Protocol Number (c) J1B-MC-FRCF

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 2 Crossover Study to Evaluate the Efficacy and Safety of LY3454738 in Adults with Chronic Spontaneous Urticaria Inadequately Controlled with H1-Antihistamines

NCT04159701

Approval Date: 10-Jun-2020

Title Page

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Protocol Number: J1B-MC-FRCF

Amendment Number: C

Compound: LY3454738

Study Phase: Phase 2

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Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana USA 46285

Regulatory Agency Identifier Numbers:

IND: 143892

EudraCT: 2019-002495-13

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

Approval Date: 10-Jun-2020 GMT

Medical monitor name and contact information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment B	*29-Jan-2020*
Amendment A	*23-Aug-2019*
Original Protocol	*12-Aug-2019*

Amendment C

This amendment is considered to be 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 rationale for the amendment is to enhance participant safety by decreasing the risk of enrolling or dosing a patient with COVID-19 disease.

Section # and Name	Description of Change	Brief Rationale
Section 1.3, Schedule of Activities	Changed visit tolerance interval from 2 days to 3 days.	Minor change for added participant flexibility.
Section 5.2, Exclusion Criteria	Clarified Exclusion Criteria 13.	Minor clarification to further define confirmed or suspected infections.
Section 5.2, Exclusion Criteria	Updated the time period for specified types of infection in Exclusion Criteria 14.	Minor clarification.
Section 5.2, Exclusion Criteria	Updated Exclusion Criteria 29 to include first generation H_1-antihistamines.	Minor clarification.
Section 5.2, Exclusion Criteria	Removed "leukotriene-receptor antagonists" from Exclusion Criteria 32.	This was a duplication with Exclusion Criteria 29.
Section 6.5.3, Other Permitted Concomitant Therapy	Clarified the use of nasal steroids are permitted.	Minor clarification.
Section 7.1.2, Criteria for Temporary Interruption (Withholding) of Study Drug	Clarified temporary withholding for confirmed or suspected infections.	Minor clarification.
Section 8.1, Efficacy Assessments; Section 8.2, Safety Assessments; Section 8.2.6, Laboratory Tests	Clarified home or virtual visits along with local safety labs are permitted, under special circumstances.	Minor clarification for added participant flexibility.
Section 9.2, Sample Size	Updated the effect size	Clarified per ethics committee

Section # and Name	Description of Change	Brief Rationale
Determination	assumption for LY3454738 and updated the power.	feedback.
Section 9.5, Interim Analyses	Clarified unblinding details which are specified in the SAP and Unblinding Plan.	Minor clarification.

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 2 Crossover Study to Evaluate the Efficacy and Safety of LY3454738 in Adults with Chronic Spontaneous Urticaria Inadequately Controlled with H_1-Antihistamines

Rationale: LY3454738 is a humanized immunoglobulin G (IgG) 4-variant monoclonal antibody (mAb) that binds to and agonizes the human inhibitory checkpoint CD200R. Binding of LY3454738 to CD200R induces a negative signal that results in functional inhibition of the target cell activity. CD200R is expressed on mast cells and basophils, both of which are critical in the pathogenesis of chronic spontaneous urticaria (CSU). Thus, LY3454738 is being developed for the treatment of CSU. This proof-of-concept study will evaluate the safety and efficacy of LY3454738 in adults with CSU.

Objectives and Endpoints

Objectives	Endpoints
Primary	
● To test the hypothesis that treatment with LY3454738 is superior to placebo as measured by patient-assessed itch severity and hive count for the treatment of adult participants with CSU	● Mean change from baseline to Week 12 in UAS7
Secondary	
● To compare the efficacy of LY3454738 to placebo as measured by improvement in signs and symptoms of CSU	● Mean change from baseline to Week 12 in ○ ISS7 ○ HSS7 ● Proportion of patients achieving UAS7 ≤6 at Week 12
● To characterize the pharmacokinetics (PK) of LY3454738	● C_{max} and AUC

Abbreviations: AUC = area under the concentration versus time curve; C_{max} = maximum plasma drug concentration; CSU = chronic spontaneous urticaria; HSS7 = Hives Severity Score Over 7 Days; ISS7 = Itch Severity Score Over 7 Days; UAS7 = Urticaria Activity Score Over 7 Days.

Overall Design: Study J1B-MC-FRCF (FRCF) is a multicenter, randomized, double-blind, placebo-controlled, Phase 2 crossover study to evaluate the efficacy and safety of LY3454738

500 mg given intravenously (IV) every 2 weeks (Q2W) versus placebo IV Q2W in adults with CSU inadequately controlled with H_1-antihistamines.

The study duration will be up to approximately 39 weeks over 4 study periods:

Period 1: Screening, starting up to 35 days before randomization

Period 2: First 12-week treatment (LY3454738 or placebo), from randomization visit through Week 12

Period 3: Second 12-week treatment (crossover), from Week 12 through Week 24

Period 4: Post-treatment follow-up for approximately 10 weeks.

Throughout the study, participants will take a second-generation H_1-antihistamine at a dose specified in approved product labeling. Certain participants may receive rescue therapy.

Disclosure Statement: This is a crossover treatment study with 2 arms that is participant-blinded and investigator-blinded.

Number of Participants:

Approximately 85 patients will be screened to achieve approximately 60 randomized participants. A total of approximately 52 evaluable participants are expected.

Intervention Groups and Duration:

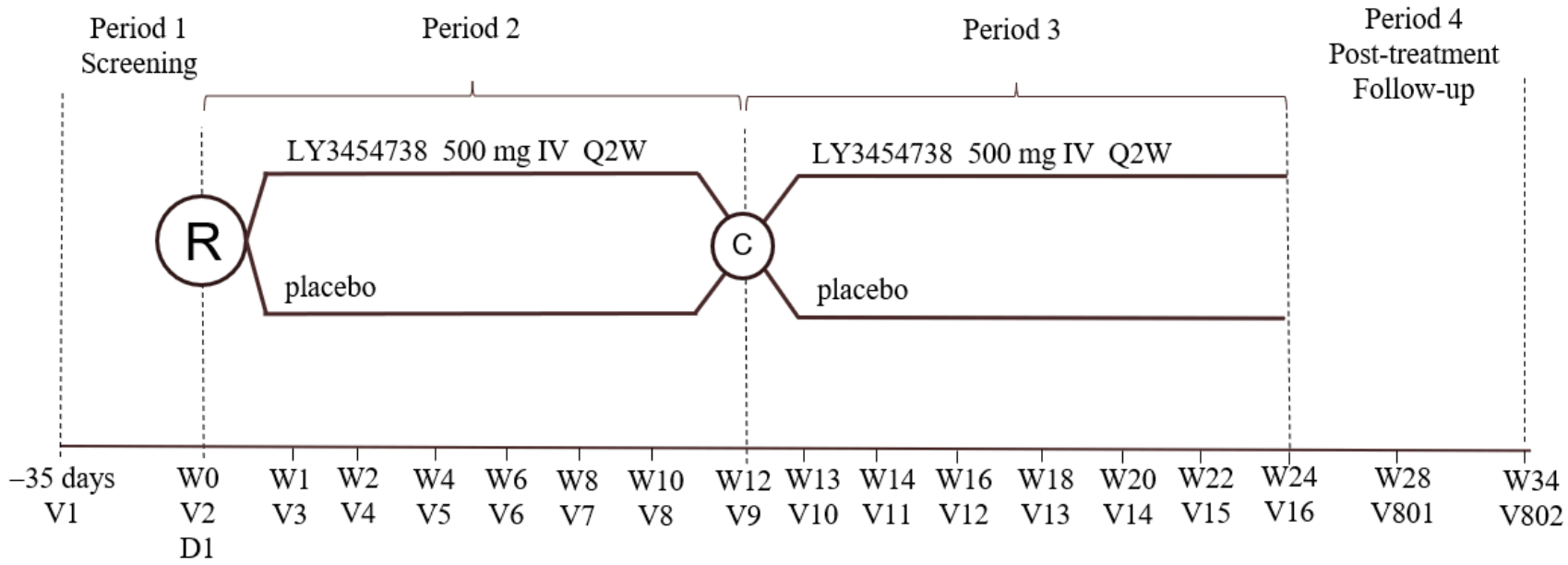
Participants will be randomized in a 3:1 ratio to either Sequence Group 1 or Sequence Group 2:

Sequence Group 1: LY3454738 500 mg IV for 12 weeks followed by placebo for 12 weeks

Sequence Group 2: Placebo for 12 weeks followed by LY3454738 500 mg IV for 12 weeks

Data Monitoring Committee: No

1.2. Schema



Abbreviations: C = crossover visit; D = day; Q2W = every 2 weeks; R = randomization visit; W = study week relative to randomization visit; V = visit.

Figure 1. Schema of Study J1B-MC-FRCF, a phase 2 study to evaluate the efficacy and safety of LY3454738 in adults with chronic spontaneous urticaria.

1.3. Schedule of Activities (SoA)

Note: Visit 1 procedures may be conducted over more than 1 day as long as all tasks are completed within the allowable visit tolerance. The early termination visit (ETV) activities in Table 1 apply to early terminations occurring prior to Visit 16. See Table 2 for procedures in post-treatment follow-up period (Period 4).

Table 1. Schedule of activities for the screening and treatment periods of Study J1B-MC-FRCF.

	Screening	Treatment Periods																
	Period 1	Period 2								Period 3							ETV	Comments
Visit number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16		
Weeks from randomization	–5	—	1	2	4	6	8	10	12	13	14	16	18	20	22	24		
Study day	–35	1	8	15	29	43	57	71	85	92	99	113	127	141	155	169		
Visit tolerance interval (days)		—	±1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		
Fasting visit		X							X							X		
Informed consent	X																	
Inclusion and exclusion criteria	X	X																
Demographics	X																	
Preexisting conditions and medical history	X																	
Prespecified medical history (indication and history of interest)	X																	
Prior treatments for indication	X																	

	Screening	Treatment Periods															
	Period 1	Period 2								Period 3							ETV	Comments
Visit number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16		
Weeks from randomization	–5	—	1	2	4	6	8	10	12	13	14	16	18	20	22	24		
Study day	–35	1	8	15	29	43	57	71	85	92	99	113	127	141	155	169		
Visit tolerance interval (days)		—	±1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		
Fasting visit		X							X							X		
Concomitant medications, including medications for indication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	For AESIs, additional data are collected.
Substance use (alcohol, tobacco, caffeine)	X																	
Height	X																	
Weight	X																	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Blood pressure, body temperature, pulse rate
Physical examination	X																	Includes assessment of skin (Section 8.2.2); tuberculosis (TB) risk factors, symptoms or signs of TB, including assessment of peripheral lymph nodes (Section 8.2.7)
Symptom-directed physical examination		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Includes assessment of skin at every visit (Section 8.2.2)

	Screening	Treatment Periods															
	Period 1	Period 2								Period 3						ETV	Comments
Visit number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16		
Weeks from randomization	−5	—	1	2	4	6	8	10	12	13	14	16	18	20	22	24		
Study day	−35	1	8	15	29	43	57	71	85	92	99	113	127	141	155	169		
Visit tolerance interval (days)		—	±1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		
Fasting visit		X							X							X		
12-lead ECG	X								X							X	X	Locally read, performed before blood sampling
Chest x-ray (posterior–anterior view)	X																	Interpreted and reported by radiologist or pulmonologist. Not performed at screening if performed within 6 months before screening and if qualifying radiographs or equivalent imaging study and/or formal report are available for investigator's review. Locally performed.
Patient Diary (Electronic)																		
Dispense electronic diary	X																	Includes Urticaria Patient Daily Diary (UPDD). The diary is completed daily.
Check electronic diary compliance		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

	Screening	Treatment Periods																
	Period 1	Period 2								Period 3							ETV	Comments
Visit number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16		
Weeks from randomization	−5	—	1	2	4	6	8	10	12	13	14	16	18	20	22	24		
Study day	−35	1	8	15	29	43	57	71	85	92	99	113	127	141	155	169		
Visit tolerance interval (days)		—	±1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		
Fasting visit		X							X							X		
Return electronic diary																		Participant should return the diary at Treatment Period ETV if the participant does not enter Post-Treatment Follow-Up period (Period 4).
Patient-Reported Outcomes (Paper)																		
DLQI		X			X		X		X			X		X		X	X	
Laboratory Tests and Sample Collections																		
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Clinical chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Lipid panel		X							X							X	X	For the fasting lipid profile, participants should not eat or drink anything except water for 12 hours prior to the test. Fasting is not required for the lipid panel at an ETV.
Urinalysis	X	X							X							X	X	
Serum pregnancy	X																	Only for women of childbearing potential and women with history of tubal ligation

	Screening	Treatment Periods															
	Period 1	Period 2								Period 3						ETV	Comments
Visit number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16		
Weeks from randomization	−5	—	1	2	4	6	8	10	12	13	14	16	18	20	22	24		
Study day	−35	1	8	15	29	43	57	71	85	92	99	113	127	141	155	169		
Visit tolerance interval (days)		—	±1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		
Fasting visit		X							X							X		
Urine pregnancy		X		X	X	X	X	X	X		X	X	X	X	X	X	X	Only for women of childbearing potential and women with a history of tubal ligation; done locally and prior to dosing at dosing visits
Follicle-stimulating hormone (FSH)	X																	Optional, performed to confirm postmenopausal status
Stool evaluation	X																	Only for participants with certain risk factors and eosinophil count >2 times ULN (see Sections 5.2 and 8.2.5)
C-reactive protein, high-sensitivity (hs-CRP)		X				X			X				X			X	X	

	Screening	Treatment Periods																
	Period 1	Period 2								Period 3							ETV	Comments
Visit number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16		
Weeks from randomization	−5	—	1	2	4	6	8	10	12	13	14	16	18	20	22	24		
Study day	−35	1	8	15	29	43	57	71	85	92	99	113	127	141	155	169		
Visit tolerance interval (days)		—	±1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		
Fasting visit		X							X							X		
Tuberculosis (TB) test	X																	Participants who had a TST will return 48 to 72 hours after placement to have their test results read (Section 8.2.7). Samples may be sent to central lab or to a local lab based on the type of test (Appendix 10.2). Local laboratory must be qualified by local regulations.
HIV screening tests	X																	
HCV screening tests	X																	A positive hepatitis C antibody laboratory assessment will be confirmed with an additional test method.
HBV screening tests	X																	
Serum immunoglobulins (IgG, IgM, IgA, IgE)		X							X							X	X	
Pharmacogenetics sample		X																

	Screening	Treatment Periods																
	Period 1	Period 2								Period 3							ETV	Comments
Visit number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16		
Weeks from randomization	−5	—	1	2	4	6	8	10	12	13	14	16	18	20	22	24		
Study day	−35	1	8	15	29	43	57	71	85	92	99	113	127	141	155	169		
Visit tolerance interval (days)		—	±1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		
Fasting visit		X							X							X		
Exploratory biomarker samples		X	X	X	X	X		X	X	X	X	X			X	X	X	
Pharmacokinetic (PK) samples		X	X	X	X			X	X	X	X	X			X	X	X	Visit 2: Samples are collected at four time points: 1) before infusion starts 2) after infusion ends 3) 1 hour after infusion ends 4) 2 hours after infusion ends. Other visits: Samples are collected before infusion starts.
Immunogenicity (ADA) samples		X		X	X				X		X	X				X	X	All samples for immunogenicity should be collected before infusion when applicable and possible. A time-matched PK sample should be collected at each immunogenicity sample time point.
TBNK panel		X		X		X			X		X					X	X	

	Screening	Treatment Periods															
	Period 1	Period 2								Period 3						ETV	Comments
Visit number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16		
Weeks from randomization	–5	—	1	2	4	6	8	10	12	13	14	16	18	20	22	24		
Study day	–35	1	8	15	29	43	57	71	85	92	99	113	127	141	155	169		
Visit tolerance interval (days)		—	±1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		
Fasting visit		X							X							X		
Receptor occupancy assay		X						X	X						X	X	X	Visit 2: Samples are collected at four time points: 1) before infusion starts 2) after infusion ends 3) 1 hour after infusion ends 4) 2 hours after infusion ends. Other visits: Samples are collected before infusion starts.
Randomization and Dosing																		
Randomization		X																
Dosing		X		X	X	X	X	X	X		X	X	X	X	X			

Abbreviations: ADA = anti-drug antibody; AESI = adverse event of special interest; DLQI = Dermatology Life Quality Index; ECG = electrocardiogram; ETV = early termination visit; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; TBNK = T-cells, B-cells, and natural killer (NK) cells; TST = tuberculin skin test; ULN = upper limit of normal; V = visit.

Table 2. Schedule of activities post-treatment follow-up period (Period 4) of Study J1B-MC-FRCF.

	Post-Treatment Follow-Up			Comment
	Period 4		Post-Treatment ETV	
Visit number	V801	V802		
Weeks from randomization	28/ ETV+4	34/ ETV+10		
Study day	197	239		
Visit tolerance interval (days)	±7	±7		
Fasting visit				No fasting in this period.
Concomitant medications, including medications for indication	X	X	X	
Adverse events	X	X	X	For AESIs, additional data are collected.
Vital signs	X	X	X	Blood pressure, body temperature, pulse rate
Symptom-directed physical examination	X	X	X	Includes assessment of skin at every visit (Section 8.2.2)
Patient Diary (Electronic)				
Check electronic diary compliance	X			The diary is completed daily.
Return electronic diary		X	X	
Patient-Reported Outcomes (Paper)				
DLQI	X	X	X	
Laboratory Tests and Sample Collections				
Hematology	X	X	X	
Clinical chemistry	X	X	X	
Urine pregnancy	X	X	X	Only for women of childbearing potential and women with a history of tubal ligation; done locally
Pharmacokinetic (PK) samples		X	X	
Immunogenicity (ADA) samples		X	X	A time-matched PK sample should be collected at each immunogenicity sample time point.

Abbreviations: ADA = anti-drug antibody, AESI = adverse event of special interest; DLQI = Dermatology Life Quality Index; ETV = early termination visit; V = visit.

2. Introduction

2.1. Study Rationale

LY3454738 is a humanized immunoglobulin G (IgG) 4-variant monoclonal antibody (mAb) that binds to and agonizes the human inhibitory checkpoint CD200R. Binding of LY3454738 to CD200R induces a negative signal that results in functional inhibition of the target cell activity. CD200R is expressed on mast cells and basophils, both of which are critical in the pathogenesis of chronic spontaneous urticaria (CSU). Thus LY3454738 is being developed for the treatment of CSU. This proof-of-concept study will evaluate the safety and efficacy of LY3454738 in adults with CSU.

2.2. Background

Chronic spontaneous urticaria is an immune-mediated skin disease that causes pruritic hives (wheals) and/or soft tissue swelling (angioedema). Histamine release from mast cells and basophils is critical in the pathogenesis of CSU (Saini and Kaplan 2018). The unpredictability of the symptoms of CSU has a negative effect on quality of life similar to that caused by ischemic heart disease (O'Donnell et al. 1997) and moderate-to-severe psoriasis (Balp et al. 2018). Antihistamines are the first-line treatment for CSU, but only about 45% to 60% of patients respond, even at higher-than-licensed doses (Maurer et al. 2011, 2017; Guillén-Aguinaga et al. 2016). Omalizumab was approved in March 2014 by the Food and Drug Administration (FDA) for the treatment of CSU, but fewer than 50% of patients treated with omalizumab have symptoms that resolve completely (Maurer et al. 2013; Saini et al. 2015). Omalizumab also has a warning for anaphylaxis in its label, so it should be administered to patients under direct medical supervision by health care workers (Xolair package insert, 2019). For patients with CSU inadequately controlled by antihistamines, there is a need for additional therapies.

Activation of CD200R may be effective in the treatment of CSU because CD200R is an inhibitory receptor that is expressed on the mast cells and other immune cell types thought to be important in the disease pathogenesis. LY3454738 binds to and agonizes CD200R.

Study J1B-MC-FRCF (FRCF) will be the first clinical study to evaluate the safety and efficacy of LY3454738 in patients with CSU.

2.3. Benefit/Risk Assessment

There are currently no human data regarding the efficacy of LY3454738 in CSU. CD200R is an inhibitory receptor that is expressed on mast cells and other immune cells that are important in CSU pathogenesis. A surrogate antibody suppressed mast cell activation in a nonclinical model. These findings support the hypothesis that LY3454738 has the potential for efficacy in CSU. Nonclinical data and safety data from the Phase 1 clinical study J1B-MC-FRCC (FRCC) support development of LY3454738 in CSU at the proposed dose.

No dose-limiting safety issues were identified in healthy volunteers receiving single or repeat doses of LY3454738 in Study FRCC. See the Investigator's Brochure (IB) for additional information.

The toxicological potential of LY3454738 was assessed in cynomolgus monkeys, a pharmacologically relevant species, that were administered the molecule for 3 months; additionally, the potential for cytokine release syndrome was evaluated in vitro with human whole blood and peripheral blood mononuclear cells, and the data generated support a low risk of cytokine release in the clinic. Although LY3454738 has agonist action on CD200R to achieve immunosuppressive effects, it is notable that nonclinical toxicology studies of immune-enhancing molecules that act by antagonizing inhibitory checkpoint receptors (for example, programmed cell death protein 1 [PD-1], programmed death ligand 1 [PD-L1], cytotoxic T-lymphocyte-associated protein 4 [CTLA-4]) have underpredicted adverse events (AEs) experienced clinically (Naidoo et al. 2015; Saber et al. 2016).

LY3454738 binding to CD200R does not block binding of the ligand (CD200). Both LY3454738 and ligand can bind at the same time and induce activity through CD200R, resulting in the inhibitory signaling cascade. All of the preclinical data support LY3454738 as an agonist to CD200R resulting in induction of the inhibitory cascade, and there is no evidence of any immune activation due to LY3454738 binding to CD200R.

Ongoing monitoring of safety data (including AEs, serious adverse events [SAEs], and selected laboratory measurements) will continue throughout the study using blinded data. Interim safety analyses may be conducted to review unblinded safety data, as described in Section 9.5 and Appendix 10.1, Section 10.1.5.

This protocol has been designed to be conducted in accordance with applicable regulations and guidances, including "Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products" (EMA 2017). All participants will be monitored for AEs at every visit and managed appropriately as needed.

More information about the known and expected benefits, risks, SAEs, and reasonably anticipated AEs of LY3454738 is presented in the IB.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To test the hypothesis that treatment with LY3454738 is superior to placebo as measured by patient-assessed itch severity and hive count for the treatment of adult participants with CSU	• Mean change from baseline to Week 12 in UAS7
Secondary	
• To compare the efficacy of LY3454738 to placebo as measured by improvement in signs and symptoms of CSU	• Mean change from baseline to Week 12 in ○ ISS7 ○ HSS7 • Proportion of patients achieving UAS7 ≤6 at Week 12
• To characterize the pharmacokinetics (PK) of LY3454738	• C_{max} and AUC
Exploratory	
Exploratory objectives and endpoints may include the following: • To evaluate signs and symptoms and measures of quality of life at various time points in Period 2 (first 12-week treatment period) and in Period 3 (second 12-week treatment period, after crossover) using the DLQI and the UPDD items. • To assess the potential development of anti-LY3454738 antibodies and their impact on the safety profile and PK of LY3454738. • To explore relationships between LY3454738 exposure and select biomarkers and clinical efficacy endpoints.	

Abbreviations: AUC = area under the concentration versus time curve; C_{max} = maximum plasma drug concentration; CSU = chronic spontaneous urticaria; DLQI = Dermatology Life Quality Index; HSS7 = Hives Severity Score Over 7 Days; ISS7 = Itch Severity Score Over 7 Days; UAS7 = Urticaria Activity Score Over 7 Days; UPDD = Urticaria Patient Daily Diary.

4. Study Design

4.1. Overall Design

Study J1B-MC-FRCF (FRCF) is a multicenter, randomized, double-blind, placebo-controlled, Phase 2 crossover study to evaluate the efficacy and safety of LY3454738 500 mg given intravenously (IV) every 2 weeks (Q2W) versus placebo IV Q2W in adults with CSU inadequately controlled with H_1-antihistamines.

The study duration will be up to approximately 39 weeks over 4 study periods, as shown below:

Period 1: Screening, lasting up to 35 days before Week 0 (Visit 2, baseline)

Period 2: First 12-week treatment, from Week 0 (Day 1) through Week 12:

- Participants will be randomized in a 3:1 ratio to receive either LY3454738 500 mg IV or placebo IV Q2W

Period 3: Second 12-week treatment (crossover), from Week 12 through Week 24:

- Participants who received LY3454738 500 mg IV in Period 2 will receive placebo IV Q2W in Period 3.
- Participants who received placebo IV in Period 2 will receive LY3454738 500 mg IV Q2W in Period 3.

Period 4: Post-treatment follow-up for approximately 10 weeks.

- Participants will not receive study drug in Period 4.
- The last dose of study drug is given at Week 22, which is 6 weeks before the first post-treatment follow-up visit (Visit 801). Thus, participants will have been withdrawn from study drug for a total of 12 weeks at the last post-treatment follow-up visit (Visit 802).

The study schema is presented in Section 1.2.

Throughout the study, participants will take a second-generation H_1-antihistamine at a dose specified in approved product labeling. Certain participants may receive rescue therapy as described in Section 6.5.2.

Participants who permanently discontinue the study drug early (Section 7.1) will undergo early termination procedures, including an early termination visit (ETV) and the post-treatment follow-up visits specified in the Schedule of Activities (SoA) (Section 1.3).

4.2. Scientific Rationale for Study Design

Patients with CSU whose symptoms are not well controlled by licensed doses of antihistamines are appropriate for a novel investigational product (IP) with immunomodulating properties. A double-blind, placebo-controlled design limits bias for both patient and investigator assessments and enables a clearer interpretation of the effects of active drug. One active dose level of

LY3454738 will allow for an evaluation of safety and efficacy and will provide information to guide dose selection in future studies.

Study treatment will be provided during two study periods (Period 2 and Period 3). Study treatment in Period 2 is designed to evaluate the primary endpoint, which is the mean change from baseline in the Urticaria Activity Score (UAS) at the Week 12 visit. The Urticaria Activity Score Over 7 Days (UAS7) assesses the burden of itch and hives in CSU. It is used widely in CSU trials and has been accepted by the FDA as a primary endpoint for trials conducted for approval of new drugs. Evaluation of the primary endpoint at the Week 12 time point is appropriate, based on previous clinical trials of systemic therapies in CSU (Maurer et al. 2013; Saini et al. 2015).

The crossover in Period 3 allows for an evaluation of safety and durability of efficacy in participants who received LY3454738 in Period 2. This study period also allows participants who were randomized to placebo in Period 2 to receive LY3454738 in Period 3 for an equal treatment duration as in Period 2.

The post-treatment follow-up in Period 4 will allow for continued safety monitoring after the last dose of LY3454738. The last dose given in Period 3 is at Week 22. This is 2 weeks before the last visit in Period 3 (Week 24, Visit 16) and a total of 12 weeks before the last post-treatment follow-up visit (Week 34, Visit 802). A follow-up period of a similar duration was used after the last dose of LY3454738 in the single- and multiple-dose cohorts in Phase 1 Study FRCC. LY3454738 is expected to be undetectable in the serum after 5 half-lives. The terminal half-life of LY3454738 is approximately 2 weeks, based on pharmacokinetic (PK) data from the Phase 1 Study FRCC. Therefore, for the present study, the planned duration of safety follow-up is adequate, as this duration covers approximately 6 half-lives.

4.3. Justification for Dose

The planned dose of 500 mg IV Q2W for patients with CSU was chosen based on an analysis with preliminary human PK and receptor occupancy data from healthy subjects who received single (1 to 1000 mg) or repeat (200 mg x 2 doses) IV doses of LY3454738 in the Phase 1 Study FRCC. Based on the preliminary analysis, the half-life of LY3454738 is approximately 2 weeks, and a Q2W dose of 500 mg is expected to achieve approximately 90% saturation of the receptor at the trough drug concentration at steady state ($C_{min,ss}$). Receptor occupancy is used as a surrogate of pharmacological activity, and receptor saturation is desired to maximize the probability of achieving clinical efficacy.

This 500 mg IV Q2W dose was predicted to achieve a steady-state exposure that is similar to the maximum exposure achieved after the highest dose tested as a single dose in Study FRCC (that is, 1000 mg). In the single-ascending dose portion of Study FRCC, there were no dose-limiting safety findings. See the IB for additional information.

Dose selection is further supported by preclinical toxicity data. LY3454738 was evaluated in cynomolgus monkeys over a 3-month dosing period, during which LY3454738 was administered once weekly at doses of 0, 15, or 50 mg/kg subcutaneous or 170 mg/kg IV (13 total doses). The no-observed-adverse-effect level (NOAEL) in this study was 170 mg/kg, and this provides a margin of safety of ≥33-fold (based on mg/kg dose or estimated human exposure) to a repeated dose of 500 mg Q2W. See the IB for additional information supportive of the dose selection.

4.4. End-of-Study Definition

A participant is considered to have completed the study if he or she has completed all required phases of the study including the last visit or the last scheduled procedure shown in the SoA (Section 1.3).

The end of the study is defined as the date of the last visit or last scheduled procedure shown in the SoA (Section 1.3) for the last participant in the trial 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 screen failures and rescreening activities within the screening period, see Section 5.4.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if they meet all of the following criteria during screening, unless otherwise specified below:

Informed consent

[1] Have provided signed informed consent as described in Appendix 10.1 and are capable of compliance with the requirements and restrictions listed in the informed consent form and in this protocol.

Participant characteristics

[2] Are male or female participants from 18 to 65 years of age, inclusive, at the time of signing the informed consent document.

[2a] Female participants:

Women of childbearing potential (WOCBP)

Women of childbearing 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, post-ovulation methods), declaration of abstinence just for the duration of the trial, and withdrawal are not acceptable methods of contraception.

Otherwise, WOCBP who participate in the study must agree to use two forms of effective contraception, where at least one form is highly effective (less than 1% failure rate) for the entirety of the study.

Abstinence or contraception must continue following completion of study drug administration until their plasma concentrations are below the level that could result in a relevant potential exposure to a possible fetus, predicted to be 90 days following last dose of study drug.

A. Women of childbearing 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 exposure. Women must also test negative for pregnancy prior to each dose.

B. Two forms of effective contraception, where at least one 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 childbearing potential may participate and include those who are

A. infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation), congenital anomaly such as mullerian agenesis; or

B. post-menopausal – defined as either

i. A woman at least 40 years of age with an intact uterus, not on hormone therapy, who has cessation of menses for at least 1 year without an alternative medical cause and a follicle-stimulating hormone (FSH) >40 IU/mL; or

ii. A woman at least 55 years of age not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea; or

iii. A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.

[2b] Male participants:

Men, regardless of their fertility status, with nonpregnant WOCBP partners must agree to either remain abstinent (if this is their preferred and usual lifestyle) or use condoms as well as one additional highly effective (less than 1% failure rate) method of contraception (such as combination oral contraceptives, implanted contraceptives, or intrauterine devices) or effective method of contraception (such as diaphragms with spermicide or cervical sponges) for the duration of the study and until their plasma concentrations are below the level that could result in a relevant potential exposure to a possible fetus, predicted to be 90 days following the last dose of study drug.

Men and their partners may choose to use a double-barrier method of contraception. Barrier protection methods without concomitant use of a spermicide are not an effective or acceptable method of contraception. Thus, each barrier method must include use of a spermicide. It should be noted, however, 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 barrier methods are combined.

Periodic abstinence (for example, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.

Men with pregnant partners should use condoms during intercourse for the duration of the study and until the end of estimated relevant potential exposure in WOCBP, predicted to be 90 days following the last dose of study drug.

Men should refrain from sperm donation for the duration of the study and until their plasma concentrations are below the level that could result in a relevant potential exposure to a possible fetus, predicted to be 90 days following the last dose of study drug.

Men who are in exclusively same-sex relationships as their preferred and usual lifestyle are not required to use contraception.

CSU-related inclusion criteria

[3] Have a diagnosis of CSU for at least 6 months before the screening visit.

Note: CSU is as defined by the 2018 revision of the EAACI/GA2LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of urticaria [Zuberbier et al. 2018]).

[4] Have hives associated with itching at any time for at least 8 consecutive weeks before the baseline (randomization) visit, despite current use of H_1-antihistamines.

[5] Are taking an approved (marketed) 24-hour oral dose of a second-generation H_1-antihistamine (cetirizine, levocetirizine, fexofenadine, loratadine, desloratadine, rupatadine, mizolastine, bilastine) for CSU for at least 10 consecutive days before the baseline (randomization) visit, and agree to continue taking this medication at the same dose every day throughout the study (Section 6.5.1).

Note: If the participant is not already taking this medication at the screening visit, he or she may be eligible for the study if he or she agrees to take this medication for at least 10 consecutive days before the baseline (randomization) visit, agrees to continue taking this medication every day throughout the study at same dose, and meets all other study eligibility criteria.

[6] Are willing and able to complete the scheduled study assessments, including twice daily diary entry.

[7] Have an urticaria activity score during a 7-day period (UAS7 score) of 16 or more during the 7 consecutive days prior to the baseline (randomization) visit.

[8] Have no more than 5 missing diary entries for the 7 days before the baseline (randomization) visit.

[9] If the participant's CSU symptoms are triggered or worsened by aspirin and/or nonsteroidal anti-inflammatory drugs (NSAIDs), the participant must agree not to use the triggering agent during the study.

5.2. Exclusion Criteria

Participants will be excluded from study enrollment if they meet any of the following criteria within the screening period.

Skin diseases and skin conditions other than CSU

[10] Have a clearly defined underlying cause for chronic urticaria other than CSU. Such causes can include, but are not limited to, the following: symptomatic dermatographism (urticaria factitia); cold-, heat-, solar-, pressure-, delayed pressure-, aquagenic-, cholinergic-, or contact-urticaria.

[11] Have diseases, other than chronic urticaria, with urticarial or angioedema symptoms. These diseases include, but are not limited to, urticarial vasculitis, urticaria pigmentosa, erythema multiforme, mastocytosis, hereditary, or acquired angioedema (for example, due to C1 inhibitor deficiency), lymphoma, leukemia, or generalized malignancy.

[12] Have any other skin disease associated with chronic itching that, in the investigator's opinion, might influence the study evaluations and results (including, but not limited to, prurigo nodularis, atopic dermatitis, bullous pemphigoid, dermatitis herpetiformis, and senile pruritus).

Infections

[13] Have a current or recent acute, active infection. For at least 30 days prior to screening, participants must have no significant symptoms including fever of 100.5°F (38°C) or above, at screening or baseline, and/or signs of confirmed or suspected infection, and must have completed any appropriate anti-infective treatment.

[14] Have had, within 6 months of screening, any of the following types of infection:
- Serious infections (requiring hospitalization, and/or intravenous antibiotic treatment)
- Opportunistic infections (as defined in Winthrop et al. 2015)
- Herpes zoster that is considered active and ongoing until all vesicles are dry and crusted over
- Chronic infections (duration of symptoms, signs, and/or treatment of 6 weeks or longer)
- Recurring infection (including, but not limited to, herpes simplex, herpes zoster, recurring cellulitis, chronic osteomyelitis)
  - Participants with only recurrent, mild, and uncomplicated orolabial and/or genital herpes may be discussed with the Lilly-designated medical monitor for possible exemption from this exclusion criterion.

[15] Have human immunodeficiency virus (HIV) infection.

[16] Have a current or past infection with hepatitis B virus (HBV) (that is, positive for hepatitis B surface antigen [HBsAg] and/or hepatitis B core antibody) (see Section 8.2.8).

[17] Have a current infection with hepatitis C virus (HCV) (that is, positive for HCV ribonucleic acid [RNA]) (see Section 8.2.9).

[18] Have current or past active tuberculosis (TB) (see Section 8.2.7).

[19] Have or have had latent TB infection (LTBI) that has not been treated with a complete course of appropriate therapy as defined by the World Health Organization (WHO) and/or the United States Centers for Disease Control and Prevention (CDC), unless such treatment is underway (see Section 8.2.7).

[20] Have received a Bacillus Calmette-Guerin (BCG) vaccination or treatment within 12 months of screening, or received any other live vaccines (that is, live attenuated), within 3 months before the screening visit, or intend to receive a live vaccine (or live attenuated vaccine) during the study or within 90 days after the last dose of study drug.

Note: Use of nonlive (inactivated) vaccinations is allowed for all participants.

[21] Have evidence of parasitic infection, defined as meeting any of the following three criteria:

1) risk factors for parasitic disease (living in an endemic area, chronic gastrointestinal symptoms, travel within the last 6 months to an endemic area and/or chronic immunosuppression)

2) an absolute eosinophil count >2 times the upper limit of normal (ULN)

3) evidence of parasitic colonization or infection on stool evaluation for ova and parasites.

Note: Stool evaluation for ova and parasites will be conducted only in participants with risk factors (#1 above) and an eosinophil count >2 times ULN (#2 above).

Other medical conditions/history

[22] Have an unstable or uncontrolled illness, including but not limited to cerebrocardiovascular (for example, unstable angina, unstable arterial hypertension, moderate-to-severe heart failure [New York Heart Association Class III/IV]), respiratory, gastrointestinal, hepatic, renal, endocrine, hematologic, or neurologic disorders that would potentially affect the participant's safety in the study or confound efficacy and safety assessments.

[23] Have a diagnosis or history of malignancy within 5 years prior to the baseline (randomization) visit, with the following exceptions:

a. Basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years,

b. Cervical carcinoma in situ, with no evidence of recurrence within the 5 years prior to baseline (randomization) visit.

[24] Have a history of anaphylaxis.

[25] Have a history of chronic alcohol abuse, IV drug abuse, or other illicit drug abuse within 1 year prior to the screening visit.

Note: Marijuana is considered an illicit drug for the purposes of this study, regardless of local laws. Cannabidiol (CBD) products may be used during the study if they are derived exclusively from hemp. Participants who use hemp-based CBD products must be on a stable dose for at least 10 days prior to the baseline visit, and participants must remain on that stable dose during the study.

[26] Have a history of asthma with severity classified greater than intermittent asthma.

Note: Intermittent asthma is defined according to "Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma Summary Report 2007 (EPR-3)" (2007 Expert Panel).

Diagnostic assessments

[27] Have any of the following specific abnormalities on screening laboratory tests:

a. Serum creatinine, aspartate aminotransferase (AST), or alanine aminotransferase (ALT) ≥2 times ULN

b. Alkaline phosphatase (ALP) ≥2 times ULN

c. Total bilirubin level (TBL) ≥1.5 times ULN

d. Hemoglobin <10.0 g/dL (<100.0 g/L)

e. Total white blood cell count <2500 cells/μL (<2.50x10^3/μL or <2.50 GI/L)

f. Neutropenia (absolute neutrophil count <1200 cells/μL) (<1.20x10^3/μL or <1.20 GI/L)

g. Lymphopenia (lymphocyte count <750 cells/μL) (<0.75x10^3/μL or <0.75 GI/L)

h. Thrombocytopenia (platelet count <100,000 cells/μL) (<100x10^3/μL or <100 GI/L)

Note: For each aforementioned test, 1 repeat testing is allowed during screening, and values resulting from repeat testing may be accepted for a participant's enrollment eligibility if the other eligibility criteria are met (see Section 5.4.1).

[28] Have screening electrocardiogram (ECG) abnormalities that, in the opinion of the investigator, are clinically significant and indicate an unacceptable risk for the participant's safety in the study.

Prior or concomitant therapy

[29] Have used any first generation H_1-antihistamine, H_2-antihistamine or leukotriene-receptor antagonist within 10 days before the baseline (randomization) visit.

Note: The first generation H_1-antihistamine diphenhydramine is allowed as rescue medication before the baseline (randomization) visit per Section 6.5.2.

Note: Participants taking H_2-antihistamines for gastroesophageal reflux disease (GERD) during the screening period may be eligible for the study if the other study eligibility criteria are met; such participants may continue to take this medication at a stable dose during the study.

[30] Have received routine administration (that is, daily or every other day for 5 or more consecutive days) of systemic glucocorticoids, hydroxychloroquine, methotrexate, cyclosporine, cyclophosphamide, doxepin, or IV immunoglobulin for any indication within 30 days before the baseline (randomization) visit.

[31] Have received prior treatment with omalizumab, ligelizumab, or any other approved or investigational biologic compound for CSU.

Note: Participants with prior use of investigational antihistamines may be eligible for the study if the other study eligibility criteria are met and if the investigational antihistamines are discontinued within 30 days or 5 half-lives, whichever is longer, before the baseline (randomization) visit.

[32] Have received within 30 days of the baseline (randomization) visit, corticosteroids (inhaled or oral), long-acting beta agonists, cromolyn, theophylline, zileuton, or monoclonal antibodies targeting interleukin-13 (IL-13), IL-4/IL-13 receptor (dupilumab), IL-5 (mepolizumab, reslizumab), or IL-5 receptor (benralizumab).

Prior or concurrent clinical study experience

[33] Are currently enrolled in any other clinical study involving an investigational product (IP) or any other type of medical research judged not to be scientifically or medically compatible with Study FRCF.

[34] Have participated within the last 30 days in a clinical study involving an IP. If the previous IP has a long half-life, at least 5 half-lives or 30 days (whichever is longer) should have passed before the baseline (randomization) visit of Study FRCF.

Other exclusions

[35] Are pregnant or breastfeeding, or intend to become pregnant or breastfeed during the study.

[36] Have donated more than a single unit of blood within 4 weeks prior to the screening visit or intend to donate blood during the course of the study.

[37] Have a contraindication to diphenhydramine.

[38] Have an inability to swallow medication in tablet form.

[39] Have significant allergies to humanized monoclonal antibodies or any components of the LY3454738 product formulation.

[40] Are investigator 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.

[41] Are employees of Eli Lilly and Company (Lilly).

5.3. Lifestyle Considerations

Not applicable.

5.4. Screen Failures

Individuals are described as having failed screening ("screen failures," "screen failed") if they consent to participate in the clinical study but are not subsequently randomized. A minimal set of information about such individuals is required to ensure transparent reporting consistent with Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. The minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

5.4.1. Rescreening of Individuals Who Failed Screening

Informed consent for rescreening

Individuals who are rescreened must sign a new informed consent form (ICF) (Appendix 10.1, Section 10.1.3) and will be assigned a new identification number.

Allowed rescreening for an administrative reason

An individual may be rescreened **one time** for an administrative reason, including, for example, but not limited to, falling out of the screening window because of scheduling conflicts. The sponsor does not need to approve rescreening for an administrative reason.

Allowed rescreening after failure to meet certain study eligibility criteria

An individual who has failed screening because of one or more of the following eligibility criteria may be rescreened **one time** if the reason for screen failure has resolved and if the sponsor has approved the rescreening:

[2a/B], specifically for women not of childbearing potential who are rescreening for postmenopausal status

[3], [4], [5], [7], to satisfy requirements for disease activity/duration

[13], [14], to satisfy requirements for infection-free time

[20], to satisfy requirement for timings of vaccination

[23], to satisfy requirement for cancer-free time

[27], to address requirements for specific abnormalities on screening laboratory tests

[29], [30], [32], [34], to satisfy medication washout periods

[36], to satisfy requirement for timing of blood donations.

Allowed retesting of screening investigations

Repeating of laboratory tests during the screening period does not constitute rescreening. See Section 8.2.7 for retesting for LTBI.

Procedures not required to be repeated during rescreening

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

All other screening procedures must be repeated during rescreening to ensure that all the study eligibility criteria are met.

6. Study Intervention

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

6.1. Study Interventions Administered

Study interventions

This study involves a single dose level of LY3454738 and placebo, as shown below.

Treatment Name	LY3454738	Placebo
Dosage Formulation	Lyophilized powder	0.9% sodium chloride
Dosage Level	500 mg	not applicable
Routes of Administration	IV infusion	IV infusion
Dosing Instructions	One dose every 2 weeks	One dose every 2 weeks

Abbreviation: IV = intravenous.

LY3454738 is supplied for clinical trial use as a lyophilized powder formulation in a glass vial. Vials will be supplied in cartons, with the appropriate quantity specific to the planned dispensing schedule of the IPs.

When the IPs are prepared for dosing according to instructions (Section 6.2) it will not be possible to distinguish LY3454738 from placebo.

All participants should be monitored for 30 minutes or longer after dosing, according to investigator practice or local standard of care. Sites must have resuscitation equipment, emergency drugs, and appropriately trained staff available during the infusion and monitoring period, or until completion of all required post-dosing activities (whichever is longer).

Packaging and labeling

Study interventions (LY3454738 and placebo) will be supplied by the sponsor or its designee in accordance with current Good Manufacturing Practice (cGMP). 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

Detailed instructions for the preparation and handling of the administered products will be provided by the sponsor in the Pharmacy Manual. Investigators should consult the study drug information provided in the Pharmacy Manual or label for the specific administration information (including warnings, precautions, contraindications, adverse reactions, and dose modifications).

Preparation

The IPs must 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 storage and handling instructions on 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 that appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention and only authorized site staff may supply 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 authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (that is, receipt, reconciliation, and final disposition records).

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 an interactive web-response system (IWRS).

Unblinded pharmacist

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 reconstitution and dispensation of all study intervention. Blinded site personnel will administer the intervention to the participant.

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 a participant's study treatment assignment is unblinded, the participant must be discontinued from the study, unless the investigator obtains specific approval from the sponsor's medical monitor for the study participant to continue in the study (Section 7.1.1).

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

Participants will receive study intervention directly from the investigator or designee at the study site, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the electronic case report form (eCRF). Deviations from the prescribed dosage regimen should be recorded in the eCRF.

6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter 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 along with

- Reason for use
- Dates of administration including start and end dates, and
- Dosage information, including dose for concomitant therapy of special interest (background H_1-antihistamine and rescue treatments).

Participants will be instructed to consult the investigator or other appropriate study site personnel before taking any new medications or supplements during the study.

The sponsor's medical monitor should be contacted if there are any questions.

6.5.1. Background Medications

Throughout the study, participants will continue taking the second-generation H_1-antihistamine that they were taking prior to the baseline (randomization) visit. The choice of background medication will be made by the participant and his or her relevant physician. Once the choice is made, the same background medication should be continued for the duration of the study.

The doses and regimens of background medications should be as follows, unless locally approved product labeling specifies another dose or regimen for CSU:

- cetirizine 10 mg once daily
- levocetirizine dihydrochloride 5 mg once daily
- fexofenadine 180 mg once daily
- loratadine 10 mg once daily
- desloratadine 5 mg once daily
- rupatadine (not available in the United States of America [USA]) 10 mg once daily
- mizolastine (not available in the USA) 10 mg once daily, and
- bilastine (not available in the USA) 20 mg once daily.

6.5.2. Rescue Therapy

Participants may be eligible for rescue therapy based on the following considerations:

- Therapy used as rescue therapy can start as soon as the background medication is started.
- The need for rescue therapy is determined by the participant, although a conversation between the participant and the investigator on parameters for use of rescue therapy is encouraged. The decision to use rescue therapy is based on the individual participant's tolerance of pruritus and angioedema.
- Rescue therapy is either diphenhydramine 25-mg tablets or the addition of a second second-generation H_1-antihistamine that the participant is currently NOT taking. This may be cetirizine, levocetirizine, fexofenadine, loratadine, desloratadine, or (outside the USA) rupatadine, mizolastine, or bilastine with the 24-hour oral dose as specified in approved product labeling.

  If the participant chooses diphenhydramine, dosing is as follows for this study: 25-mg tablets, with 1 tablet every 4 to 6 hours as needed up to a maximum of 3 tablets (75 mg) in a 24-hour period of time.

The date of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded on the eCRF.

6.5.3. Other Permitted Concomitant Therapy

Unless prohibited in Section 6.5.4 or in the study entry criteria (Section 5), concomitant therapies are permitted, including, for example, ophthalmic steroids, nasal steroids, and inhaled short-acting beta-2-selective adrenergic agonists.

6.5.4. Prohibited Concomitant Therapy

The following table lists medications that are prohibited as concomitant therapy during the study, unless an exception is noted in the "Exceptions" column. Of note, patients who have received monoclonal antibodies that target IgE (for example, omalizumab, ligelizumab) are not eligible

for study enrollment (Section 5.2), and the use of such medications during the study is prohibited.

Prohibited as Concomitant Therapy	Exceptions
Aspirin, if participant has history of CSU symptoms triggered or worsened by aspirin	Allowed if participant has no such history
Bacillus Calmette-Guerin (BCG) vaccine	
Cromolyn	
Cyclophosphamide	
Cyclosporine	
Doxepin	
H_2-antihistamines (for example, ranitidine, famotidine, etc.)	Allowed for treatment of GERD
Hydroxychloroquine	
Investigational biologic for CSU	
IV immunoglobulin	
Leukotriene-receptor antagonists (for example, montelukast, zafirlukast, etc.)	
Live or live attenuated vaccine	
Long-acting beta agonists (for example, salmeterol, formoterol, etc.)	
Methotrexate	
Monoclonal antibodies targeting IL-13 (for example, tralokinumab) IL-4/IL-13 receptor (for example, dupilumab) IL-5 (for example, mepolizumab, reslizumab) IL-5 receptor (for example, benralizumab), or IgE (for example, omalizumab, ligelizumab)	
NSAIDs, if participant has history of CSU symptoms triggered or worsened by NSAIDs (for example, ibuprofen, naproxen, etc.)	Allowed if participant has no such history
Systemic corticosteroids/glucocorticoids (inhaled or oral), for example: beclomethasone budesonide ciclesonide flunisolide fluticasone mometasone methylprednisolone prednisone, etc.)	
Theophylline	
Zileuton	

Abbreviations: CSU = chronic spontaneous urticaria; GERD = gastroesophageal reflux disease; IgE = immunoglobulin E; IL = interleukin; IV = intravenous; NSAID = nonsteroidal anti-inflammatory drug.

6.6. Dose Modification

Modification of the dose of the study intervention is not permitted in this study.

6.7. Intervention after the End of the Study

LY3454738 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

- permanent or temporary discontinuation of study drug, or
- participant's discontinuation (withdrawal) from the study.

Discontinuation of the study as a whole or of particular study sites is described in Appendix 10.1, 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 (V801, V802).

The investigator will complete any AE reporting and necessary follow-up (Section 8.3).

7.1.1. Criteria for Permanent Discontinuation of Study Drug

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

Participant Decision

- The participant requests to discontinue the study drug.

Prohibited Concomitant Medication Use

- The participant requires treatment with a prohibited medication (Section 6.5.4).
- The participant changes the background H_1-antihistamine.

Safety Considerations

- The participant develops any of the following during the study:
  - malignancy (except for successfully treated basal or squamous cell skin carcinoma)
  - HIV/acquired immune deficiency syndrome (AIDS) infection
  - active TB or untreated LTBI (Section 7.1.2; Section 8.2.7)
  - HCV RNA positive
- The investigator determines that a clinically significant hypersensitivity reaction has occurred. A clinically significant systemic hypersensitivity reaction is one that occurs after administration of the investigational intervention (for example, drug-related

symptomatic bronchospasm or hypotension) and is different from the participant's baseline CSU symptoms, requires parenteral medication, does not respond to symptomatic medication, results in clinical sequelae, or is an anaphylactic reaction (Section 8.3.7.2). Study drug should be discontinued after a systemic hypersensitivity event or anaphylaxis.

- The participant experiences any 1 of the following events on 2 consecutive samples taken at least 48 hours apart:
  - Total white blood cell count (WBC) <1000 cells/μL
  - Absolute neutrophil count (ANC) <500 cells/μL
  - Absolute lymphocyte count (ALC) <200 cells/μL
- The participant becomes pregnant (see Section 8.2.6.1).
- Noncompliance with LTBI treatment (see Section 8.2.7).
- The participant has an AE or SAE that, in the opinion of the investigator or sponsor, would preclude the participant from continuing to receive study drug.

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 one of the following conditions after consultation with the medical monitor (see Section 8.2.10):

  - 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 international normalized ratio (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

- Unblinding: If an investigator, site personnel performing assessments, or participant is unblinded, 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 or designee for the participant to continue.

Participants discontinuing from the study drug prematurely for any reason will complete AE and other follow-up procedures as specified in the SoA (Section 1.3), Section 8.2 ("Safety Assessments"), and Section 8.3 ("Adverse Events and Serious Adverse Events"), including ETV **and** post-treatment follow-up visits (V801, V802).

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

Dosing may be interrupted and resumed in participants who experience the following reductions in WBC counts, but do not meet the criteria for permanent discontinuation (Section 7.1.1):

- interrupt if total WBC count is <2000 cells/μL (leukopenia) and resume when total WBC count is ≥2000 cells/μL
- interrupt if ANC is <1000 cells/μL (neutropenia) and resume when ANC is ≥1000 cells/μL
- interrupt if ALC is <500 cells/μL (lymphopenia) and resume when ALC is ≥500 cells/μL.

Temporary withholding of study intervention is allowed when the participant has positive microbial lab results or clinical signs of a confirmed or suspected infection (Section 5.2) after consultation with the sponsor's medical monitor.

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

- Serious or opportunistic infections, as defined in Exclusion Criteria (Section 5.2). Study intervention is to be withheld until resolution of all acute clinical signs and symptoms, and completion of all appropriate anti-infective treatment (exception for LTBI, noted below).
- Participants diagnosed with LTBI during the study are to be permanently discontinued from study intervention unless a participant is a candidate for LTBI treatment, and is treated for LTBI as follows:
  - Study intervention is temporarily held for at least the first 4 weeks of LTBI treatment.
  - After receiving at least 4 weeks of appropriate LTBI therapy (as per World Health Organization 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 intervention may be resumed.
  - The participant must complete appropriate LTBI therapy to remain eligible to receive study intervention.

7.1.3. Discontinuation of Inadvertently Enrolled Participants

If the sponsor or investigator identifies 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 study treatment. If the investigator and the sponsor agree that it is medically

appropriate to continue, the investigator must obtain documented approval from the sponsor 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 1.3), Section 8.2 ("Safety Assessments"), and Section 8.3 ("Adverse Events and Serious Adverse Events"), including ETV **and** post-treatment follow-up visits (V801, V802).

7.2. Participant Discontinuation/Withdrawal from the Study

Participants will be discontinued (withdrawn) from the study in the following circumstances:

- enrollment in any other clinical study involving an IP or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and Good Clinical Practice (GCP)
- investigator decision
  - the investigator decides that the participant should be discontinued from the study
  - 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 before introduction of the new agent.
- participant decision
  - the participant requests to be withdrawn from the study.

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/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

Participants discontinuing from the study prematurely for any reason should have AE and other safety follow-up specified for the ETV. See safety follow-up as outlined in the SoA (Section 1.3), Section 8.2 ("Safety Assessments"), and Section 8.3 ("Adverse Events and Serious Adverse Events"), including ETV **and** post-treatment follow-up visits (V801, V802).

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 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. Contact attempts should be documented in the participant's medical record.

If the participant continues to be unreachable, he or she will be considered to have withdrawn from the study.

8. Study Assessments and Procedures

Study procedures and the study visits at which they are performed, including tolerance limits for the study visits, are listed in the SoA (Section 1.3). Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

8.1. Efficacy Assessments

Visits and order of efficacy assessments

Efficacy assessments occur as specified in the SoA (Section 1.3). Procedures at study visits should be timed so that participants' self-assessments, including Urticaria Patient Daily Diary (UPDD) and Dermatology Life Quality Index (DLQI), are completed before any clinical assessments or sample collections are performed.

Home or virtual health visits are permitted to evaluate clinical efficacy under special circumstances (for example, site closure or other restrictions), after consultation with the sponsor's medical monitor. The home or virtual health visits should be documented in the CRF. If required under special circumstances and after consultation with the sponsor's medical monitor, the DLQI can be read over the phone exactly as it is written, in the patient's native language, without any additional words or explanations. Responses should be documented by site staff, retained as source documentation, and entered into the CRF

Urticaria Patient Daily Diary (UPDD)

The UPDD is a daily diary completed twice per day (morning and evening) via an electronic, handheld device. Items asking about itch severity and number of hives pertain to the past 12 hours and are asked twice per day. The remaining items are asked once per day and pertain to the past 24 hours: interference with sleep, interference with daily activities, use of rescue medication (number of tablets), presence (and treatment) of angioedema, and any calls placed to healthcare professionals. While developed originally on paper, the electronic version of the UPDD has been shown to be equivalent to the paper version from a measurement perspective, and is considered a valid and reliable assessment of urticaria symptoms (Flood et al. 2013).

Pruritus, angioedema, and hives are monitored as clinical endpoints in the UPDD and would not constitute AEs. However, if any of these events is an SAE as defined in Appendix 10.3, Section 10.3.2, the event should be reported as an SAE. See Section 8.3.6 for more information.

There is no overall UPDD score calculation. The primary endpoint assessment (Urticaria Activity Score Over 7 Days [UAS7]) and key secondary endpoint assessments (Itch Severity Score Over 7 Days [ISS7] and Hives Severity Score Over 7 Days [HSS7]) are derived from data collected via the UPDD, as described below (Sections 8.1.1 and 8.1.2, respectively).

Appropriateness and devices/questionnaires for assessments

The UAS7, which is derived from the UPDD, has been used in previous CSU trials and is being used as the primary endpoint for trials conducted for registration (Xolair package insert, 2019; ligelizumab studies NCT03580369 and NCT03580356 [ClinicalTrials.gov]).

The secondary and exploratory measures of disease activity and quality of life in this study are also generally recognized as reliable, accurate, and relevant.

The self-reported questionnaires will be administered via either an electronic participant diary (UPDD) or on paper (DLQI), and in countries where the questionnaires have been translated into the native language of the region and linguistically validated.

8.1.1. Primary Efficacy Assessment

8.1.1.1. Urticaria Activity Score Over 7 Days (UAS7)

The weekly UAS7 is calculated using data from the UPDD. The UAS7 is the sum of the daily urticaria activity scores (UAS) over a 7-day period and ranges from 0 to 42. The daily UAS is the sum of the daily itch severity score (ISS) and daily number of hives score, and ranges from 0 to 6. The baseline UAS7 is the sum of the daily UAS over the 7 days prior to the first treatment. A higher UAS or higher UAS7 indicates greater urticaria disease activity.

The minimally important difference (MID) for UAS7 is defined as a reduction from baseline in weekly Urticaria Activity Score of 9.5 to 10.5 points or more (Mathias et al. 2015).

8.1.2. Secondary Efficacy Assessments

8.1.2.1. Itch Severity Score Over 7 Days (ISS7)

The weekly ISS7 is calculated using data from the UPDD. The ISS7 is the sum of the daily ISS over a 7-day period and ranges from 0 to 21. The daily ISS is the average of the morning and evening ISS on a 4-point scale of 0 (none), 1 (mild), 2 (moderate), and 3 (severe). The baseline ISS7 is the sum of the daily ISS over the 7 days prior to the first treatment. A higher ISS or higher ISS7 indicates more severe itching.

The MID for ISS7 is defined as a reduction from baseline in weekly itch severity score of 4.5 to 5.0 points or more (Mathias et al. 2015).

8.1.2.2. Hives Severity Score Over 7 Days (HSS7)

The weekly HSS7 is calculated using data from the UPDD. The HSS7 is the sum of the daily number of hives over a 7-day period and ranges from 0 to 21. The daily number of hives score (also called HSS) is the average of the morning and evening number of hive scores on a four-point scale of 0 (none), 1 (between 1 and 6 hives, inclusive), 2 (between 7 and 12 hives, inclusive), and 3 (greater than 12 hives). The baseline weekly HSS7 is the sum of the HSS over the 7 days prior to the first treatment. A higher HSS or higher HSS7 indicates a greater number of hives.

The MID for HSS7 is defined as a reduction from baseline in weekly number of hives score of 5.0 to 5.5 points or more (Mathias et al. 2015).

8.1.3. Exploratory Assessments

8.1.3.1. Dermatology Life Quality Index

The Dermatology Life Quality Index (DLQI) is a participant-rated, 10-item questionnaire that covers 6 domains including symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. The recall period of this scale is over the "last week." Response categories include "a little," "a lot," and "very much," with corresponding scores of 1,

2, and 3, respectively, and "not at all," or unanswered ("not relevant") responses scored as 0. Scores range from 0 to 30, with higher scores indicating greater impairment of quality of life. A DLQI total score of 0 to 1 is considered as having no effect on a participant's health-related quality of life (Hongbo et al. 2005), and a 4-point change from baseline is considered the minimal clinically important difference threshold (Basra et al. 2015).

8.2. Safety Assessments

Visits and order of safety assessments

Safety assessments occur at visits specified in the SoA (Section 1.3). Home or virtual health visits are permitted to assess the safety of the participant under special circumstances (for example, site closure or other restrictions), after consultation with the sponsor's medical monitor. The home or virtual health visits should be documented in the CRF.

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

1) ECG (if applicable) and vital signs first
2) other safety assessments, including physical examinations and AE collection, and finally
3) blood sample collection for clinical laboratory, PK, pharmacodynamic (PD), pharmacogenetic, biomarker, and immunogenicity testing.

Data collection and reporting

The AE data collection and reporting requirements are described in Section 8.3 and Appendix 10.3. 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. Additional requirements regarding adverse events of special interest are described in Section 8.3.

Safety monitoring

The principle investigator will monitor safety and laboratory data throughout the study and should discuss safety concerns with the sponsor immediately upon occurrence or awareness of the concern in order to determine whether the participant should continue or discontinue study drug.

The sponsor will periodically review evolving safety data, including AEs and SAEs, discontinuations, vital signs, concomitant medications, and medical history in monthly blinded reviews and via other appropriate methods. These methods include review by a functionally independent safety physician and/or clinical research scientist who regularly reviews SAE reports in real time and across studies, and 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.

As noted in Section 8.1, pruritus, angioedema, and hives are monitored as clinical endpoints and would not constitute AEs. However, if any of these events is an SAE as defined in Appendix 10.3, Section 10.3.2, the event should be reported as an SAE. See Section 8.3.6 for more information.

8.2.1. Vital Signs

Measurements of vital signs (body temperature, blood pressure, and pulse rate) will be conducted at the study visits specified in the SoA (Section 1.3) and as clinically indicated. Additional vital signs may be measured during each study period as per judgment of the investigator.

Blood pressure and pulse rate should be measured after the participant has been sitting for at least 5 minutes. Orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. If orthostatic measurements are required, participants should be supine for at least 5 minutes and stand for at least 3 minutes. If the participant feels unable to stand, only supine vital signs will be recorded.

8.2.2. Physical Examinations

One complete physical examination will be performed at Visit 1. This examination includes a visual examination of the skin and an assessment of peripheral lymph nodes but excludes pelvic, rectal, and breast examinations.

A symptom-directed physical examination that includes a visual examination of the skin will be performed at other visits, as specified in the SoA (Section 1.3) or as clinically indicated.

8.2.3. Electrocardiograms

For each participant, 12-lead electrocardiograms (ECGs) will be collected as specified in the SoA (Section 1.3). Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

Electrocardiograms should be taken before collecting any blood for safety or PK tests; however, aberrations to this specified time will not be considered protocol deviations as long as the ECGs are taken and the actual recording time is documented. Electrocardiograms may be obtained at additional visits and times when deemed clinically necessary. Collection of additional ECGs is allowed to ensure high-quality records.

Electrocardiograms will be interpreted by a qualified physician (the investigator or qualified designee) at the study site 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.

8.2.4. Chest Radiography

A posterior–anterior (PA) chest x-ray CXR, interpreted and reported by a radiologist or pulmonologist, will be obtained at screening, as specified in the SoA (Section 1.3). 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 two conditions are met:

- the CXR was performed within 6 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 or images or a radiology report must be available to the investigator for review before the participant is randomized. Certain findings from CXR may be consistent with a condition that excludes a participant from the study; see Section 5.2.

> Note: Results of a chest computerized tomography (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. Stool Testing

The stool evaluation will be conducted only for participants with certain risk factors and an eosinophil count >2 times ULN (Section 5.2). To be randomized, these participants must have a negative stool culture indicating no enteric pathogens (ova or parasites) are isolated.

Retesting is allowed within the screening period if there is a technical difficulty in performing or reporting the stool culture assay (Section 5.4.1).

8.2.6. Laboratory Tests

Appendix 10.2 lists the clinical laboratory tests to be performed, and the SoA (Section 1.3) specifies the study visits at which samples are routinely collected for clinical laboratory tests.

Under special circumstances (for example, site closure or other restrictions), local laboratory testing is permitted after consultation with the sponsor's medical monitor as specified if indicated per PI to evaluate AEs .

If a participant elects, or is advised by the site, to have local labs drawn via home health or by presenting to a local lab, the lab analytes to be tested for safety assessment must be ordered at the local lab by the PI/site. The specific lab analytes for safety assessment will be drawn, sampled, tested, and reported back to the PI/site. The PI must sign and date review of safety labs as per normal process.

Additional samples for laboratory testing will be obtained in the event of anaphylaxis or systemic allergic/hypersensitivity reactions, as described in Section 8.3.7.2 and Appendix 10.2. Additional tests may be performed at any time during the study as deemed necessary by the investigator or as required by local regulations.

All protocol-required laboratory assessments, as defined in Appendix 10.2, must be conducted in accordance with the laboratory manual and the SoA.

Reviewing and recording test results

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents.

If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (for example, SAE or AE or dose modification), the results must be recorded in the CRF.

Repeat testing after clinically significant abnormal findings

Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. Laboratory tests with values that are clinically significantly abnormal during participation in the study or within 12 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 medical monitor. If the 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 (Appendix 10.2).

Sample retention

Unless otherwise specified in the subsections of Section 8 or in Appendix 10.1, Section 10.1.12 ("Long-Term Sample Retention"), 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.

8.2.6.1. Pregnancy Testing

Pregnancy testing is to be performed on women of childbearing potential and women with a history of tubal ligation (see Section 5.1). Participants who are pregnant will be discontinued from the study (Section 7.1.1).

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 at visits specified in the SoA (Section 1.3). The urine pregnancy test must be "negative" within 24 hours prior to administration of study drug at every study visit.

Urine pregnancy testing may be performed at additional time points during the 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 serum pregnancy test is an acceptable alternative.

Optional FSH Testing

Assessment of FSH levels can assist in determining if a woman meets the definition of "postmenopausal" as described in Section 5.1. The participant's FSH level can be obtained

during screening at the discretion of the investigator. The FSH level can also be optionally obtained during the study to determine the participant's postmenopausal status (see Section 1.3 and Appendix 10.2).

8.2.7. 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, for TB progression, and for 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 and assessment of peripheral lymph nodes (Section 8.2.2), and
  - PA 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 tuberculin skin test (TST) using purified protein derivative (PPD) or positive *Mycobacterium tuberculosis* interferon gamma release assay (IGRA) must have one of the following:

- Purified Protein Derivative (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. 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 in
    - ¤ HIV-infected persons
    - ¤ A recent contact of a person with TB disease
    - ¤ Persons with fibrotic changes on chest radiograph consistent with prior TB
    - ¤ Persons with organ transplants
    - ¤ Persons who are immunosuppressed for other reasons (for example, taking the equivalent of >15 mg/day of prednisone for 1 month or longer, taking tumor necrosis factor-α antagonists)
  - An induration of 10 or more millimeters is considered positive in all other potential clinical trial participants.

  - Two-step testing (repeat TST 1 to 3 weeks after the first TST) is recommended for certain participant groups, including:
    - persons receiving immunosuppressant treatment
    - persons with a history of temporally remote increased risk of TB infection
    - persons for whom the first test is negative, as per local public health and/or professional medical society recommendations.
- Interferon Gamma Release Assay (IGRA) for *M tuberculosis*. Ensure that specimen handling, transport, timing, and laboratory procedures meet all requirements per package insert. If the investigator suspects a false-positive IGRA result in a participant with no increased risk of TB infection during lifetime, and no evidence of prior or current TB on physical examination and/or on CXR interpreted by radiologist and/or pulmonologist (investigator assessment by history and physical examination, and CXR report documented in eCRF), the investigator may discuss retesting with the sponsor's designated medical monitor.

Retesting

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

Diagnosed LTBI

Participants diagnosed with LTBI are excluded unless they are candidates for LTBI treatment, are treated for LTBI, and the following criteria are met:

- After receiving at least 4 weeks of appropriate LTBI therapy (as per World Health Organization and/or the United States Centers for Disease Control guidelines), there is no evidence of hepatotoxicity (ALT/AST must remain ≤2 times ULN) or other treatment intolerance. The participant may be rescreened, and is not excluded due to LTBI.
- The participant must continue and complete appropriate LTBI therapy in order to remain eligible to continue to receive study intervention.

8.2.8. 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, the participant is excluded.

8.2.9. 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 polymerase chain reaction (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 (Section 7.1.1), and the participant should receive appropriate follow-up medical care.

8.2.10. Hepatic Safety Monitoring

If a study participant experiences elevated ALT ≥3 times ULN, ALP ≥2 times ULN, or TBL ≥2 times ULN, liver testing (described in Appendix 10.5) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the study medical monitor. Monitoring of ALT, AST, TBL, and ALP should continue until levels normalize or return to approximate baseline levels.

Hepatic Safety Data Collection

Additional safety data should be collected via the hepatic eCRF packet if 1 or more of the following conditions occur:

- elevation of serum ALT to ≥5 times ULN on 2 or more consecutive blood tests
- elevated serum 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
- participant discontinued from treatment due to a hepatic event or abnormality of liver tests, or
- hepatic event considered to be an SAE.

8.3. Adverse Events and Serious Adverse Events

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

The investigator and qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE (Appendix 10.3, Section 10.3.1) or SAE (Appendix 10.3, Section 10.3.2) and remain responsible for follow-up of AEs through an appropriate health care option (Section 8.3.3).

As noted in Section 8.1, pruritus, angioedema, and hives are monitored as clinical endpoints and would not constitute AEs. However, if any of these events is an SAE as defined in Appendix 10.3, Section 10.3.2, the event should be reported as an SAE. See Section 8.3.6 for more information.

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 Appendix 10.3, 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 AE and SAE Information

All AEs occurring after signing the ICF are recorded in the eCRF and assessed for serious criteria.

The SAE reporting to the sponsor begins after the participant has signed the ICF and has received IP. However, if an SAE occurs after signing the ICF, but prior to receiving IP, the SAE should be reported to the sponsor as per SAE reporting requirements and timelines (see Appendix 10.3, Section 10.3.3 and Section 10.3.4) if the SAE is considered reasonably possibly related to study procedure.

All SAEs will be recorded and reported to the sponsor or designee immediately upon investigator awareness of the event; under no circumstance should this exceed 24 hours from the time of awareness, as indicated in Appendix 10.3. The investigator will likewise submit any updated SAE data to the sponsor within 24 hours of its availability.

Investigators are not obligated to actively seek AEs or SAEs in study participants 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 reasonably possibly related to the study treatment or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 10.3, 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 AEs and SAEs

After the initial AE or SAE report, the investigator is required to proactively follow each event at subsequent visits and/or contacts with the participant.

All SAEs and AEs that are otherwise medically important, or that are considered related to the IP or study procedures, or that caused the participant to discontinue the IP before completing the study, will be followed up until the event is resolved, stabilized, or otherwise explained, or until the participant is lost to follow-up (as defined in Section 7.3). The frequency of follow-up evaluations is at the discretion of the investigator.

Further information on follow-up procedures is provided in Appendix 10.3, Section 10.3.3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE, as stated in Section 8.3.1, is essential so that legal obligations and ethical responsibilities toward 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 related to safety reporting to the regulatory authority, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

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 all pregnancies in female participants and female partners of male participants, details will be collected for pregnancies that begin at any point after the start of study drug and until at least 12 weeks after the participant's last dose of study drug.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 10.3, Section 10.3.3 and Section 10.3.4; and Appendix 10.4.

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

8.3.6. Study Endpoints Not Qualifying as Adverse Events

The following events are being captured as study endpoints and will not be reported as AEs:

- Pruritus (itching)
- Angioedema
- Hives (wheals)

Information on these events will be captured via the UPDD (patient electronic diary).

However, if any of these events is an SAE as defined in Appendix 10.3, Section 10.3.2, the event should be reported as an SAE.

8.3.7. Adverse Events of Special Interest

Adverse events of special interest for this study include anaphylaxis, infusion reactions, and infections. If such AEs are reported, sites will be prompted to collect additional data as described in the following subsections.

8.3.7.1. Infusion Reactions

Symptoms of a local infusion site reaction may include erythema, induration, pain, and edema. Worsening of CSU symptoms present at baseline does not necessarily constitute an infusion reaction, per the investigator's determination (see Section 8.3.6). If an infusion site event is reported, the AE will be recorded, and additional data will be provided to the sponsor in the eCRF.

8.3.7.2. Allergic Reactions and Hypersensitivity Events

All biologic agents carry the risk of systemic allergic/hypersensitivity reactions. Clinical manifestations of these reactions may include but are not limited to:

- skin rash
- dyspnea
- hypotension, and
- anaphylactic reaction (Sampson et al. 2006).

Participants with clinical manifestations of systemic allergic/hypersensitivity reactions should be treated per local standard of care. Additional data describing each symptom should be provided to the sponsor in the eCRF.

Blood sample collection for systemic allergic/hypersensitivity events

In case of anaphylaxis or a systemic hypersensitivity event, additional blood samples should be collected as close as possible to the onset of the event. Follow-up samples should be obtained at the next regularly scheduled visit or 4 weeks after the event, whichever is later. The laboratory test results are provided to the sponsor via the central laboratory. See Appendix 10.2 for selected tests for which samples should be collected in the event of anaphylaxis or generalized urticaria.

8.3.7.3. Infections

Completion of the Infection eCRF page is required for each infection reported as an AE/SAE. The sponsor will identify infections considered to be opportunistic based on the article by Winthrop et al. (2015) (Appendix 10.6).

8.3.8. Complaint Handling

Lilly collects product complaints on investigational medicinal products used in clinical trials in order to ensure the safety of study participants, monitor quality, and facilitate process and product improvements. Participants should be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational medicinal product so that the situation can be assessed.

8.4. Treatment of Overdose

For the purposes of this study, an overdose of LY3454738 is considered any dose higher than the dose assigned through randomization.

The treatment for overdose is supportive care (see the IB for LY3454738).

8.5. Pharmacokinetics

Visits and times

At the visits and times specified in the SoA (Section 1.3), venous blood samples will be collected to determine the serum concentrations of LY3454738. The actual date and time (24-hour clock time) of dosing and sample collection will be recorded.

Blood samples for PK are requested to be collected at the specified times. However, deviations from the specified sampling times will not be considered protocol deviations as long as the samples are collected and the actual sampling time is recorded. It is essential that the actual times of doses and samples are recorded accurately on the appropriate forms.

Collection, handling, and storage of 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 and stored at a facility designated by the sponsor.

Concentrations of LY3454738 will be determined using a validated enzyme-linked immunosorbent (ELISA) assay method. Analyses of samples collected from placebo-treated participants are not planned.

Additional and unused samples

A maximum of 3 additional samples for exploratory analyses such as bioanalytical method development or validation exercises may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor.

In the case of systemic allergic/hypersensitivity reactions, additional blood samples will be obtained for PK analysis (Section 8.3.7.2).

Any excess samples collected for PK testing may be pooled and used for exploratory analyses such as bioanalytical assay validation or cross-validation exercise.

Blinding

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

Sample retention

Samples collected to measure IP concentration will be retained at a facility selected by the sponsor or its designee. These samples will be retained for the purposes and maximum duration specified in Appendix 10.1, Section 10.1.12.

8.6. Pharmacodynamics

In addition to exploratory biomarker sample collections described below (Section 8.8), samples for other PD evaluations will be collected for exploratory analyses at the visits and times specified in the SoA (Section 1.3), where local regulations allow. These evaluations may include high-sensitivity C-reactive protein (hs-CRP), characterization of white blood cell differential counts, and soluble CD200R levels.

8.7. Genetics

A whole blood sample will be collected for pharmacogenetic analysis as specified in the SoA (Section 1.3), where local regulations allow.

Sample use

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable exposure or response to LY3454738 and to investigate genetic variants thought to play a role in CSU. 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 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.

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 investigator site personnel. The sponsor will store the blood and/or deoxyribonucleic acid (DNA) samples in a secure storage space with adequate measures to protect confidentiality.

Sample retention

Samples will be retained at a facility selected by the sponsor or its designee. These samples will be retained for the purposes and maximum duration specified in Appendix 10.1, Section 10.1.12, or for a shorter period if local regulations and/or Ethical Review Boards (ERBs)/IRBs impose shorter time limits.

8.8. Biomarkers

Serum, plasma, whole blood RNA, and whole blood for nonpharmacogenetic biomarker research will be collected at the visits and times specified in the SoA (Section 1.3), where local regulations allow.

Sample use

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, pharmacodynamics, mechanism of action, variability of participant response (including safety), and/or clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules including DNA, RNA, proteins, lipids, and other cellular elements.

Samples will be used for research on the drug target, CSU disease process, variable response to LY3454738, pathways associated with CSU, mechanism of action of LY3454738, and/or research method or in validating diagnostic tools or assays related to CSU or to LY3454738.

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 investigator site personnel.

Sample retention

Samples will be retained at a facility selected by the sponsor or its designee. These samples will be retained for the purposes and maximum duration specified in Appendix 10.1, Section 10.1.12, or for a shorter period if local regulations and/or ERBs/IRBs impose shorter time limits.

8.9. Immunogenicity Assessments

Visits and times

At the visits and times specified in the SoA (Section 1.3), predose venous blood samples will be collected to determine antibody production against LY3454738. The actual date and time (24-hour clock time) of each sample collection will be recorded.

To aid interpretation of these results, a predose blood sample for PK analysis will be collected at the same time points.

Sample collection, handling, and use

Instructions for the collection and handling of blood samples will be provided by the sponsor.

Immunogenicity will be assessed by a validated assay designed to detect anti-drug antibodies (ADAs) in the presence of LY3454738 at a laboratory approved by the sponsor. Antibodies will be further evaluated for their ability to neutralize the activity of LY3454738, when available.

Sample retention

Samples will be retained at a facility selected by the sponsor or its designee. These samples will be retained for the purposes and maximum duration specified in Appendix 10.1, Section 10.1.12, or for a shorter period if local regulations and/or ERBs/IRBs impose shorter time limits.

8.10. Health Economics or Medical Resource Utilization and Health Economics

This section is not applicable.

9. Statistical Considerations

9.1. Statistical Hypotheses

The study will compare LY3454738 with placebo in adults with CSU. The primary study objective is to demonstrate superior efficacy of LY3454738 over placebo.

The primary comparison of interest is the mean change of the UAS7 from baseline to Week 12. Secondary comparisons include the mean change of the ISS7 and the HSS7 from baseline to Week 12 as well as the proportion of participants achieving a UAS7 ≤6 at Week 12.

Efficacy comparisons will be made regardless of treatment discontinuation and without regard to changes to any background therapies. No adjustments for multiplicity will be made across the efficacy assessments.

9.2. Sample Size Determination

Assuming a 30% screen fail rate, approximately 85 participants will be screened to achieve 60 participants randomly assigned to study intervention for an estimated total of 52 evaluable participants.

The sample of 52 evaluable participants provides about 87% power to the primary endpoint. This calculation is based on a 2-sample t-test, assuming a mean change from baseline to Week 12 in the UAS7 for LY3454738 and for placebo of 17 points and 10 points, respectively, a standard deviation of 7 points for the change from baseline, and a 0.05 two-sided significance level.

9.3. Populations for Analyses

The following populations are defined for this study:

Population	Description
Entered	All participants who sign the informed consent form
Modified Intent-to-Treat (mITT)	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention to which they were assigned.
Safety	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received within each study period.
Pharmacokinetic (PK) Analysis	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention and have PK data available.

9.4. Statistical Analyses

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

Any change to the data analysis 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 statistical analysis plan (SAP) and clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

The SAP will be finalized prior to unblinding. It 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 most important endpoints including primary and key secondary endpoints.

9.4.1. General Considerations

Efficacy analyses will be conducted on the Modified Intent-to-Treat (mITT) Population. This set includes all data from all randomized participants receiving at least 1 dose of the IP according to the treatment the participants were assigned.

Safety analyses will be conducted on the Safety Population. This set includes all data from all randomized participants receiving at least 1 dose of the IP according to the treatment the participants actually received.

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated. All confidence intervals (CIs) will be given at a 2-sided 95% level. Descriptive summaries of continuous data will present the group mean, standard deviation, median, minimum, maximum, and sample size. Descriptive summaries of discrete data will report the number of participants and incidence as a frequency and as a percentage.

The baseline value for Period 2 is defined as the last nonmissing measurement on or before the date of first study drug administration (expected at Week 0). The baseline value for Period 3 is the last available value before the initial dose in Period 3 (expected at Week 12). Other definitions of the baseline value may be used to conduct additional supporting analyses.

A number of efficacy outcome measures are in the form of weekly scores derived from patient daily diary data. For these measures, the weekly score will be derived from the 7 days immediately prior to the study visit. The baseline score will be derived from the 7 days prior to Day 1.

9.4.1.1. Participant Disposition

A detailed description of participant disposition will be provided, including a summary of the number and percentage of participants entered into the study, enrolled in the study, and treated, as well as number and percentage of participants completing the study (participants who receive at least 1 dose of study drug and have at least 1 postbaseline assessment), or discontinuing (overall and by reason for discontinuation). A summary of all important protocol deviations will be provided.

9.4.1.2. Participant Characteristics

Demographic data are collected and reported to demonstrate that the study population represents the target patient population. A summary of baseline participants and disease characteristics, historical diagnoses, pre-existing conditions, and prior therapies will be reported by cohort using descriptive statistics. Other participant baseline characteristics will be summarized by group as deemed appropriate.

9.4.1.3. Missing Data Imputation

Missing continuous scores will be imputed using baseline observation carried forward (BOCF) analyses.

The UAS7 score is the sum of the daily UAS scores over 7 days each week. The daily score is the average of 2 results when both entries are made, or it is the single result when only 1 entry is made in a given day. When 1 or more of the daily UAS scores are missing, the following principles will be applied to handle the missing data:

- If a participant has at least 4 nonmissing daily UAS scores within the 7 days prior to the study visit, the UAS7 score is calculated as the sum of the available UAS scores in that week, divided by the number of days that have a nonmissing diary UAS score, multiplied by 7.
- If there are less than 4 nonmissing daily UAS scores within the prior 7 days, then the UAS7 score is missing for the week.

The same principles will be applied to handle the missing data for all of the weekly outcomes.

- Nonresponder imputation (NRI): All participants who discontinue the study or the study treatment at any time for any reason will be defined as nonresponders for the analysis of categorical efficacy variables at discontinuation and subsequent visits.
- Mixed-effects model of repeated measures (MMRM): Continuous variables will be assumed to be missing after discontinuation for which an MMRM analysis will be performed.
- BOCF, as previously stated.

9.4.2. Primary Endpoints

The primary efficacy endpoint is the change in UAS7 score from baseline to Week 12 in Period 2, defined as the Week 12 UAS7 score minus the baseline UAS7 score.

The analysis of the primary endpoint will consist of treatment comparisons made using analysis of covariance (ANCOVA) controlling for baseline UAS7 score. The ANCOVA model will be based on the mITT population. Missing Week 12 scores will be imputed by carrying forward the participants' baseline scores (BOCF).

The objective of the primary endpoint is to establish superiority of LY3454738 over placebo.

9.4.3. Secondary Endpoints

Secondary comparisons of interest are described below. The objective of these secondary endpoints is to demonstrate superiority of LY3454738 over placebo.

9.4.3.1. Change from Baseline in ISS7 at Week 12

Change from baseline in ISS7 at Week 12 is the Week 12 ISS7 score minus the baseline ISS7 score. An ANCOVA model similar to the one described for the primary endpoint will be used for analysis of this secondary endpoint.

9.4.3.2. Change from Baseline in HSS7 at Week 12

Change from baseline in HSS7 at Week 12 is the Week 12 HSS7 score minus the baseline HSS7 score. An ANCOVA model similar to the one described for the primary endpoint will be used for analysis of this secondary endpoint.

9.4.3.3. Proportion of Patients with UAS7 ≤6 at Week 12

The proportions of participants who achieve a UAS7 score ≤6 at Week 12 will be presented for each treatment group. Participants will be classified as nonresponders at Week 12 (that is, did not achieve UAS7 ≤6 at Week 12) if they have a missing UAS7 score at Week 12.

The Cochran-Mantel-Haenszel test stratified by baseline UAS7 (< median versus ≥ median) will be performed to compare the proportions of participants with UAS7 ≤6 at Week 12 in the LY3454738 group versus placebo.

9.4.3.4. Pharmacokinetic Analysis

Serum concentrations of LY3454738 will be analyzed using a population approach via nonlinear mixed effects modeling (NONMEM) with the NONMEM software. Model-estimated individual clearance values will be used to calculate area under the plasma concentration versus time curve (AUC) for individual participants. The PK data from Study FRCF may be combined with data from the Phase 1 study FRCC to improve PK parameter estimation.

9.4.4. Exploratory Endpoints

Exploratory analyses for PD and biomarker data will be described in the SAP that is finalized before database lock. Relationships between LY3454738 exposure and the primary efficacy endpoint, UAS7 score at Week 12, and other efficacy endpoints and biomarkers may be explored.

9.4.4.1. Evaluation of Immunogenicity

Frequencies and percentages will be tabulated for the following:

- participants with pre-existing ADA, and
- participants who are treatment-emergent ADA positive (TE-ADA+) to LY3454738.

Treatment-emergent ADAs are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution if no ADAs were detected at baseline (treatment-induced ADA) or those with a 4-fold (2 dilutions) increase in titer compared with baseline if ADAs were detected at baseline (treatment-boosted ADA). For the TE ADA+ participants, the distribution of maximum titers will be described. The frequency of neutralizing antibodies, when available, will also be tabulated for the TE-ADA+ participants.

The relationship between the presence of antibodies and the PK parameters and PD response including safety and efficacy to LY3454738 may be assessed. Additional details may be provided in the SAP.

9.4.5. Safety Analyses

Safety data will be descriptively summarized for the Safety Population by treatment group and analyzed using the methods described in Section 9.4.

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities and summarized by system organ class, preferred term, severity, and relationship to the IP. A treatment-emergent adverse event (TEAE) is defined as an event that first occurred or worsened in severity after baseline. For each event classification term, the number of participants experiencing a TEAE with that classification term will be tabulated.

Treatment-related TEAEs are defined as events that are indicated by the investigator on the eCRF to be related to treatment. For events that are gender specific, the denominator and computation of the percentage will include only participants from the given gender.

9.5. Interim Analyses

Analysis for the primary database lock will be conducted when all participants have completed the Period 2 (or discontinued Period 2 treatment). An interim analysis prior to the primary database lock may be conducted when approximately 50% of the participants have had the opportunity to complete Period 2 (including those who discontinued Period 2 treatment). Other interim analyses may be conducted as needed. All interim analyses will be used to support planning activities associated with the development program. No adjustment of type I error will be performed.

The assessment will be conducted by an internal assessment committee with a limited number of prespecified team members who do not have direct site contact or data entry/validation responsibilities (see Appendix 10.1, Section 10.1.5). A limited number of pre-identified individuals may gain access to the limited unblinded data, as specified in the unblinding plan, prior to the interim or final database lock. To minimize bias, the SAP and PK/PD analysis plan will be finalized and approved before unblinding. Unblinding details are specified in the SAP and Unblinding Plan. Information that may unblind the study during the analyses will not be reported to study sites or the blinded study team until the study has been unblinded.

Ongoing monitoring of safety data (including AEs, SAEs, and selected laboratory measurements) will continue throughout the study using blinded data. Interim safety analyses may be conducted to review unblinded safety data. The analyses will be conducted and reviewed by an internal assessment committee composed of personnel who do not have direct site contact or data entry/validation responsibilities. Details are specified in the SAP.

9.6. Data Monitoring Committee (DMC)

Not applicable. An internal assessment committee will be used to conduct the interim analysis (see Section 9.5 and Appendix 10.1, 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 International Council for Harmonisation (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.

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
- Providing oversight of the conduct of the study at the site 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.

After reading the protocol, each principal investigator will sign the separate protocol signature page and send a copy of the signed page to a Lilly representative.

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 1 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 representative 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 participated in any study procedures or received the investigational intervention. The statement must include the date on which the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF(s).

Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

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

Participants who are rescreened are required to sign a new ICF.

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 only the identifier; participant names or any information that 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. The participant will be required to give consent for their 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.

10.1.5. Committee Structure

Internal Assessment Committee (IAC)

In addition to the safety reviews routinely performed by the blinded study team, an IAC will review the unblinded efficacy and safety data at the time of any interim analysis. The IAC will include, at a minimum, a Lilly medical physician, a statistician, and a representative from the Lilly Global Patient Safety organization, but will not include any Lilly study team members. Details about the IAC membership, purpose, responsibilities, and operation will be described in an IAC charter. Investigator sites 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 publically 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 case report forms, 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.clinicalstudydatarequest.com.

10.1.7. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF 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 CRF. This might include laboratory tests, 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.

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 (central, remote, or on-site monitoring), are described in the monitoring plan, associated sponsor documentation, and required standards and regulations.

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 CRF by authorized site personnel are accurate, complete, and verifiable from source documents;
- the safety and rights of participants are being protected; and

- 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 and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion 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 electronic data capture (EDC) system will be used in this study for the collection of CRF 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 CRF.

Additionally, clinical outcome assessment (COA) data (participant-focused outcome instrument) will be collected by the participant, via a paper source document per the SoA, and will be transcribed by the investigator site personnel into the EDC system.

Additionally, electronic Clinical Outcome Assessment (eCOA) data (participant-focused outcome instrument) will be directly recorded by the participant, into an instrument per the SoA (for example, hand-held smartphone). The eCOA data will serve as the source documentation and the investigator does not maintain a separate, written or electronic record of these data.

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/electronic transfers will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the Sponsor 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. Current medical records must be available. What constitutes source data can be found in Appendix 10.1, 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 will be open for recruitment of participants.

The first act of recruitment is the opening of the first site. The date of that opening will be considered the study start date.

The sponsor or sponsor's designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. 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 there is reasonable cause 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 drug development.

Premature Termination or Suspension of the Study ("Stopping Rules")

The internal assessment committee (IAC) will evaluate unblinded safety data if

- three or more participants experience TEAEs in the same system organ class, and
- these TEAEs are assessed as severe by the investigator and/or meet at least 1 serious criterion, and
- these TEAEs are judged as related to blinded study treatment by the investigator.

Pending the evaluation by the IAC study, enrollment and/or further dosing may be stopped, or the dose and/or other study parameters may be modified (Section 9.5 and Section 10.1.5). For details about the IAC operations (including meeting frequency), see the IAC Charter.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IRBs/IECs, 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 should assure appropriate therapy and/or follow-up for the participant.

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. Information about Participating Investigators

Physicians with experience in the diagnosis and treatment of CSU 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 response that may not be observed until later in the development of LY3454738 or after LY3454738 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. Any samples remaining after the specified retention period will be destroyed.

Sample Type	Custodian	Retention Period after Last Participant Visit
Pharmacokinetics	Sponsor or designee	1 year
Long-term storage samples	Sponsor or designee	15 years
Biomarkers	Sponsor or designee	15 years
Genetics/DNA	Sponsor or designee	15 years
Immunogenicity	Sponsor or designee	15 years

Abbreviation: DNA = deoxyribonucleic acid.

10.2. Appendix 2: Clinical Laboratory Tests

Hematology [a,b]	**Clinical Chemistry** [a,b]
Hemoglobin	Sodium
Hematocrit	Chloride
Erythrocyte count (RBCs)	Bicarbonate
Mean cell volume	Potassium
Mean cell hemoglobin	Total bilirubin
Mean cell hemoglobin concentration	Total protein
Leukocytes (WBCs)	Direct bilirubin
Differential	Alkaline phosphatase (ALP)
Neutrophils, segmented	Alanine aminotransferase (ALT)
Lymphocytes	Aspartate aminotransferase (AST)
Monocytes	Gamma-glutamyl transferase (GGT)
Eosinophils	Blood urea nitrogen (BUN)
Basophils	Creatinine
Platelets	Creatine kinase (CK)
Cell morphology	Uric acid
	Calcium
Urinalysis [a,b]	Glucose
Specific gravity	Albumin
pH	Cholesterol (total)
Protein	Triglycerides
Glucose	
Ketones	**Lipid Panel (fasting)** [a,b,c,k]
Bilirubin	High-density lipoprotein
Urobilinogen	Low-density lipoprotein
Blood	
Nitrite	**Hormones (female)**
Urine leukocyte esterase	Pregnancy test (serum [a,b,d,h] and urine [f])
Microscopic examination of sediment	Follicle-stimulating hormone (FSH) [a,b,g]
	Stool evaluation [a,b,i]

table continues

Biomarkers [a,b]	**Serology**
C-reactive protein, high-sensitivity [l]	Tuberculosis (TB) testing:
Receptor occupancy assay [l]	QuantiFERON-TB Gold test [a,b, d] or T-SPOT [d,j] or TST [d,j]
	HIV testing [a,b,d]
Serum immunoglobulins (IgG, IgM, IgA, IgE) [a]	HCV testing:
	Hepatitis C antibody [a,b,d,e]
Pharmacogenomics sample [l]	HBV testing:
	Hepatitis B core antibody [a,b]
Stored Samples [l]	Hepatitis B surface antigen [a,b]
Exploratory storage samples:	
Serum	
Plasma	**Pharmacokinetic Samples** [a,l]
Whole blood (DNA EDTA)	LY3454738 concentration
RNA	Pharmacokinetics (PK) for immunogenicity (stored)
Immunogenicity Samples [a,l]	**Flow Cytometry** [a]
Anti-LY3454738 antibodies	TBNK panel
Anti-LY3454738 antibodies neutralization	

Abbreviations: DNA = deoxyribonucleic acid; EDTA = ethylenediamine tetraacetic acid; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; RBC = red blood cell; TBNK = T-cells, B-cells, and natural killer (NK) cells; TST = tuberculin skin test; WBC = white blood cell.

a Assayed by Lilly-designated laboratory.

b Results will be confirmed by the central laboratory/other at the time of initial testing.

c For the fasting lipid profile, participants should not eat or drink anything except water for 12 hours prior to test.

d Performed at screening only.

e A positive hepatitis C antibody laboratory assessment will be confirmed with an additional test method.

f Urine pregnancy test to be performed only on women of childbearing potential and women with history of tubal ligation. Done locally and prior to dosing visits.

g Optional, performed to confirm postmenopausal status.

h Serum pregnancy test to be performed only on women of childbearing potential and women with history of tubal ligation.

i Only for participants with certain risk factors and eosinophil count >2 times ULN (see Section 5.2 and Section 8.2.5).

j Participants who had a TST will return 48 to 72 hours after placement to have their test results read. Local laboratory must be qualified by local regulations.

k Fasting is not required for the lipid panel at an early termination visit.

l Results will not be provided to the investigative sites.

Selected tests may be obtained in the event of anaphylaxis or systemic allergic/hypersensitivity reactions.

Hypersensitivity Tests [a]	
Anti-LY antibodies (immunogenicity)	Tryptase
LY concentration (PK)	N-methylhistamine
	Drug Specific IgE [b]
	Basophil Activation Test [b]
	Complements
	Cytokine Panel

Abbreviation: PK = pharmacokinetics.

a Assayed by Lilly-designated laboratory.

b Will be performed if a validated assay is available.

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 either an increase in frequency and/or intensity of the condition. – New condition detected or diagnosed after study intervention administration even though it 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 or 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 fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition
– Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. – 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, appendectomy). Note: 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

If an event is not an AE per the definitions above, the event cannot be an SAE even if serious conditions are met (for example, hospitalization for signs/symptoms of the disease under study, 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 that hypothetically might have caused death, if the event 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) that 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 in lieu of completion of the AE/SAE CRF page.

There may be instances when copies of medical records for certain cases are requested. 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.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and 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 1 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 an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 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 disease(s), 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 Investigator's Brochure (IB) 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. 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.

The investigator may change his/her opinion of causality in light of follow-up information and send an 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 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 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 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 to the sponsor or the sponsor's designee will be the electronic data collection tool. If the electronic system is unavailable or if a pregnancy is reported, then the site will use the paper SAE or pregnancy data collection tools to report the event within 24 hours. The site will enter 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 offline 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 offline, then the site can report this information directly to the sponsor. Contacts for SAE reporting can be found in site training documents.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

A female is considered a "woman of childbearing potential (WOCBP)" after menarche and until she is a "woman not of childbearing potential." A "woman not of childbearing potential" is defined in Section 5.1.

Contraception guidance for women of childbearing potential [WOCBP]:

See Section 5.1.

Contraception guidance for men:

See Section 5.1.

Collection of pregnancy information:

Male participants with partners who become pregnant

The investigator will attempt to collect pregnancy information on a male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive LY3454738.

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 also be followed up 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 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 up 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 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 <22 weeks gestational age) or still birth (occurring at >22 weeks 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 8.3.5. While the

investigator is not obligated to actively seek this information in former study participants, the investigator may learn of an SAE through spontaneous reporting.

See Section 7.1 about the discontinuation of participants who become pregnant.

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-Up Assessments

Samples for selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required during follow-up with participants in consultation with the clinical research physician of the sponsor or designee.

Hepatic Monitoring Tests

Hepatic Hematology [a]	**Haptoglobin [a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation [a]**
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils, segmented	
Lymphocytes	**Hepatic Serologies [a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry [a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody [a]**
AST	
GGT	**Alkaline Phosphatase Isoenzymes [a]**
CPK	
	Anti-smooth muscle antibody (or anti-actin antibody) [a]

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

[a] Assayed by sponsor-designated or local laboratory.

[b] Reflex/confirmation dependent on regulatory requirements and/or testing availability.

10.6. Appendix 6: Examples of Infections That May Be Considered Opportunistic in the Setting of Biologic Therapy

The following are examples of infections that may be considered opportunistic in the setting of biologic therapy (adapted from Winthrop et al. [2015]). This table is provided to aid the investigator in recognizing infections that may be considered opportunistic in the context of biologic therapy. 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. (2015).

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)
	Strongyloidosis (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. (2015).

10.7. Appendix 7: Definitions and Selected Abbreviations

Term	Definition
ADA	anti-drug antibody
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AESI	adverse event of special interest
ALC	absolute lymphocyte count
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
anti-HBc	antibody to hepatitis B core antigen
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
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.
CBD	cannabidiol
CFR	United States Code of Federal Regulations
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
CSU	chronic spontaneous urticaria
CXR	chest x-ray
DLQI	Dermatology Life Quality Index
DNA	deoxyribonucleic acid

EDC	electronic data capture
ECG	electrocardiogram
eCOA	electronic Clinical Outcome Assessment
eCRF	electronic case report form
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.
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)
ETV	early termination visit
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HSS7	Hive Severity Score Over 7 Days
IAC	Internal Assessment Committee
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee (see IRB)
IGRA	interferon gamma release assay
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.
IRB	Institutional Review Board (IRB), also called Independent Ethics Committee (IEC) or Ethical Review Board (ERB)
ISS7	Itch Severity Score Over 7 Days
ITT	intention to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a participant (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that participant allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IV	intravenous, intravenously
IWRS	interactive web-response system
LTBI	latent tuberculosis infection
MMRM	mixed-effects model of repeated measures
NONMEM	nonlinear mixed effects modeling
NSAID	nonsteroidal anti-inflammatory drug
PA	posterior–anterior
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.
PD	pharmacodynamic
PK	pharmacokinetic
PPD	purified protein derivative
Q2W	every 2 weeks
RNA	ribonucleic acid
SAE	serious adverse event

SAP	statistical analysis plan
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.
SoA	Schedule of Activities
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
TB	tuberculosis
TBL	total bilirubin level
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.
TST	tuberculin skin test
UAS7	Urticaria Activity Score Over 7 Days
ULN	upper limit of normal
UPDD	Urticaria Patient Daily Diary
USA	United States of America; also United States
WBC	white blood cell
WOCBP	women of childbearing potential (see Appendix 10.4)

10.8. Appendix 8: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment A (23 Aug 2019)

This amendment was considered to be nonsubstantial 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 because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment

The purpose for the amendment was to provide clarification of the timing of the first post-treatment follow-up visit (Visit 801) relative to the last dosing visit (Visit 15, Week 22).

Section # and Name	Description of Change	Brief Rationale
Section 4.1, Overall Design	Corrected the sentence that describes the interval between the last dosing visit and the first post-treatment follow-up visit. The interval should be written as "6 weeks," not "2 weeks" in Section 4.1.	For accuracy and consistency with information provided in Section 4.2 and in the Schedule of Activities.

Amendment B (29 Jan 2020)

This amendment is considered to be nonsubstantial 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 because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

The rationale for the amendment is to mainly address regulatory feedback received in January 2020.

Section # and Name	Description of Change	Brief Rationale
Table 1, Schedule of activities for the screening and treatment periods of Study J1B-MC-FRCF	Added ECG assessments for visits V9, V16, and ETV for the treatment period	Changed per request from the regulatory agency
Section 5.2, Exclusion Criteria	Deleted the following text from criterion [32]: "or during the study"	Changed per request from the regulatory agency

Section # and Name	Description of Change	Brief Rationale
Section 8.1.3.1, Dermatology Life Quality Index	Corrected the scoring classification for DLQI	Corrected an error
Section 8.3.7.2, Allergic Reactions and Hypersensitivity Events *and* Section 11, References	Added the citation for Sampson et al. 2006	Changed per request from the regulatory agency
Section 10.1.9, Study and Site Start and Closure	Added the "stopping rules" for the study	Changed per request from the regulatory agency

11. References

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Leo Document ID = d84f48a2-ea55-48ea-ba85-6d019973e54c

Approver:PPD

Approval Date & Time: 10-Jun-2020 20:53:34 GMT

Signature meaning: Approved

Approver:PPD

Approval Date & Time: 10-Jun-2020 21:26:05 GMT

Signature meaning: Approved