic signs/symptoms[a], or ALT or AST ≥5 times ULN
ALP ≥3 times ULN
TBL ≥2 times ULN (except for patients with Gilbert's syndrome)

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin level; ULN = upper limit of normal.

[a] **Hepatic signs/symptoms are severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.**

At a minimum, this evaluation should include a physical examination and a thorough medical history, as outlined above, as well as

- tests for prothrombin time (PT-INR)
- tests for viral hepatitis A, B, C, and E, and
- tests for autoimmune hepatitis, and an abdominal imaging study (for example, ultrasound or CT scan).

Based on the participant's history and initial results, further testing should be considered in consultation with the sponsor's designated medical monitor, including tests for

- hepatitis D virus (HDV)
- cytomegalovirus (CMV)
- Epstein-Barr virus (EBV)
- acetaminophen levels
- acetaminophen protein adducts
- urine toxicology screen

- Wilson's disease
- blood alcohol levels
- urinary ethyl glucuronide, and
- serum phosphatidylethanol.

Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a

- hepatologist/gastroenterologist consultation
- magnetic resonance cholangiopancreatography (MRCP)
- endoscopic retrograde cholangiopancreatography (ERCP)
- cardiac echocardiogram, or
- liver biopsy.

8.2.9.1. Additional Hepatic Data Collection in Participants Who Have Abnormal Liver Tests During the Study

Additional hepatic safety data collection (hepatic safety eCRF) should be performed for participants who meet 1 or more of the following conditions:

- Elevation of serum ALT to ≥5 times ULN on 2 or more consecutive blood tests
- Elevated TBL to ≥2 times ULN (except for cases of known Gilbert's syndrome)
- Elevation of serum ALP to ≥2 times ULN on 2 or more consecutive blood tests
- Hepatic event considered to be an SAE.
- Discontinuation of study drug due to a hepatic event (Section 7.1).

Note: The interval between the 2 consecutive blood tests should be at least 2 days.

8.2.10. Suicidal Ideation and Behavior Risk Monitoring

Participants should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior, especially at the beginning and end of the course of intervention. Participants who have signs of suicidal ideation or behavior should be considered for discontinuation of study drug, following a risk assessment (see Section 7). See Section 8.3.1.1 for timing of AE collection relative to collection of the C-SSRS.

8.2.10.1. Columbia Suicide-Severity Rating Scale

The C-SSRS is a scale that captures the occurrence, severity, and frequency of suicidal ideation and behavior during the assessment period via a questionnaire. The scale was developed by the National Institute of Mental Health (NIMH) trial group (TASA) for the purpose of being counterpart to the Columbia Classification Algorithm of Suicide Assessment (C-CASA) categorization of suicidal events.

For this study, the C-SSRS is adapted for the assessment of the ideation and behavior categories only. The Intensity of Ideation and Lethality of Behavior sections are removed.

The C-SSRS data will entered in the eCRF.

8.2.10.2. Depression Assessment with 16-Item Quick Inventory of Depressive Symptomatology–Self Report

The QIDS-SR16 is a self-administered, 16-item instrument intended to assess the existence and severity of symptoms of depression as listed in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 5th Edition.[19] A participant is asked to consider each statement as it relates to the way he or she has felt for the past 7 days. There is a 4-point scale for each item ranging from 0 to 3. The 16 items corresponding to 9 depression domains are summed to give a single score ranging from 0 to 27, with higher scores denoting greater symptom severity. The domains assessed by the instrument include

1) sad mood
2) concentration
3) self-criticism
4) suicidal ideation
5) interest
6) energy/fatigue
7) sleep disturbance (initial, middle, and late insomnia or hypersomnia)
8) decrease/increase in appetite/weight, and
9) psychomotor agitation/retardation.

The QIDS-SR16 data will be collected via a tablet device and/or a web-based collection system.

8.3. Adverse Events and Serious Adverse Events

Adverse events will be reported by the participant or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or the study (see Section 7).

Pregnancy after maternal or paternal exposure to IP does not meet the definition of an AE. However, to fulfill regulatory requirements, any pregnancy should be reported using the SAE process described in Section 10.3.4, to collect data on the outcome for both mother and fetus. See also Section 8.3.5.

8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All AEs will be collected from the time of the participant's signing of the ICF until the participant's last post-treatment follow-up visit.

Likewise, all SAEs will be collected from the signing of the ICF until the last post-treatment follow-up visit.

Adverse events that begin before the start of study intervention but after signing of the ICF will be recorded on the Adverse Event eCRF.

Although all AEs after signing the ICF are recorded by the site in the eCRF/electronic data entry tool, SAE reporting to the sponsor begins after the participant has signed the ICF and has received study drug. However, if an SAE occurs after signing the ICF but prior to receiving study drug, the SAE needs to be reported ONLY if the SAE is considered reasonably possibly related to study procedures.

All SAEs will be recorded and reported to the sponsor or the sponsor's designee immediately, and under no circumstance should this exceed 24 hours, as indicated in Appendix 3, Section 10.3.4. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAEs after the conclusion of study participation, that is, once the participants have discontinued and/or completed the study (the Participant Study Disposition eCRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.1.1. Adverse Event Monitoring with a Systematic Questionnaire

Nonleading (spontaneous) AE collection should occur before the collection of the C-SSRS.

If a suicide-related event is discovered during the C-SSRS collection, but was not captured during the nonleading AE collection, sites should not change the AE form. However, if an AE is serious or leads to discontinuation, the AE should be included on the AE form. Also, the process for reporting SAEs should be followed.

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3, Section 10.3.3 and Section 10.3.4.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of Adverse Events and Serious Adverse Events

After the initial AE or SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs as well as AESIs, as defined in Section 8.3.6, will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up, as defined in Section 7.3. Further information on follow-up procedures is provided in Appendix 3, Section 10.3.3.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/ IEC, and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (for example, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

For female participants and female partners of male participants, details will be collected for all pregnancies occurring from after the start of study intervention and until 12 weeks after the last dose.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the reporting procedures outlined in Appendix 4, Section 10.4.3.

Abnormal pregnancy outcomes (for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6. Adverse Events of Special Interest

Adverse events of special interest for this study include

- systemic allergic/hypersensitivity reactions, including CRS
- serious infections and opportunistic infections, and
- injection site reactions.

If such AESIs are reported, sites will be prompted to collect additional data as described in the following subsections.

8.3.6.1. Systemic Hypersensitivity Reactions

Many drugs, but particularly biologic agents, carry the risk of systemic hypersensitivity reactions. If such a reaction occurs, additional data describing each symptom should be provided to the sponsor in the eCRF.

Sites should have appropriately trained medical staff and appropriate medical equipment available when the study participants are receiving study drug. It is recommended that participants who experience a systemic hypersensitivity reaction be treated per national and international guidelines.

Blood sample collection for systemic allergic/hypersensitivity events, including cytokine release syndrome

In the case of generalized urticaria or anaphylaxis, additional samples as described in Appendix 2, Section 10.2.2 should be collected. Laboratory results are provided to the sponsor via the central laboratory.

8.3.6.2. Serious Infections and Opportunistic Infections

Completion of the Infection eCRF page is required for each infection reported as an AE or SAE. The sponsor will identify infections considered to be opportunistic based on the article by Winthrop et al.[16] (see Appendix 6).

8.3.6.3. Injection Site Assessment

Symptoms of a local injection site reaction may include erythema, induration, pain, pruritus, and edema.

If a participant reports symptoms (that is, an unsolicited event, volunteered by participant) and the investigator's designee or the investigator determines that a clinically relevant injection site reaction has occurred, the event will be captured in the eCRF as an AE. In addition, the injection site reaction form in the eCRF will be completed. The event will be followed up to completion.

See Section 6.3 for activities relating to injection site reactions.

8.3.7. Complaint Handling

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a trial intervention. The sponsor collects product complaints on IPs and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Participants will be instructed to contact the investigator as soon as possible if they have a complaint or problem with the IP so that the situation can be assessed.

Note: Any AEs/SAEs that are associated with a product complaint will follow the processes outlined in Section 8.3.3 and Appendix 3.

Time period for detecting product complaints

Product complaints that result in an AE will be detected, documented, and reported to the sponsor during all periods of the study in which the drug/device is used. If the investigator learns

of any product complaint at any time after a participant has been discharged from the study, and such problem is considered reasonably related to a drug/device provided for the study, the investigator will promptly notify the sponsor.

Prompt reporting of product complaints to the sponsor

Product complaints will be reported to the sponsor within 24 hours after the investigator becomes aware of the complaint. The Product Complaint Form will be sent to the sponsor by methods designated by the sponsor.

Follow-up of product complaints

Follow-up applies to all participants, including those who discontinue study intervention. The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the product complaint. New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator and submitted to the sponsor.

8.4. Treatment of Overdose

For this study, an overdose of LY3471851 is considered any dose greater than the highest dose planned to be used in this study. The treatment for suspected overdose is supportive care.

In the event of an overdose, the investigator should:

1. Contact the sponsor's medical monitor immediately.
2. Closely monitor the participant for any AE, SAE, or laboratory abnormalities for at least 12 weeks.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the sponsor's medical monitor based on clinical evaluation of the participant.

8.5. Pharmacokinetics

Pharmacokinetic sample visits and times

At the visits and times specified in the SoA, venous blood samples will be collected to determine the plasma concentrations of LY3471851. The actual date and time (24-hour clock time) of dosing and sample collection must be recorded accurately on the appropriate forms.

Collection, handling, and analysis of pharmacokinetic samples

Instructions for the collection and handling of blood samples will be provided by the sponsor. Samples will be analyzed at a laboratory approved by the sponsor. Concentrations of LY3471851 will be assayed using a validated PK assay. Analyses of samples collected from participants while receiving placebo are not planned.

Additional and unused pharmacokinetic samples

A maximum of 3 additional samples may be collected at additional time points during the study, if warranted and agreed upon between both the investigator and sponsor. Any excess samples collected for PK testing may be used for exploratory analyses, such as bioanalytical methods

development, assay validation or cross-validation exercises, protein binding, and/or metabolism work.

In the case of systemic allergic/hypersensitivity reactions, additional blood samples will be obtained for PK analyses (Section 8.3.6.1).

Blinding pharmacokinetic data

Drug concentration information that may unblind the study will not be reported to investigative sites or to personnel who are blinded to study data.

Pharmacokinetic sample retention

The purpose of retention, the maximum duration of retention, and facility for long-term storage of samples is described in Appendix 1, Section 10.1.12.

8.6. Pharmacodynamics

The PD biomarkers to be measured include changes in T-cell subsets.

Pharmacodynamic biomarker sample visits and times

At the visits and times specified in the SoA, blood samples will be collected for the exploratory analysis of PD biomarkers.

Pharmacodynamic biomarker sample retention

The purpose of retention, the maximum duration of retention, and facility for long-term storage of samples is described in Appendix 1, Section 10.1.12.

8.7. Genetics

Where local regulations and IRB/IEC allow, a whole blood sample will be collected from consenting participants, as specified in the SoA, for pharmacogenetic analysis .

Genetic sample use

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to

- genetic determinants that impact drug absorption, distribution, metabolism, and excretion
- mechanism of action of the drug
- disease etiology, and/or
- molecular subtype of the disease being treated.

Samples may be used for research related to LY3471851 and its mechanism of action, the drug target, genetic variants thought to play a role in UC, on the disease process and pathways associated with the disease or related diseases. The samples may also be used to develop tests or diagnostic tools or assays related to UC or to LY3471851. The samples may also be used to investigate variable exposure or response to LY3471851. The assessment of variable response may include evaluation of AEs or differences in efficacy.

Molecular technologies are expected to improve during storage period and therefore cannot be specifically named. However, existing genetic research approaches include whole genome or exome sequencing, genome-wide association studies, and candidate gene studies. Regardless of technology utilized, genotyping data generated will be used only for the specific research scope described in this protocol. The samples may be analyzed as part of single or multi-study assessment of genetic factors involved in the response to LY3471851 or to study interventions of this class to improve understanding of the disease or related conditions, and additional analyses may be conducted, if necessary, to further understand the clinical data of this study.

Genetic sample confidentiality

All samples will be coded with the participant number. These samples and any data generated can be linked back to the participant only by the investigative site personnel. The sponsor will store the blood and/or DNA samples in a secure storage space with adequate measures to protect confidentiality.

Genetic sample retention

Samples will be retained at a facility selected by the sponsor or its designee. Samples will be retained as long as research on the study indication, study intervention, or the class of study intervention continues, but no longer than the maximum retention time specified in Appendix 1, Section 10.1.12.

8.8. Biomarkers

The following samples will be collected at the visits and times specified in the SoA, where local regulations allow:

- serum
- plasma
- whole blood RNA
- whole blood epigenetic samples for nonpharmacogenetic biomarker research
- fecal matter, and
- colonic tissue samples.

Biomarker sample use

Samples may be used for research on the

- drug target
- disease process
- variable response to LY3471851
- pathways associated with UC
- mechanism of action of LY3471851, and/or

- research methods or in validating diagnostic tools or assays related to UC or to LY3471851.

Biomarker sample confidentiality

All samples will be coded with the participant number. These samples and any data generated can be linked back to the participant only by the investigative site personnel.

Biomarker sample retention

The purpose of retention, the maximum duration of retention, and facility for long-term storage of samples is described in Appendix 1, Section 10.1.12.

8.10. Medical Resource Utilization and Health Economics

This section is not applicable.

9. Statistical Considerations

9.1. Statistical Hypotheses

The null hypothesis for the primary endpoint is that there is no difference between LY3471851 and placebo in inducing clinical remission in patients with moderately to severely active UC, as measured by the proportion of study participants in clinical remission at Week 12.

9.2. Sample Size Determination

Approximately 200 total participants, in total, may be randomized across all study stages.

- During Stage 1, approximately 100 participants will be randomized to 1 of 3 treatment groups in a 2:2:1 ratio:
  - a high dose (CCI µg) of LY3471851
  - a lower (CCI µg) dose of LY3471851, or
  - placebo.
- During Stage 2, up to approximately 100 additional participants will be randomized. As stated in Section 4.1, Stage 2 will have a placebo group and may have more LY3471851 treatment groups than Stage 1, or fewer, based on decisions taken after the last interim analysis of Stage 1. The randomization ratio for Stage 2 will determined and documented as part of the decision-making about the number of treatment groups. This decision making will occur following Stage 1, and the choice in allocation ratio may be adjusted to achieve the planned allocation across treatment arms.

The power calculations for this study assume the following:

- At end of study, three non-placebo treatment groups will have sample size of approximately either 40, 60, or 80 patients.
- At end of study, the placebo group will have a sample size of approximately 40.
- For the sake of simplicity in the power calculation, it is assumed that there is no difference in treatment effect between advanced therapy-failed and conventional-failed patients. To simplify, it is also assumed that all treatment groups have the same treatment effect.
- It is assumed that the true placebo response rate is approximately 5% and the true treatment response is approximately 35%.
- Power is calculated for 3 tests, 1 for each treatment group against placebo, and adjust for multiple comparisons using the conservative Bonferroni adjustment. Power is calculated using a family-wise error rate of α=.05.

Given these assumptions, the power to reject the null hypotheses for the treatment groups with sample sizes equal to 40, 60, and 80 are 89.5%, 94.5%, and 96.5%, respectively. As an example, in a fixed design, with the placebo and LY3471851 treatment groups each having 80 participants, a 17% or larger difference between the groups can be detected with 90% power and assuming a 5% placebo effect.

9.3. Populations for Analyses

This table describes the populations planned for use in the analyses. The mITT population, as defined below, will be used in analyses of efficacy and PRO, unless otherwise noted in the SAP.

Population	Description
ITT Population	All randomized participants. Participants will be analyzed according to the treatment to which they were assigned.
mITT Population	All randomized participants who receive at least 1 dose of study treatment (regardless of whether the participant fails to receive the correct treatment, or otherwise fails to follow the protocol). Participants will be analyzed according to the treatment to which they were assigned.
Safety Population	Same as mITT population
Pharmacokinetic Evaluable	All participants who receive at least 1 dose of investigational product and have sufficient blood sampling to allow for pharmacokinetic evaluation.

Abbreviations: GCP = Good Clinical Practice; ITT = intent-to-treat; mITT = modified intent-to-treat; SAP = statistical analysis plan.

9.4. Statistical Analyses

9.4.1. General Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee.

Efficacy analyses will be conducted on the mITT population. Safety analyses will be conducted on the mITT population (Safety Population). The efficacy analysis of the primary endpoint and secondary endpoints will be repeated for ITT population. Additional safety analyses may be performed as deemed appropriate.

The baseline MMS is calculated from valid daily diary entries obtained prior to endoscopy during the screening period and the endoscopic appearance of the mucosa at this screening endoscopy. For other efficacy, health outcome and safety assessments, baseline is defined as the last non-missing assessment recorded on or prior to the date of the randomization visit (Visit 2).

Summary statistics for continuous variables may include mean, standard deviation, median, and minimum and maximum values. Categorical variables will be presented as counts and percentages. Unless otherwise specified, variables will be analyzed in the original scale on which they are measured. The parametric approach will be employed by default for statistical analysis except when nonparametric analysis, such as by a rank-based method, is considered to be more fitting. Additional exploratory analyses of the data will be conducted as deemed appropriate.

Unless otherwise specified, analysis of hypotheses will be tested without multiplicity control at a significance level of 0.05. A 2-sided 95% CI will be provided along with the p-value. For other analyses, statistical tests without multiplicity control will be conducted using a 2-sided significance level of 0.05. The corresponding p-value along with its 95% 2-sided CI will be provided. Additional analyses may also include subgroup analyses for the primary and the secondary endpoints.

For assessments of the primary endpoint and other categorical efficacy endpoints, the CMH chi-square test will be used to compare the treatment groups with the following factors:

- previous advanced therapy failure status (yes/no)
- baseline corticosteroid use (yes/no)
- baseline disease activity (MMS: [4 to 6] or [7 to 9]), and
- region (North America/Europe/Other).

The CMH chi-square p-value and the relative risk along with its 2-sided CI will be provided. In addition, the absolute treatment difference in proportions will be provided along with the 2-sided CI estimate. The differences between each treatment group and placebo will also be tested separately using a logistic regression model that controls for at least previous advanced therapy failure status (yes/no) and corticosteroid use (yes/no). If deemed necessary, additional analyses of categorical efficacy variables may be conducted to address sparse data and/or small sample sizes.

Treatment comparisons of continuous efficacy and health outcome variables with multiple postbaseline time points will be made using MMRM analysis. The MMRM will include the following effects and covariates:

- treatment group
- previous advanced therapy failure status (yes/no)
- corticosteroid use (yes/no)
- disease activity (MMS: [4 to 6] or [7 to 9]) at baseline)
- region (North America/Europe/Other)
- baseline value in the model
- visit, and
- the interactions of treatment-by-visit and baseline-by-visit as fixed factors.

The covariance structure to model the within-participant errors will be unstructured. If the unstructured covariance matrix results in a lack of convergence, the heterogeneous Toeplitz covariance structure, followed by the heterogeneous autoregressive covariance structure, will be used. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. Type III sums of squares for the LS means will be used for the statistical comparison; the 95% CI will also be reported.

Treatment comparisons of continuous efficacy and health outcome variables with a single postbaseline time point will be made using ANCOVA with the following in the model:

- treatment group
- previous advanced therapy failure status (yes/no)
- corticosteroid use (yes/no)
- disease activity (MMS: [4 to 6] or [7 to 9]) at baseline)
- region (North America/Europe/Other), and

- baseline value.

Type III sums of squares for LS means will be used for statistical comparison between treatment groups. The LS mean difference, standard error, p-value, and 95% CI, unless otherwise specified, will also be reported. Missing data imputation method for the ANCOVA model will be specified in the SAP.

Any change to the data analysis methods or imputation methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the SAP and the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

The SAP will be finalized prior to unblinding or interim analysis, whichever occurs first. The SAP will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1.1. Estimands

The estimand[35] associated with each endpoint and analysis is documented in this table.

Estimand Topic	Location
Population of interest	"Inclusion Criteria" and "Exclusion Criteria" (Section 5.1 and 5.2) and "Populations for Analyses" (Section 9.3)
Endpoints and variables	"Objectives and Endpoints" (Section 3)
handling of intercurrent events	Objectives and Endpoints" (Section 3) and additional details to be provided in the SAP
Population summary measures	"General Considerations" (Section 9.4.1)

9.4.1.2. Missing Data Imputation

While every effort will be made to minimize missing data, the missing data imputation methods described here will be used to provide a conservative approach for assessing efficacy endpoints when participants are permanently discontinued from study drug or otherwise have missing data.

- Nonresponder imputation (NRI): For analysis of categorical efficacy and health outcomes variables, missing data will be imputed using an NRI method. Participants will be considered nonresponders for the NRI analysis if they do not meet the categorical efficacy criteria or have missing clinical efficacy data at a time point of interest.
- The NRI method may be used when the estimand of interest uses the composite strategy[35] for handling intercurrent events. In this strategy, participants with any intercurrent events that lead to the permanent discontinuation of assigned study treatment are defined to have failed treatment for all subsequent timepoints.
- In addition, participants who were not adequately assessed to determine if they meet the clinical requirements for response at the time point of interest are also considered to have failed treatment.
- Mixed-effect Model for Repeated Measures (MMRM): For continuous variables, the primary analysis will be MMRM with the missing at random assumption for handling

missing data. This analysis takes into account both missingness of data and the correlation of the repeated measurements. No additional imputation methods will be applied to the MMRM analysis. The MMRM method may be justified when the estimand of interest uses the hypothetical strategy[35] for handling intercurrent events. In this strategy, the scientific question of interest is to assess the effect of study treatment in a hypothetical trial where all patients have complete data and continue to take study treatment without dropping out of the study or receiving rescue therapy.

For participants discontinuing study drug for any other reason, the last nonmissing postbaseline observation before discontinuation will be carried forward to the corresponding primary endpoint for evaluation.

Additional missing data imputation methods, for example, modified baseline observation carried forward (mBOCF) may be considered as sensitivity analyses and will be described in the SAP. Using mBOCF imputation, participants who discontinue the study drug due to an AE or lack of efficacy will have their baseline observation carried forward to the corresponding primary endpoint for evaluation. Other missing data imputations methods, for example, based on multiple imputations (MI) or hybrid approaches (NRI and MI-based) may also be considered. Those sensitivity analyses and other additional methods of handling missing data or analyzing the data that may be required to satisfy regulatory needs or for other purposes will be specified in the SAP.

9.4.1.3. Adjustment for Multiple Comparisons

Adjustment for multiple comparisons will not be employed in the analysis for this study.

9.4.2. Treatment Group Comparability

9.4.2.1. Participant Disposition

The number of randomized participants will be summarized. Frequency counts and percentages of all participants who are randomized, complete the study, and those who discontinue the study drug or the study early will be presented. Reasons for discontinuing the study drug or the study will be summarized.

9.4.2.2. Participant Characteristics

Demographic data are collected and responded to demonstrate that the study population represents the target patient population. A summary of baseline participant characteristics, historical diagnoses, preexisting conditions, and prior therapies will be reported by treatment group using descriptive statistics. Other participant characteristics will be summarized by treatment group, or listed, as deemed appropriate.

9.4.2.3. Concomitant Therapy

Current concomitant therapy (reported after randomization) will be summarized by treatment group and will be presented by Anatomical Therapeutic Chemical (ATC) drug classes using the latest version of the WHO drug dictionary. Previous concomitant therapy (reported before randomization and after ICF) will be listed.

9.4.2.4. Treatment Compliance

Participants who are noncompliant with treatment will be listed by treatment group. The details of noncompliance will be defined in the SAP. No analyses are planned to assess treatment compliance.

9.4.3. Efficacy Analyses

9.4.3.1. Primary Analyses

The primary efficacy end point of clinical remission will be assessed using the MMS, a 9-point instrument that includes the SF, RB, and ES subscores of the Mayo Score (see Section 8.1).

At the screening visit, each participant will be asked to identify how many stools he or she had in a 24-hour period when in remission from UC. If the participant does not report that he or she has achieved remission, then he or she will be asked to identify the number of stools he or she had per day before initial onset of signs and symptoms of UC. The response to these questions will be used as the reference SF for the calculation of the Mayo SF subscore.

For the study visits associated with an endoscopy, the SF and RB subscores of the Mayo Score will be calculated from the patient-reported daily electronic diary data. Details regarding the calculation will be provided in the SAP.

The primary endpoint analysis will utilize the CMH test as described in Section 9.4.1.

Additional analyses of the primary endpoint may be considered and details will be provided in the SAP.

9.4.3.2. Secondary Analyses

The secondary efficacy and health outcome endpoints will use the analysis methods described in Section 9.4.1.

9.4.4. Safety Analyses

Safety analyses will include AEs, SAEs, AESIs, C-SSRS, QIDS-SR16, vital signs, ECGs, and laboratory analytes, using the Safety Population data descriptively summarized by treatment group. Categorical safety measures will be summarized with incidence rates. Continuous safety measures will be summarized as mean change by visit. Exposure to study intervention will be calculated for each participant and summarized by treatment group.

Adverse events will be coded according to MedDRA and summarized by system organ class, preferred term, severity, and relationship to the study intervention. A TEAE is defined as an event that first occurred or worsened in severity after baseline, with baseline defined as all pre-existing conditions recorded at Visit 1 and any AEs recorded before the first dose of study intervention (that is, during the interval between Visits 1 and 2, and recorded with the time of onset before the first dose of study intervention). The treatment period will be used as the postbaseline period for the analysis. For events that are gender specific, the denominator and computation of the percentage will include only participants from the given gender.

The number and percentage of participants who experienced TEAEs, TEAEs by maximum severity, deaths, SAEs, TEAEs related to study intervention, discontinuations from the treatment due to an AE, and AESIs will be summarized. Treatment-emergent adverse events (all, by

maximum severity), SAEs including deaths, and AEs that lead to treatment discontinuation will be summarized and analyzed by MedDRA SOC and preferred term.

Treatment-related TEAEs (TEAEs related to study intervention) are defined as events that are indicated by the investigator on the eCRF to be related to treatment.

Adverse events of special interest will be identified by a standardized MedDRA query (SMQ) or a Lilly-defined MedDRA preferred term listing.

Follow-up emergent AEs, SAEs including deaths, and AEs that lead to study discontinuation will be summarized. All AEs, including pre-existing conditions, will be listed by participant, visit, preferred term, treatment group, severity, and relationship to the treatment.

The Fisher exact test will be used to perform the between-treatment group comparisons for AEs, discontinuations, and other categorical safety data. The change from baseline in continuous vital signs, physical characteristics, and other continuous safety variables, including laboratory variables, will be summarized visit and by treatment. The change from baseline to last observation value will be analyzed with ANOVA model with baseline as a covariate. The last non-missing observation in the treatment period will be used as the last observation.

9.4.5. Pharmacokinetic/Pharmacodynamic Analyses

Plasma concentrations of LY3471851 will be listed by time point using descriptive statistics. The PK of LY3471851 may also be characterized using graphical evaluations and mixed-effect (population PK) modeling approaches via NONMEM with the NONMEM software.

Analyses of exposure-response relationships may be conducted using both exploratory graphical approaches and model based approaches. For example, exploratory graphical analysis approaches may consist of graphs showing the percentages of study participants who achieve clinical response, clinical remission, and endoscopic normalization at different percentiles (for example, quartiles) of exposure of LY3471851 at Week 12. Model-based analyses may utilize population exposure-response logistic regression models or longitudinal exposure response models.

Additional analyses may be conducted if deemed appropriate. Data from this study may be combined with other study data, if appropriate. Further details on PK and PK/PD analyses will be provided in the PK/PD analysis plan.

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9.4.7. Subgroup, Supplemental, and Other Exploratory Analyses

Subgroup analyses

Subgroup analyses will be conducted for the primary endpoint and select secondary endpoints. Subgroups to be evaluated may include

- sex
- age category
- body weight
- race
- geographic region
- baseline disease severity and activity
- duration and location of disease
- previous systemic therapy
- previous advanced therapy, and
- concomitant therapy for UC.

If any group within the subgroup is less than 10% of the total population, only summaries of the efficacy data will be provided (that is, no inferential testing). Additional subgroup analysis will be defined in the SAP

Supplemental analyses

Supplemental analyses will be performed on the primary endpoint using a using a logistic random effects model with treatment, baseline, visit, and visit-by-treatment interaction. Additional analyses of secondary endpoints may be performed using the same random effects model. Analysis details will be provided in the SAP.

Exploratory analyses

Exploratory efficacy endpoint data, PD data, and biomarker data will be analyzed as described in the SAP.

9.5. Interim Analyses

Analyses for the primary database lock will be conducted when all participants have completed the Induction Period (that is, had completed the Week 12 visit) or else have discontinued study treatment.

As noted in Section 4.1, several interim analyses will be conducted prior to the primary database lock. These interim analyses will be used to support planning activities associated with this study and the LY3471851 clinical development program. Since the study may terminate early only for

safety reasons, for futility, or for both, no adjustment of type I error will be performed. Interim futility details will be provided in the SAP.

The following interim analyses may be considered.

Interim analysis to…	an interim analysis of	Will be conducted when…
Support planning activities, possibly including early termination	mITT population	Approximately 50 patients have completed 12 weeks of treatment or discontinued treatment.
Support planning activities, possibly including early termination	mITT population	Approximately 100 patients have completed 12 weeks of treatment or discontinued treatment.

Additional interim analyses may be performed only if deemed necessary by the sponsor to address critical questions.

An assessment of unblinded interim data will be conducted by an internal assessment committee (IAC) with a limited number of prespecified team members who do not have direct site contact or data entry or validation responsibilities (see Appendix 1, Section 10.1.5). Only the IAC is authorized to evaluate unblinded interim efficacy and safety analyses.

Prior to the interim or final database locks, a limited number of preidentified individuals may gain access to the unblinded data in order to initiate the population PK/PD model development processes for interim or final analyses. To minimize bias, the SAP and PK/PD analysis plan will be finalized and approved before any unblinding. Unblinding details will be specified in the SAP and Unblinding Plan. Information that may unblind the study during the analyses will not be reported to study sites or to the blinded study team until the prespecified milestone for unblinding of study results. Study sites will receive information about interim results only if they need to know for the safety of their participants.

9.6. Data Monitoring Committee

Not applicable. An IAC will be used to conduct the interim analysis (see Section 9.5 and Appendix 1, Section 10.1.5).

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH GCP Guidelines, and
- Applicable laws and regulations.

The protocol, protocol amendments and addenda, ICF, IB, and other relevant documents (for example, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures, and
- Providing oversight of study conduct for participants under their responsibility and adherence to requirements of 21 United States Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

Investigator sites are compensated for participation in the study as detailed in the clinical trial agreement (CTA).

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for one year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his or her representative will explain the nature of the study, including the risks and benefits, to the participant or his or her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary.

Participants or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant was entered in the study, and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants who are rescreened are required to sign a new ICF (see Section 5.4).

Participants must be reconsented to the most current version of the ICF during their participation in the study.

A copy of the ICF must be provided to the participant or the participant's legally authorized representative and is kept on file.

10.1.4. Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets, or tissue samples that are transferred to the sponsor will contain the identifier only. Participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his or her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for his or her data to be used as described in the informed consent.

The participant must be informed that his or her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The sponsor has processes in place to ensure data protection, information security and data integrity. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

10.1.5. Committees Structure

Internal Assessment Committee (IAC)

In addition to the safety reviews routinely performed by the blinded study team, an IAC will review the safety data in an unblinded fashion periodically or on an ad hoc basis during the study and will determine whether any changes (for example, dose reductions or other protocol modifications) should be made (see also Section 10.1.9).

The IAC reviewing the safety data will be fully independent from the study team and will include, at a minimum, a Lilly medical physician, a statistician, and a representative from the Lilly Global Patient Safety organization. Details about IAC membership, purpose, responsibilities, and operation will be described in an IAC charter, which will be approved prior to the first unblinding.

Investigators and site personnel will receive information about interim analysis results only if they need to know for the safety of their study participants.

10.1.6. Dissemination of Clinical Study Data

Reports

The sponsor will disclose a summary of study information, including tabular study results, on publicly available websites where required by local law or regulation.

Data

The sponsor provides access to all individual participant data collected during the trial, after anonymization, with the exception of PK or genetic data. Data are available to request 6 months after the indication studied has been approved in the United States and European Union and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available.

Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, SAP, clinical study report, and blank or annotated CRFs, will be provided in a secure data sharing environment for up to 2 years per proposal.

For details on submitting a request, see the instructions provided at www.vivli.org.

10.1.7. Data Quality Assurance

Investigator responsibilities

All participant data relating to the study will be recorded on a printed or eCRF unless transmitted to the sponsor or designee electronically (for example, laboratory data).

The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF. This documentation might include laboratory and diagnostic test reports, medical records, and clinical notes.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Data monitoring and management

Monitoring details describing strategy (for example, risk-based initiatives in operations and quality, such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques are provided in the Monitoring Plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data. The sponsor assumes accountability for actions delegated to other individuals (for example, contract research organizations).

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records retention and audits

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the CTA unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

In addition, the sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by the sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data Capture System

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor.

An EDC system will be used in this study for the collection of eCRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided EDC system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the eCRF.

Additionally, some of the clinician-administered questionnaire data will be collected by the authorized site personnel via a paper source document and will be transcribed by the authorized site personnel into the EDC system. See the SoA for scales administered via paper.

Additionally, eCOA data (patient-reported outcome and clinician-administered questionnaires) will be directly recorded by the participant and authorized study personnel into an instrument (for example, tablet and/or a web-based collection system). The eCOA data will serve as the source documentation, and the investigator does not maintain a separate, written or electronic record of these data. See Section 1.3 for scales administered electronically.

Data collected via the sponsor-provided data capture systems will be stored at third parties. The investigator will have continuous access to the data during the study and until decommissioning of the data capture systems. Prior to decommissioning, the investigator will receive an archival copy of pertinent data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system, and reports will be provided to the investigator for review

and retention. Data will subsequently be transferred from the central vendor to the sponsor's data warehouse.

Data from complaint forms submitted to the sponsor will be encoded and stored in the global product complaint management system.

10.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The definition of what constitutes source data can be found in Section 10.1.7.

10.1.9. Study and Site Start and Closure

The study start date is the date on which the clinical study is open for recruitment of participants.

The study or a study site will be discontinued if the sponsor or its designee judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Closure of study sites

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided a reasonable cause exists and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include, but are not limited to,

- failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- inadequate recruitment of participants by the investigator, and
- discontinuation of further study intervention development.

Study stopping rules

The IAC will convene to evaluate unblinded safety data if

- 5 or more participants experience TEAEs in the same SOC or 3 or more participants experience a TEAE of CRS, and
    - these TEAEs are judged as either serious or severe, and
    - these TEAEs are related to blinded study treatment.

Study enrollment and/or further dosing may be stopped, pending the decision of the IAC (Section 9.5 and Section 10.1.5). If the study is not stopped, the IAC will meet periodically. Details are provided in the IAC charter.

Interim analyses will be performed as described in Section 9.5. Details will be provided in the SAP. If the study is deemed futile, study enrollment and/or further dosing may be stopped.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organizations used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and assure appropriate participant therapy and/or follow-up.

10.1.10. Publication Policy

In accordance with the sponsor's publication policy, the results of this study will be submitted for publication by a peer-reviewed journal.

10.1.11. Investigator Information

Physicians with a specialty in gastroenterology will participate as investigators in this clinical trial.

10.1.12. Long-Term Sample Retention

Sample retention enables use of new technologies, response to regulatory questions, and investigation of variable responses that may not be observed until later in the development of LY3471851 or after LY3471851 becomes commercially available.

The following table lists the maximum retention period for sample types.

The retention period begins after the last participant visit for the study.

The maximum retention times may be shorter, if specified in local regulations and/or if ERBs/IRBs impose shorter time limits, or by decision of the sponsor.

Any samples remaining after the specified retention period will be destroyed.

The sample retention facility will be selected by the sponsor or its designee.

Sample Type	Custodian	Retention Period after Last Participant Visit
Pharmacokinetics	Sponsor or designee	2 years
CCI [redacted]	Sponsor or designee	Up to 15 years
Pharmacogenetics	Sponsor or designee	Up to 15 years
CCI [redacted]	Sponsor or designee	Up to 15 years

10.2. Appendix 2: Clinical Laboratory Tests

10.2.1. Clinical Laboratory Tests

The clinical laboratory tests detailed here will be performed by a central laboratory or by a local laboratory as specified in the tables.

If laboratory tests are done to obtain laboratory results with an intent to resume the study drug after a temporary interruption of study drug, the samples should be assayed centrally.

Additional tests may be performed at any time during the study as determined necessary by the investigator or as required by local regulations.

Protocol-specific requirements for the inclusion or exclusion of participants are specified in Section 5.

Pregnancy testing is described in the SoA, in Section 8.2.5.1, and in the table in this section.

Investigators must document their review of the laboratory safety results.

Laboratory test results that could unblind the study will not be reported to investigative sites or other blinded personnel.

	Notes
Hematology	Assayed by Lilly-designated laboratory.
Hemoglobin	
Hematocrit	
Erythrocyte count (red blood cells [RBC])	
Mean cell volume	
Mean cell hemoglobin	
Mean cell hemoglobin concentration	
Leukocytes (white blood cells [WBC])	
Absolute count of:	
Neutrophils, segmented	
Neutrophils, juvenile (bands)	
Lymphocytes	
Monocytes	
Eosinophils	
Basophils	
Platelets	
Cell morphology (RBC and WBC)	

	Notes
Clinical Chemistry	Assayed by Lilly-designated laboratory.
Sodium	
Potassium	
Chloride	
Bicarbonate	
Total bilirubin (TBL)	
Direct bilirubin	
Alkaline phosphatase (ALP)	
Alanine aminotransferase (ALT)	
Aspartate aminotransferase (AST)	
Gamma-glutamyl transferase (GGT)	
Blood urea nitrogen (BUN)	
Creatinine	
Estimated glomerular filtration rate (eGFR)	See calculations below, in this appendix.
Creatine kinase (CK)	
Uric acid	
Total protein	
Albumin	
Calcium	
Glucose	

	Notes
Lipid Panel	Assayed by Lilly-designated laboratory. Participant should not eat or drink anything except water for 12 hours before the test. If participant is nonfasting at time of collection, this is not a protocol deviation.
Low-density lipoprotein (LDL)	
High-density lipoprotein (HDL)	
Cholesterol (total)	
Triglycerides	

	Notes
Urinalysis	Assayed by Lilly-designated laboratory.
Specific gravity	
pH	
Protein	
Glucose	
Ketones	
Bilirubin	
Urobilinogen	
Blood	
Nitrite	
Urine leukocyte esterase	
Microscopic examination of sediment	

	Notes
Hormones (females)	
Pregnancy test – serum	Assayed by Lilly-designated laboratory. To be performed only on women of childbearing potential and women with history of tubal ligation.
Pregnancy test – urine	Evaluated locally. To be performed only on women of childbearing potential and women with history of tubal ligation. Result must be negative before dosing at each dosing visit.
Follicle-stimulating hormone (FSH)	Assayed by Lilly-designated laboratory Optional, performed to confirm postmenopausal status.

	Notes
Additional Testing	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
CCI	

	Notes
TB, HIV, and Hepatitis Serology	
Tuberculosis (TB) test:	TB test based on local standard of care
QuantiFERON®-TB Gold test	Assayed by Lilly-designated laboratory.
T-SPOT®.TB	Evaluated locally. Local laboratory must be qualified by local regulations.
Tuberculin skin test (TST)	Local testing. Local laboratory must be qualified by local regulations.
Human immunodeficiency virus (HIV)	Assayed by Lilly-designated laboratory.
Hepatitis C virus (HCV) testing:	Assayed by Lilly-designated laboratory.
Hepatitis C antibody	
HCV RNA	
Hepatitis B virus (HBV) testing:	Assayed by Lilly-designated laboratory.
Hepatitis B surface antigen (HBsAg)	
Hepatitis B core antibody (anti-HBc)	
HBV DNA	Performed only for participants who test positive for anti-HBc.

	Notes
Pharmacokinetics (PK) Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
LY3471851 concentration	

	Notes
CCI	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.

	Notes
Flow Cytometry	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Lymphocyte subsets - T regulatory cells	
T-cell subsets	

	Notes
Genetics Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Genetics sample	

	Notes
CCI	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
	Endoscopic biopsy sample collection

	Notes
Stool Samples	Assayed by Lilly-designated laboratory.
Stool culture	
Clostridium difficile testing	Confirmed by a test for *C. difficile* toxin gene expression.
CCI	Results will not be provided to the investigative sites.

Clinical Laboratory Calculations

eGFR (MDRD)

- For creatinine results reported in conventional units (mg/dL):

GFR (mL/min/1.73 m^2) = 175 × $(S_{cr})^{-1.154}$ × $(Age)^{-0.203}$ × (0.742 if female) × (1.212 if African American)

- For creatinine results reported in SI units (pmol/L):

GFR (mL/min/1.73 m^2) = 175 × $(S_{cr}/88.4)^{-1.154}$ × $(Age)^{-0.203}$ × (0.742 if female) × (1.212 if African American)

10.2.2. Laboratory Tests to be Obtained at Time of a Systemic Hypersensitivity Event

Selected tests may be obtained in the event of anaphylaxis or systemic allergic/hypersensitivity reactions. The samples should be collected as close as possible to the onset of the event.

Hypersensitivity Tests[a]

CCI	
LY concentration (PK)	N-methylhistamine
	Complements
	Cytokine panel

Abbreviation: LY = LY3471851; NMH = N-methylhistamine; PK = pharmacokinetics.

[a] Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.

CCI

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow up and Reporting

10.3.1. Definition of AE

AE Definition

An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (for example, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (that is, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition, including an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration, even though they may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, per se, will not be reported as an AE or SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

"Lack of efficacy" or "failure of expected pharmacological action", per se, will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE, if they fulfill the definition of an AE or SAE.

Events Not Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.CCI [redacted]
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.

- Medical or surgical procedure (for example, endoscopy or appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing diseases or conditions present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

Note: If an event is not an AE per definition above, then it cannot be an SAE, even if serious conditions are met (for example, hospitalization for signs/symptoms of the disease under study or death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been admitted to hospital for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (for example, sprained ankle), which may interfere with or prevent everyday life functions, but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency, or drug abuse.

10.3.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (for example, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will then record all relevant AE/SAE information in the CRF.

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of the AE/SAE CRF page.

There may be instances when copies of medical records for certain cases are requested by sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to sponsor or designee.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- **Mild:** An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- **Moderate:** An event that causes sufficient discomfort and interferes with normal everyday activities.
- **Severe:** An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

Note: An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying diseases, concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.

For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor or designee.

The investigator may change his or her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any post-mortem findings, including histopathology.

New or updated information will be recorded in the originally completed CRF.

The investigator will submit any updated SAE data to sponsor or designee within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting via an Electronic Data Collection Tool

The primary mechanism for reporting an SAE will be the electronic data collection tool.

If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.

The site will enter the SAE data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.

If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form or to the sponsor by telephone.

Contacts for SAE reporting can be found in site training documents.

SAE Reporting via Paper CRF

Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the sponsor.

Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

Contacts for SAE reporting can be found in site training documents.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Definitions

Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below). If fertility is unclear (for example, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Woman NOT of Childbearing Potential

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy
- Infertile due to congenital anomaly such as Mullerian agenesis.

For individuals with permanent infertility due to an alternate medical cause other than the above (for example, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Determination can come from the authorized site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female, defined as women meeting 1 of the following criteria:
    - Surgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note
    - Spontaneous amenorrhea for at least 12 months, not induced by a medical condition such as anorexia nervosa and not taking medications during the amenorrhea (for example, oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators, or chemotherapy that induced the amenorrhea); additionally, if less than or equal to 40 years of age, has a FSH of ≥40 mIU/mL
    - At least 40 years of age with an intact uterus, not on hormone therapy, with cessation of menses for at least 1 year, and without an alternative medical cause, AND an FSH of ≥40 mIU/mL

- At least 55 years of age, not on hormone therapy, having at least 12 months of spontaneous amenorrhea
- At least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.

10.4.2. Contraception

Females

Women of child-bearing potential

Women of child-bearing potential who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) or in a same sex relationship (as part of their preferred and usual lifestyle) must agree to either remain abstinent or stay in a same sex relationship without sexual relationships with males. Periodic abstinence (for example, calendar, ovulation, symptothermal, or post-ovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.

Otherwise, women of child-bearing potential participating must agree to use 2 forms of effective contraception, where at least 1 form is highly effective (less than 1% failure rate), for the entirety of the study. Contraception must continue following completion of study drug administration for 12 weeks.

- Women of child-bearing potential participating must test negative for pregnancy prior to initiation of treatment as indicated by a negative serum pregnancy test at the screening visit followed by a negative urine pregnancy test within 24 hours prior to first exposure to study drug.
- Two forms of effective contraception, where at least 1 form is highly effective (such as combination oral contraceptives, implanted contraceptives, or intrauterine devices), will be used. Effective contraception (such as male or female condoms with spermicide, diaphragms with spermicide, or cervical sponges) may be used as the second therapy. Barrier protection methods without concomitant use of a spermicide are not a reliable or acceptable method. Thus, each barrier method must include use of a spermicide (that is, condom with spermicide, diaphragm with spermicide, female condom with spermicide). It should be noted that the use of male and female condoms as a double-barrier method is not considered acceptable due to the high failure rate when these methods are combined.

Women not of child-bearing potential

Women who are not-WOCBP may participate in the study, if they meet all study entry criteria. For such women, there are no contraception requirements.

Males

No male contraception is required except in compliance with specific local government study requirements.

10.4.3. Collection of Pregnancy Information

Male participants with partners who become pregnant

The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.

After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of gestational age, fetal status (presence or absence of anomalies), or indication for the procedure.

Female participants who become pregnant

The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.

The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of gestational age, fetal status (presence or absence of anomalies), or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

A spontaneous abortion (occurring at less than 20 weeks gestational age) or still birth (occurring at 20 weeks or greater gestational age) is always considered to be an SAE and will be reported as such.

Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study intervention and be withdrawn from the study. If the participant is discontinued from the study intervention, follow the standard discontinuation process and continue directly to the study follow-up phase. The follow-up on the pregnancy outcome should continue independent of intervention or study discontinuation.

10.5. Appendix 5: Liver Safety: Hepatic Monitoring Tests

See Section 8.2.9 for guidance on appropriate test selection.

The Lilly-designated central laboratory must complete the analysis of all selected testing except for microbiology testing.

Local testing may be performed in addition to central testing when necessary for immediate participant management.

Results will be reported if a validated test or calculation is available.

Hepatic Evaluation Testing

Hematology	**Clinical Chemistry**
Hemoglobin	Total bilirubin
Hematocrit	Direct bilirubin
Erythrocytes (RBCs - red blood cells)	Alkaline phosphatase (ALP)
Leukocytes (WBCs - white blood cells)	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Lymphocytes	Creatine kinase (CK)
Monocytes	**Other Chemistry**
Basophils	Acetaminophen
Eosinophils	Acetaminophen protein adducts
Platelets	Alkaline phosphatase isoenzymes
Cell morphology (RBC and WBC)	Ceruloplasmin
Coagulation	Copper
	Ethyl alcohol (EtOH)
Prothrombin time, INR (PT-INR)	Haptoglobin
Serology	Immunoglobulin A (IgA; quantitative)
Hepatitis A virus (HAV) testing:	Immunoglobulin G (IgG; quantitative)
HAV total antibody	Immunoglobulin M (IgM; quantitative)
HAV IgM antibody	Phosphatidylethanol (PEth)
Hepatis B virus (HBV) testing:	**Urine Chemistry**
Hepatitis B surface antigen (HBsAg)	Drug screen
Hepatitis B surface antibody (anti-HBs)	Ethyl glucuronide (EtG)
Hepatitis B core total antibody (anti-HBc)	**Other Serology**
Hepatitis B core IgM antibody	Anti-nuclear antibody (ANA)
Hepatitis B core IgG antibody	Anti-smooth muscle antibody (ASMA)[a]
HBV DNA[d]	Anti-actin antibody[b]
Hepatis C virus (HCV) testing:	Epstein-Barr virus (EBV) testing:
HCV antibody	EBV antibody
HCV RNA[d]	EBV DNA[d]
Hepatitis D virus (HDV) testing:	Cytomegalovirus (CMV) testing:
HDV antibody	CMV antibody

Hepatitis E virus (HEV) testing:	CMV DNA[d]
HEV IgG antibody	Herpes simplex virus (HSV) testing:
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA[d]	HSV (Type 1 and 2) DNA[d]
Microbiology[c]	Liver kidney microsomal type 1 (LKM-1) antibody
Culture:	
Blood	
Urine	

[a] Not required if anti-actin antibody is tested.

[b] Not required if anti-smooth muscle antibody (ASMA) is tested.

[c] Assayed ONLY by investigator-designated local laboratory; no central testing available.

[d] Reflex/confirmation dependent on regulatory requirements, testing availability, or both.

10.6. Appendix 6: Examples of Infections That May Be Considered Opportunistic in the Setting of Biologic Therapy

The following table lists examples of infections that may be considered opportunistic in the setting of biologic therapy (adapted from Winthrop et al.[16]). This table is provided to aid the investigator in recognizing such infections. This list is not exhaustive. Infections will be categorized by Lilly as opportunistic according to *Opportunistic Infections and Biologic Therapies in Immune-Mediated Inflammatory Diseases: Consensus Recommendations for Infection Reporting during Clinical Trials and Postmarketing Surveillance* by Winthrop et al.[16]

Examples of Infections That May Be Considered Opportunistic in the Setting of Biologic Therapy

Bacterial
Bartonellosis (disseminated disease only)
Campylobacteriosis (invasive disease only)
Legionellosis
Listeriosis (invasive disease only)
Nocardiosis
Tuberculosis
Non-tuberculous mycobacterial disease
Salmonellosis (invasive disease only)
Shigellosis (invasive disease only)
Vibriosis (invasive disease due to *Vibrio vulnificus*)
Viral
BK virus disease including polyomavirus-associated nephropathy
Cytomegalovirus disease
Hepatitis B virus reactivation
Hepatitis C virus progression
Herpes simplex (invasive disease only)
Herpes zoster (any form)
Post-transplant lymphoproliferative disorder (Epstein-Barr virus)
Progressive multifocal leukoencephalopathy (PML), John Cunningham (JC) virus
Fungal
Aspergillosis (invasive disease only)
Blastomycosis
Candidiasis (invasive disease or oropharyngeal, esophageal. Not isolated lingual.)

Coccidioidomycosis
Cryptococcosis
Histoplasmosis
Paracoccidioides infections
Penicilliosis
Pneumocystosis
Sporotrichosis
Other invasive molds: Mucormycosis (zygomycosis) (*Rhizopus*, *Mucor,* and *Lichtheimia*), *Scedosporium*/*Pseudallescheria boydii*, *Fusarium*
Parasitic
Leishmaniasis (visceral only)
Strongyloidiasis (hyperinfection syndrome or disseminated disease)
Microsporidiosis
Toxoplasmosis
Trypanosoma cruzi infection (Chagas' disease progression) (disseminated disease only)
Cryptosporidiosis (chronic disease only)

Source: adapted from Winthrop et al.[16]

10.7 Appendix 7: Prohibited Medications

This section outlines medications that are prohibited during the treatment phase of the study.

These prohibitions include windows for washout of medications prohibited prior to the screening endoscopy, if applicable.

After a patient discontinues study drug and completes the ETV, use of the medications listed in this appendix is allowed, at discretion of the investigator.

Drug Class	**Prohibited Medication Restrictions**
Anti-TNF antibodies (for example, infliximab, adalimumab, or golimumab)	Discontinue at least 4 weeks prior to screening endoscopy and prohibited throughout duration of study.
Anti-integrin antibodies (for example, vedolizumab)	Discontinue at least 12 weeks prior to screening endoscopy and prohibited throughout duration of study.
Anti-IL12p40 antibodies (for example, ustekinumab [Stelara®]) or anti-IL-23p19 antibodies (for example, mirikizumab [LY3074828], risankizumab [BI-655066], brazikumab [MEDI-2070], guselkumab [CNTO1959], tildrakizumab [MK-3222]) for any indication, including investigational use	Discontinue at least 4 weeks prior to screening endoscopy and prohibited throughout duration of study.
Agents depleting B or T cells (for example, rituximab, alemtuzumab, or visilizumab)	Discontinue at least 12 months prior to baseline. Participants remain excluded, if evidence of persistent targeted lymphocyte depletion at the time of screening endoscopy.
Immunomodulatory medications, including oral cyclosporine, IV cyclosporine, tacrolimus, mycophenolate mofetil, thalidomide, or JAK inhibitors (for example, tofacitinib or baricitinib)	Discontinue at least 2 weeks prior to screening endoscopy and prohibited throughout duration of study.
Rectally administered 5-ASA therapies (enemas or suppositories)	Discontinue at least 2 weeks prior to screening endoscopy and prohibited throughout duration of study.
Rectally administered investigational preparations for UC such as arsenic preparations	Discontinue at least 4 weeks prior to screening endoscopy and prohibited throughout duration of study.
Rectally administered corticosteroids (enemas or suppositories or foam applications)	Discontinue at least 2 weeks prior to screening endoscopy and prohibited throughout duration of study.
IV corticosteroids	Discontinue at least 2 weeks prior to screening endoscopy. A course of IV corticosteroids is prohibited throughout duration of study.

Drug Class	Prohibited Medication Restrictions
Systemic corticosteroids for non-UC indications (oral or IV)	Participants requiring systemic corticosteroids for non-UC indications (except corticosteroids to treat adrenal insufficiency) are excluded. Locally administered corticosteroids (for example, inhaled, intranasal, intra-articular, or topical) are allowed.
Oral budesonide standard formulation (that is, not the oral budesonide extended release tablet formulation [budesonide MMX])	Discontinue at least 2 weeks prior to screening endoscopy and prohibited throughout duration of study.
Any investigational therapy (biologic or nonbiologic) not otherwise mentioned in this table	Biologic: Discontinue at least 8 weeks, or 5 half-lives, whichever is longer, prior to screening endoscopy and prohibited throughout duration of study. Nonbiologic: Discontinue at least 4 weeks, or 5 half-lives, whichever is longer, prior to screening endoscopy and prohibited throughout duration of study.
Interferon therapy	Discontinue at least 8 weeks prior to screening endoscopy and prohibited throughout duration of study.
Leukocyte apheresis (leukapheresis, for example, Adacolumn)	Discontinue at least 3 weeks prior to screening endoscopy.
Bacillus Calmette-Guerin (BCG) vaccine	Last vaccination (if any) given at least 12 months prior to baseline. BCG vaccination is prohibited throughout the duration of the study and for 20 weeks after discontinuation of study drug.
Live attenuated vaccines	Last vaccination (if any) given at least 3 months prior to baseline. Live attenuated vaccines are prohibited throughout the duration of the study and for 20 weeks after discontinuation of study drug.

Abbreviations: 5-ASA = 5-aminosalicyclic acid; IL = interleukin; IV = intravenous; JAK = Janus Kinase; TNF = tumor necrosis factor; UC = ulcerative colitis.

10.8. Appendix 8: Permitted Medications with Dose Stabilization

Drug Class	Dose Stabilization Guidance
Oral 5-ASAs for UC (for example, mesalamine, balsalazide, olsalazine and sulfasalazine)	The prescribed dose must have been stable for at least 2 weeks prior to the screening endoscopy, with stable dose encouraged during the study.
Oral corticosteroids for UC (prednisone ≤20 mg/day or equivalent, budesonide MMX 9 mg/day, or beclomethasone dipropionate [gastro-resistant prolonged-release tablet] 5 mg/day)	Prescribed dose must have been stable for at least 2 weeks before screening endoscopy. See Section 6.5 for instructions on tapering of oral corticosteroid therapy.
Corticosteroids for non-UC indications: corticosteroids to treat adrenal insufficiency, or locally administered corticosteroids (for example, inhaled, intranasal, intra-articular, or topical)	May continue corticosteroids to treat adrenal insufficiency or locally administered corticosteroids during study with stable dose encouraged.
Immunomodulators (for example, AZA, 6-MP, or methotrexate)	Prescribed at stable dose for at least 8 weeks before screening endoscopy; doses should remain stable throughout study unless medication is discontinued due to a toxicity related to the medication.
Antidiarrheals (for example, loperamide or diphenoxylate with atropine)	May continue during study with stable doses encouraged.
Low-dose or baby aspirin (75 to 162.5 mg)	Daily use for cardiovascular prophylaxis permitted.
Non-live (killed, inactivated, or subunit) vaccines	Allowed during the study. The efficacy of non-live vaccinations with concomitant LY3471851 treatment is unknown.

Abbreviations: 5-ASA = 5-aminosalicyclic acid; 6-MP = 6-mercaptopurine; AZA = azathioprine; UC = ulcerative colitis.

10.9. Appendix 9: Mayo Scoring System for the Assessment of Ulcerative Colitis Activity

Stool Frequency Subscore	**Score**
Normal number of stools for subject	0
1 to 2 stools more than normal	1
3 to 4 stools more than normal	2
5 or more stools than normal	3
Rectal Bleeding Subscore	**Score**
No blood seen	0
Streaks of blood with stool less than half of the time	1
Obvious blood (more than just streaks) or streaks of blood with stool most of the time	2
Blood alone passed	3
Endoscopic Subscore	**Score**
Normal or inactive disease	0
Mild disease (erythema, decreased vascular pattern)	1
Moderate disease (marked erythema, absent vascular pattern, friability, erosions)	2
Severe disease (spontaneous bleeding, ulceration)	3
Physician's Global Assessment	**Score**
Normal	0
Mild disease	1
Moderate disease	2
Severe disease	3
Mayo Score = Stool Frequency + Rectal Bleeding + Endoscopic Subscore + Physician's Global Assessment	

Note: The Mayo score ranges from 0 to 12, with higher scores indicating more severe disease. Modified Mayo score excludes the Physician's Global Assessment and ranges from 0 to 9. Composite stool frequency and rectal bleeding score ranges from 0 to 6. The original description of the Mayo score included friability in the definition of an endoscopic subscore of 1. Consistent with current clinical practice and regulatory guidance, this study excludes friability from the definition of an endoscopic subscore of 1. Stool frequency reports the number of stools in a 24-hour period, relative to the normal number of stools for that patient. The reference "normal" stool frequency for that patient will be recorded electronically at the screening visit. The Normal SF refers to when the patient was in remission or, if the patient has never achieved remission, the reported stool frequency before initial onset of signs and symptoms of UC. Remission refers to a period of time since being diagnosed with UC when the patient is not experiencing any signs or symptoms relating to UC. This period of time may last a few weeks or a few months or may even last several years. The patient will record this electronically as source data at the screening study visit.
Source: Adapted from Schroeder et al.[17] and Scherl et al.[20]

10.10. Appendix 10: Geboes Scoring for the Assessment of Histological Activity

Subgrades	Scoring
Grade 0 Structural (architectural change)	0.0 No abnormality 0.1 Mild abnormality 0.2 Mild or moderate diffuse or multifocal abnormalities 0.3 Severe diffuse or multifocal abnormalities
Grade 1 Chronic inflammatory infiltrate	1.0 No increase 1.1 Mild but unequivocal increase 1.2 Moderate increase 1.3 Marked increase
Grade 2A Lamina propria eosinophils	2A.0 No increase 2A.1 Mild but unequivocal increase 2A.2 Moderate increase 2A.3 Marked increase
Grade 2B Lamina propria neutrophils	2B.0 None 2B.1 Mild but unequivocal increase 2B.2 Moderate increase 2B.3 Marked increase
Grade 3 Neutrophils in epithelium	3.0 None 3.1 <5% crypts involved 3.2 <50% crypts involved 3.3 >50% crypts involved
Grade 4 Crypt destruction	4.0 None 4.1 Probable—local excess of neutrophils in part of crypt 4.2 Probable—marked attenuation 4.3 Unequivocal crypt destruction
Grade 5 Erosion or ulceration	5.0 No erosion, ulceration, or granulation tissue 5.1 Recovering epithelium + adjacent inflammation 5.2 Probable erosion—focally stripped 5.3 Unequivocal erosion 5.4 Ulcer or granulation tissue

Note: For each histological feature assessed, the highest grade in which there is evidence of disease is assigned. For example, if <50% crypts involved is checked (that is, Geboes grade 3 is assigned a 2) and Crypt destruction is noted as 'none' (4.0) and Erosion or ulceration is 'No erosion, ulceration, or granulation tissue' (5.0), the participant will be assigned a score of 3.2.

Source: Adapted from Geboes et al.[24]

10.11. Appendix 11: Patient-Reported Outcome Instruments

Daily Diary for Review

Stool Frequency
Rectal Bleeding
Nocturnal Stool
Bristol Stool Scale
Urgency NRS
Abdominal Pain NRS
Fatigue NRS
PGR-S

Abbreviations: NRS = numeric rating scale; PGR-S = Patient's Global Rating of Severity.

The following are additional descriptions of PRO instruments used in the patient eDiary or tablet device (and/or a web-based collection system) for this study.

Used in the Patient eDiary

Nocturnal Stool: The Nocturnal Stool instrument is a single item asking the participant to record the number of stools they had during the night (or day, for shift workers) causing them to waken from sleep. Participants will be provided with an electronic diary tool during screening to record information daily pertaining to their nocturnal stool count.

Bristol Stool Scale: The Bristol Stool Scale is a single item that provides a pictorial and verbal description of stool consistency and form ranging from Type 1 (Hard Lumps) to Type 7 (Watery/liquid). Participants will be provided with an electronic diary tool during screening to record information daily pertaining to their stool.

Urgency NRS: A single item that measures the severity for the urgency (sudden or immediate need) to have a bowel movement in the past 24 hours using an 11-point NRS ranging from 0 (no urgency) to 10 (worst possible urgency). Participants will be provided with an electronic diary tool during screening to record information daily pertaining to their severity of urgency.

Abdominal Pain NRS: A single item that measures the "worst abdominal pain in the past 24 hours" using an 11-point NRS ranging from 0 (no pain) to 10 (worst possible pain). Participants will be provided with an electronic diary tool during screening to record information daily pertaining to their worst abdominal pain experience.

Fatigue NRS: The Fatigue NRS is a single item that measures the "worst fatigue (weariness, tiredness) in the past 24 hours" using an 11-point NRS ranging from 0 (no fatigue) to 10 (as bad as you can imagine). Participants will be provided with an electronic diary tool during screening to record information daily pertaining to their worst fatigue experience.

Patient's Global Rating of Severity (PGR-S): The PGR-S is a 1-item patient-rated questionnaire designed to assess the patients' rating of their disease symptom severity over the past 24 hours. Responses are graded on a 6-point scale in which a score of 1 indicates the

participant has no symptoms (that is, "none") and a score of 6 indicates that the participant's symptom(s) are "very severe." Participants will be provided with an electronic diary tool during screening to record information daily pertaining to their disease experience.

Used in the Tablet Device and/or Web-Based Collection System

Patient's Global Impression of Change (PGI-C): The PGI-C scale is a patient-rated instrument designed to assess the patients' rating of change in their symptom(s). Responses are graded on a 7-point Likert scale in which a score of 1 indicates that the subject's symptom(s) is "very much better," a score of 4 indicates that the subject's symptom has experienced "no change," and a score of 7 indicates that the subject's symptom(s) is "very much worse." Participants will record their response to the PGI-C electronically as source data at appropriate visits.

Inflammatory Bowel Disease Questionnaire (IBDQ): A 32-item patient-completed questionnaire that measures 4 aspects of patients' lives: symptoms directly related to the primary bowel disturbance, systemic symptoms, emotional function, and social function.[21-23] Responses are graded on a 7-point Likert scale in which 7 denotes "not a problem at all" and 1 denotes "a very severe problem." Scores range from 32 to 224; a higher score indicates a better quality of life. Participants will record their responses to the IBDQ electronically as source data at appropriate visits.

16-Item Quick Inventory of Depressive Symptomatology–Self Report (QIDS-SR16): See Section 8.2.10.2.

10.12. Appendix 12: Abbreviations

Term	Definition
5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immune deficiency syndrome
ALC	absolute lymphocyte count
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
ANOVA	analysis of variance
anti-HBc	antibody to hepatitis B core antigen
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
AZA	azathioprine
BCG	Bacillus Calmette-Guerin
Blinding	A double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the participants are aware of the treatment received.
CFR	United States Code of Federal Regulations
CI	confidence interval
CK	creatine kinase
clinical research physician	Individual responsible for the medical conduct of the study. Responsibilities of the clinical research physician may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CMH	Cochran–Mantel–Haenszel
CMV	cytomegalovirus

Term	Definition
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CPK	creatinine phosphokinase (see CK)
CRF	case report form (see eCRF)
CCI	
CRS	cytokine release syndrome
C-SSRS	Columbia–Suicide Severity Rating Scale
CT	computerized tomography
CTA	clinical trial agreement
CXR	chest x-ray
DALM	dysplasia-associated lesion or mass
DNA	deoxyribonucleic acid
EBV	Epstein-Barr virus
ECG	electrocardiogram
eCOA	electronic Clinical Outcome Assessment
eCRF	electronic case report form (see CRF)
EDC	electronic data capture system
eDiary	electronic diary
eGFR	estimated glomerular filtration rate
CCI	
Enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
Enrollment	The act or time point of randomization or treatment assignment, or the condition of have been assigned to a treatment.
Enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	Ethical Review Board (see IRB)
ES	endoscopic subscore(s)
ETV	early termination visit

Term	Definition
FSH	follicle-stimulating hormone
GCP	good clinical practice
GGT	gamma-glutamyl transferase
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDV	hepatitis D virus
HIV	human immunodeficiency virus
CCI	
IAC	internal assessment committee
IB	Investigator's Brochure
IBD	inflammatory bowel disease
IBD-U	inflammatory bowel disease unclassified
IBDQ	Inflammatory Bowel Disease Questionnaire
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee (see IRB)
IgA	immunoglobulin A
IGRA	interferon gamma release assay
IL	interleukin
Informed consent	A process by which a participant voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
INR	international normalized ratio
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product (IP)	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IP	investigational product

Term	Definition
IRB	institutional review board (IRB), also called independent ethics committee (IEC) or ethical review board (ERB)
ISR	injection site reaction
IT	information technology
ITT	intent to treat
IV	intravenous
IWRS	interactive web-response system
JAK	Janus kinase
LS	least squares
LTBI	latent tuberculosis infection
MedDRA	Medical Dictionary for Regulatory Activities
mBOCF	modified baseline observation carried forward
MI	multiple imputations
mITT	modified intent-to-treat
MDRD	Modification of Diet in Renal Disease
MMRM	mixed-effects model of repeated measures
MMS	modified Mayo score
NK	natural killer
NONMEM	nonlinear mixed effects modeling
NRI	nonresponder imputation
NRS	numeric rating scale
Participant	Equivalent to Clinical Data Interchange Standards Consortium (CDISC) term "subject," meaning an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control. In this protocol, the term "participant" is used to indicate an individual who participates in a clinical trial, either as a recipient of an investigational medicinal product or as a control. This usage reflects preferences indicated by patient advocates to more accurately reflect the role of people who take part in clinical trials. The terms "patient" and "subject" are also used.
PD	Pharmacodynamic
PEG	polyethylene glycol
PGA	Physician's Global Assessment
PGI-C	Patient's Global Impression of Change

Term	Definition
PGR-S	Patient's Global Rating of Severity
PK	Pharmacokinetic
PK/PD	pharmacokinetics/pharmacodynamics
PPD	purified protein derivative
PRO	patient-reported outcomes
PT-INR	prothrombin time
Q2W	every 2 weeks
QIDS-SR16	16-Item Quick Inventory of Depressive Symptomatology–Self Report
QTc	corrected QT interval
RB	rectal bleeding
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SF	stool frequency
SLE	systemic lupus erythematosus
SoA	Schedule of Activities, as described in Section 1.3 of the protocol
SOC	system organ class
study drug	See "study intervention"
study intervention	Any investigational intervention, marketed product, placebo, or medical device intended to be administered to a study participant according to the study protocol
subject	see "participant"
TB	tuberculosis
TBL	total bilirubin level
Tcons	conventional T cells
TE-ADA	treatment-emergent anti-drug antibody
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.

Term	Definition
TNF	tumor necrosis factor
Tregs	regulatory T cells
TST	tuberculin skin test
UC	ulcerative colitis
CCI	[redacted]
ULN	upper limit of normal
WBC	white blood cell count
WHO	World Health Organization
WOCBP	women of childbearing potential

10.13. Appendix 13: Provisions for Changes in Study Conduct During Exceptional Circumstances

Implementation of this appendix

The changes to procedures described in this appendix are temporary measures intended to be used only during specific time periods as directed by the sponsor in partnership with the investigator.

Exceptional circumstances

Exceptional circumstances are rare events that may cause disruptions to the conduct of the study. Examples include pandemics or natural disasters. These disruptions may limit the ability of the investigators, participants, or both to attend on-site visits or to conduct planned study procedures.

Implementing changes under exceptional circumstances

In an exceptional circumstance, after receiving the sponsor's written approval, sites may implement changes if permitted by local regulations.

Ethical Review Boards (ERBs), regulatory bodies and any other relevant local authorities, as required, will be notified as early as possible to communicate implementation of changes in study conduct due to exceptional circumstances. To protect the safety of study participants, urgent changes may be implemented before such communications are made, but all changes will be reported as soon as possible following implementation. If approval of ERBs, regulatory bodies, or both is required per local regulations, confirmation of this approval will be retained in the study records.

In the event written approval is granted by the sponsor for changes in study conduct, additional written guidance, if needed, will be provided by the sponsor.

Considerations for making a change

The prevailing consideration for making a change is ensuring the safety of study participants. Additional important considerations for making a change are

- Good Clinical Practice compliance, and
- minimization of risk to study integrity.

Such changes are intended to

- mitigate risks of participants missing visits
- allow participants to continue safely in the study, and
- maintain the data integrity of the study.

Informed Consent

Additional consent from the participant will be obtained, as applicable, for

- participation in remote visits (as defined in the "Changes in Study Conduct" section below)
- a change in the method, location, or both, of study intervention administration,
- dispensation of additional study drug during an extended treatment period
- alternate delivery of study intervention and ancillary supplies, and,
- provision of their personal or medical information required prior to implementation of these activities.

Changes in Study Conduct

Changes in study conduct not described in this appendix, or not consistent with applicable local regulations, are not allowed.

The following changes in study conduct will not be considered protocol deviations. Missing data will be captured as protocol deviations.

1. Remote visits and adjustments to visit interval tolerance

Whenever possible and safe to do so, as determined by the investigator's discretion, participants should complete the usual SoA. To maximize the possibility that the study visits can be conducted as on-site visits, the visit interval tolerances (visit windows) may be adjusted within the ranges specified in the following table. This minimizes missing data and preserves the intended conduct of the study.

The table also shows the acceptable location types for various study visits. Remote options described in the sponsor's guidance and written approval may include: a) telephone, IT-assisted virtual, or both; b) mobile healthcare; and c) other. More information on these options follows the table.

Screening and Induction Period (SOA Table 1)		
For this visit...	**Permitted Visit Types**	**Visit Interval Tolerance[a]**
Visit 1	on-site only	same as shown in SOA, but flexibility can be considered following consultation with, and with prior approval by, the sponsor
Visit 2	on-site only	same as shown in the SOA
Visit 3 through Visit 8	remote	same as shown in the SOA
Visit 9	remote	for endoscopy: 3 days before to 28 days after the targeted visit date (inclusive) for other procedures: same as shown in the SOA
Maintenance Treatment Period (SOA Table 2)		
Visit 10 through Visit 28	remote	same as shown in the SOA
Visit 29	remote	for endoscopy: from 3 days before to 56 days after the targeted visit date (inclusive) for other procedures: same as shown in the SOA
Extension Induction and Extension Maintenance Treatment Periods (SOA Table 3)		
Visit 10 through Visit 15	remote	same as shown in the SOA

Visit 16	remote	for endoscopy: from 3 days before to 28 days after the targeted visit date (inclusive) for other procedures: same as shown in the SOA
Visit 17 through Visit 28	remote	same as shown in the SOA
Visit 29	remote	for endoscopy: from 3 days before to 56 days after the targeted visit date (inclusive) for other procedures: same as shown in the SOA
Early termination, Unscheduled visits, and Post-Treatment Follow-Up Period (SOA Table 4)		
Early termination visit (ETV)	remote	for endoscopy: within 56 days after the early termination decision Note: Endoscopy and colon biopsy sample collection are recommended at ETV based on judgment of the investigator and after discussion with the sponsor's medical monitor. If not performed at ETV, this will not be considered a protocol deviation.. for other procedures: same as shown in the SOA
Visit 997	remote	not applicable
Visit 801	remote	same as shown in the SOA
Visit 802	remote	same as shown in the SOA

[a] **Note:** For participants whose visits have extended windows, additional study drug may need to be provided to avoid study drug interruption and maintain overall integrity of the study.

Telephone, IT-assisted virtual visits, or both (telemedicine): Telephone or IT-assisted virtual visits to complete appropriate assessments are acceptable. In source documents, the study site should capture the visit location and method, with a specific explanation for any data missing because of missed in-person site visits. Assessments to be completed in this manner may include, but are not limited to, tobacco use assessment, evaluation of CCI and PROs via a tablet and/or a web-based collection system.

Mobile healthcare: Healthcare visits may be performed by a mobile healthcare provider at locations other than the study site when participants cannot travel to the site due to an exceptional circumstance. if written approval is provided by the sponsor. Procedures performed at such visits may include, but are not limited to, vital signs, weight, physical examinations, evaluations for CCI ECGs, collection of blood and urine samples, PROs via a tablet or a web-based collection system, and administration of study intervention.

Other alternative locations: Procedures which could be done at an alternate location in very exceptional circumstances include, but are not limited to, ECGs, chest x-rays, endoscopies, colon biopsy sample collections, collections of blood and urine samples.

Regardless of the type of remote visits implemented, the protocol requirements regarding the reporting of AEs, SAEs, and product complaints remain unchanged. Furthermore, every effort should be made to enable participants to return to on-site visits as soon as reasonably possible, while ensuring the safety of both the participants and the site staff.

2. Local laboratory testing option

Local laboratory testing may be conducted in lieu of central laboratory testing. However, central laboratory testing must be retained for the following samples: CCI PK,

CCI [redacted] flow cytometry panel, genetics sample, tests of CCI [redacted], and tests obtained because of a systemic hypersensitivity event. The local laboratory must be qualified in accordance with applicable local regulations.

3. Investigational product and ancillary supplies (including participant diaries)

When a participant is unable to go to the site to receive study supplies during normal on-site visits, the site should work with the sponsor to determine appropriate actions. These actions may include

- asking the participant to go to the site and receive study supplies from site staff without completion of a full study visit
- asking the participant's designee to go to the site and receive study supplies on a participant's behalf,
- arranging delivery of study supplies, and
- working with the sponsor to determine how study intervention is to be administered to the participant, for example, administration of study drug to the participant during a mobile healthcare visit or at an alternate location.

These requirements must be met before action is taken:

- Alternate delivery of IP should be performed in a manner that does not compromise treatment blinding and ensures product integrity. The existing protocol requirements for product accountability remain unchanged, including verification of participant's receipt of study supplies.
- When delivering supplies to a location other than the study site (for example, participant's home), investigator, sponsor, or both should ensure oversight of the shipping process to ensure accountability and product quality (that is, storage conditions maintained and intact packaging upon receipt).
- Instructions may be provided to the participant or designee on the final disposition of any used or unused study supplies.

In addition, if study intervention is to be administered to the participant during a mobile healthcare visit or at an alternate location, this additional requirement must be met: only personnel authorized by the primary investigator or by the sponsor may supply or administer study intervention.

Missing Endoscopies

During exceptional circumstances, some sites might not be able to conduct endoscopies. Gastrointestinal societies have recommended that patients with IBD who do not have COVID-19 should stay on IBD therapies with a goal of sustaining remission.[33,34] For participants in a clinical study, remaining on an assigned study treatment might be protective against immediate risk of disease worsening or recurrence. Remaining on study treatment might also alleviate stress

for the participant, the healthcare provider, and the medical system insofar as stress is created by withdrawing participants study treatment and then needing to find alternative therapies for the withdrawn participants.

This section of this appendix addresses the retention of participants in the study who, in the opinion of the investigator, could benefit from continuing to receive study treatment, despite their inability to have certain protocol-specified endoscopies. Such participants are referred to herein as "Impacted Patients."

A determination of clinical response status, as described in Section 8.1 of the protocol, relies upon stool frequency and rectal bleeding data. Therefore, if a participant is found to be noncompliant with their daily diary entry to the extent that an assessment of clinical response status cannot be made, the participant will not be eligible to be regarded as an Impacted Patient.

The investigator or designee must notify the sponsor and make a request to classify a participant as an "Impacted Patient." However, before doing so, the options for extended visit interval tolerances (wider windows) should be exhausted. Also, other options to enable performing the endoscopy within the allowed timing should be considered, for example, use of an alternate, approved endoscopy site. If, after considering these options, an endoscopy must nevertheless be missed, the investigator or designee must describe in the Impacted Patient's source documents both the reason for the missed endoscopy and the options which were considered but rejected.

Without data from postbaseline endoscopies, it is not possible to use per protocol criteria to determine the participant's status as a responder or nonresponder at the end of the Induction Period or to determine a participant's response to Extension Induction or Extension Maintenance dosing, or to determine clinical response/remission status at Week 52.

Therefore, when Impacted Patients miss any of the endoscopies after randomization, then, instead of the protocol-defined clinical response definition, a standardized Clinical Benefit criterion will be used for Impacted Patients.

The specific definition of Clinical Benefit for Impacted Patients will be provided separately from the protocol.

Impacted Patients who demonstrate Clinical Benefit at Week 12 will enter the blinded maintenance period. Impacted Patients who do not demonstrate Clinical Benefit at Week 12 will enter the extension induction period.

Impacted Patients who demonstrate Clinical Benefit at the end of the extension induction period will enter the extension maintenance period, whereas those who do not will undergo early discontinuation procedures.

Documentation

Documentation of changes in study content

Changes to study conduct will be documented.

Sites will identify and document the details of how participants, visits types, and conducted activities were affected by exceptional circumstances. Dispensing/shipment records of study intervention and relevant communications, including delegation, should be filed with site study records.

Source documents generated at a location other than the study site should be part of the investigator's source documentation and should be transferred to the site in a secure and timely manner.

Missing data and other protocol deviations

Missing data will be captured as protocol deviations. The study site should document specific explanations for any missing data and other protocol deviations. Although protocol deviations may be unavoidable in an exceptional circumstance, documentation of protocol deviations and missing data will be important for data analysis and reporting.

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