J1H-MC-LAJA Protocol (d)

A Safety, Tolerability, and Pharmacokinetics Study of LY3451838 in Health Subjects

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Confidential Information

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Clinical Protocol Amendment Electronically Signed and Approved by Lilly on date provided below.

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A Safety, Tolerability, and Pharmacokinetics Study of LY3451838 in Healthy Subjects

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1 Protocol Synopsis

Title of Study:
A safety, tolerability, and pharmacokinetics study of LY3451838 in healthy subjects.

Rationale:
LY3451838 is a fully human immunoglobulin G (IgG4-variant monoclonal antibody) that potently and selectively binds and neutralizes pituitary adenylate cyclase-activating polypeptide (PACAP). LY3451838 is being developed as a treatment for primary headache conditions including prevention of episodic or chronic migraine and/or cluster headache. This first-in-human study of LY3451838, J1H-MC-LAJA, will investigate the safety, tolerability, and pharmacokinetics (PK) of LY3451838 administered intravenously (IV) and subcutaneously (SC) in healthy subjects.

Objective(s)/Endpoints:

Objectives	Endpoints
Primary	
Evaluate the safety and tolerability of a single dose of LY3451838 in healthy subjects	• Adverse events • Serious adverse events
Secondary	
Evaluate the pharmacokinetics of LY3451838 in healthy subjects following a single dose of LY3451838.	• AUC • C_{max}

Abbreviations: AUC = area under the concentration-time curve; C_{max} = maximum drug concentration

Summary of Study Design:

Study J1H-MC-LAJA is a first-in-human, investigator- and subject-blind, placebo-controlled, randomized, 2-part study in healthy subjects to evaluate the safety, tolerability, and pharmacokinetics of LY3451838. In Part A, the single ascending doses of LY3451838 will be administered IV in up to 6 cohorts of 8 subjects each. In Part B, a single dose of LY3451838 will be administered SC in up to 2 cohorts of 8 subjects each.

Safety / tolerability, pharmacokinetic, immunogenicity, and exploratory pharmacodynamic assessments will be performed at prescribed time points during the stay at the clinical research unit (CRU) and at subsequent study visits.

All available safety and PK data will be reviewed before each dose escalation. The proposed doses may be adjusted after review of available data from previous dose levels after consultation with a Safety Review Panel (SRP) that is independent of the team.

Treatment Arms and Planned Duration for an Individual Subject:
In both parts, within each cohort, subjects will be randomly assigned to receive LY3451838 or placebo in a 6:2 ratio.

Part A: LY3451838 will be administered IV, at single ascending dose levels, starting at 25 mg and escalated up to 1500 mg.

Part B: LY3451838 will be administered SC as a single dose, which is planned as a 250 mg dose or a dose that matches that of Cohort 3 in Part A. Up to 2 cohorts in Part B may be enrolled to explore various features of SC dosing at the same dose level.

In both parts, subjects will be followed for approximately 20 weeks following administration of the study drug.

Number of Subjects:
Up to 80 healthy subjects may be enrolled so that approximately 6 subjects in each LY3451838 dosing group complete the 20-week study. Any subject who was withdrawn before completion of all study activities may be replaced at the discretion of the Sponsor.

Statistical Analysis:

Safety: The primary safety endpoints are the numbers and types of treatment-emergent serious adverse events and adverse events. Summary statistics for each cohort will be provided by dose level and for all placebo subjects combined.

Pharmacokinetics: Plasma LY3451838 PK (e.g., C_{max}, $AUC_{0-\infty}$) will be calculated using noncompartmental methods. Pharmacokinetic parameters will be summarized by dose level using descriptive statistics. Dose proportionality will be assessed. Mean and individual LY3451838 plasma concentration-time curves will be presented. Absolute bioavailability will be calculated based on data from the IV and SC cohorts.

2 Schedule of Activities

Study Schedule Protocol JAH-MC-LAJA – Part A (Intravenous Administration) and Part B (Subcutaneous Administration)

Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16[a]**
Study Day	**-28**	**-1**	**1**	**2**	**3**	**5**	**7**	**9 (-1 to +2)**	**15 (±2)**	**22 (±3)**	**29 (±3)**	**43 (±3)**	**57 (±4)**	**71 (±4)**	**85 (±7)**	**141 / ED (±7)**
Visit Type	S	A	I	I	D	O	O	O	O	O	O	O	O	O	O	O
Informed consent	X															
Medical history	X															
Height/weight[b]	X		X								X		X		X	X
Medical Assessment[c]	X	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Neurological examination	X	X[d]		X			X				X					X
Electrocardiogram[e]	X	X[d]	Predose, 1, 3 h	24 h (± 90 m)	X	X	X	X	X	X	X		X		X	X
Vital signs[f, g]	X	X[d]	Predose, EOI[h], 1, 3 h	24 h (± 90 m)	X	X	X	X	X	X	X	X	X	X	X	X
Orthostatic BP and pulse rate			Predose, 1 h	24 h			X		X		X					X
Pregnancy test (urine)	X	X[d]									X		X			X
Screening tests	X															
Eligibility review		X[d]														
Study drug administration			X													
Hematology and chemistry[i]		X[d]	Predose	X	X	X	X	X	X	X	X	X	X	X	X	X
C3, C4, CRP and ESR	X		Predose	X			X		X		X					
Urine analysis		X[d]		X			X		X		X					
PK sample[i]			EOI[h], 3, 6, 8, 12 h	24 h (± 60 m), 36 h (± 60 m)	48 h (±60 m)	X	X	X	X	X	X	X	X	X	X	X
PACAP sample[i]			Predose, EOI[h] 6, 12 h	24 h	48 h		X		X		X		X		X	X
Immunogenicity sample			Predose				X		X		X		X		X	X
Samples for infusion and hypersensitivity reactions[j]			Predose													
Non-genetic biomarker sample			Predose				X									
PGx sample[k]			Predose													

Study Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16[a]
Study Day	**-28**	**-1**	**1**	**2**	**3**	**5**	**7**	**9 (-1 to +2)**	**15 (±2)**	**22 (±3)**	**29 (±3)**	**43 (±3)**	**57 (±4)**	**71 (±4)**	**85 (±7)**	**141 / ED (±7)**
Visit Type	S	A	I	I	D	O	O	O	O	O	O	O	O	O	O	O
Adverse events		← X →														
Concomitant medications	← X →															

Abbreviations: A = CRU admission; BP = blood pressure; CRU = clinical research unit; D = CRU discharge; ED = early discontinuation; EOI = end of infusion; h = hour; I = inpatient stay; m = minute; O = outpatient; C3 = total complement C3; C4 = total complement C4; CRP = C reactive Protein; ESR = erythrocyte sediment rate; PACAP = pituitary adenylate cyclase-activating polypeptide; PGx = pharmacogenomics; S = screening.

Note: if multiple procedures take place at the same time point, the following order of the procedure should be used: electrocardiogram, vital signs, and venipuncture. Unless otherwise specified, predose samples may be taken at any time prior to dosing, based on CRU activity schedule.

a in case of early discontinuation/withdrawal, the subject should undergo all Visit 16 activities.

b Height will be collected at Screening only.

c Full medical assessment prior to first dose (on Day -1 or Day 1), discharge, and discontinuation visits. Symptom-driven medical assessment as deemed necessary by the Investigator.

d Day -1 samples/activities could be collected/performed up to 5 days before the scheduled day of dosing. The medical assessment, neurological examination and eligibility review may be performed pre-dose on Day 1. If screening visit is within 1 week (inclusive) of Day -1, neurological examination, ECG, hematology and chemistry do not need to be repeated.

e Single electrocardiogram will be collected at Screening and CRU admission only. Triplicate electrocardiograms will be collected at all other timepoints.

f Vital signs include blood pressure, pulse rate, and body temperature. Single measurements at Screening and CRU admission. Supine triplicate blood pressure and pulse rate at all other timepoints.

g Body temperature to be obtained as single measurement.

h End of infusion procedures are only required for Part A of the study – to be performed within 10 minutes from infusion completion..

i Predose and 24 h (postdose) samples to be collected after at least 8 hours of fasting. PK samples on day 5 and beyond should be obtained at approximately (± 2 hr) the same time of day as the dosing time on day 1.

j Samples for infusion reactions and hypersensitivity reactions will be collected and stored for all subjects. Post treatment samples (up to 3) will only be collected in subjects who experience moderate to severe infusion reactions or hypersensitivity reactions (as defined in Section 9.4.5.2).

k If sample not collected as indicated in Study Schedule table, it may be collected a following visit.

3 Introduction

3.1 Study Rationale

LY3451838 is a fully human immunoglobulin G (IgG4-variant monoclonal antibody) that potently and selectively binds and neutralizes pituitary adenylate cyclase-activating polypeptide (PACAP). LY3451838 will be assessed for clinical efficacy in primary headache conditions including prevention of episodic or chronic migraine and/or treatment of cluster headache. This first-in-human study of LY3451838, J1H-MC-LAJA, will investigate the safety, tolerability, and pharmacokinetics (PK) of LY3451838 administered intravenously (IV) and subcutaneously (SC) in healthy subjects.

3.2 Background

PACAP is a member of the glucagon/secretin/VIP (Vasoactive Intestinal Peptide) family of neuropeptides. The peptide is encoded by the ADCYAP1 gene and is expressed as a prepro-protein that undergoes posttranslational processing to either a PACAP27 or PACAP38 form with the first 27 amino acids being identical. PACAP is evolutionarily conserved with sequence identity across all mammalian species including rodent and primates. PACAP is expressed in the central nervous system as well as in peripheral tissue. As a neuropeptide found in neurons, PACAP undergoes release, and modulates adjacent synaptic activity. The PACAP38 form predominates in most tissues, though a greater percentage of PACAP27 localizes to the trigeminal ganglia, a potential site of action for headache disorders.

Migraine is a disabling neurological disorder typically characterized by recurring moderate-to-severe, unilateral throbbing headache that lasts for 4-72 hours associated with varying combinations of nausea, vomiting, photophobia, phonophobia, and aggravation of symptoms by physical activity. Plasma PACAP levels are elevated during a migraine attack (Zagami et al. 2014). Human provocation studies have shown that PACAP38 administration induces migraine attacks in migraine patients. These data implicate PACAP in the pathophysiology of primary headaches including migraine.

LY3451838 binds to both PACAP27 and PACAP38 with similar affinity. In the nonclinical pharmacology studies, LY3451838 blocked PACAP27 and PACAP38 activation of human PAC1, vasoactive intestinal polypeptide receptor 1 (VPAC1) and VPAC2 receptors, without blocking VIP activation of VPAC1 and VPAC2 in vitro. LY3451838 blocked PACAP38-induced increases plasma cAMP in vivo. In addition, LY3451838 inhibits the trigeminal ganglia stimulation-induced increase in dura plasma protein extravasation. These data suggest LY3451838 may be effective for the migraine prevention by blocking the PACAP pathway in humans.

The toxicity of LY3451838 was assessed in 2-month rat and monkey studies and in an in vitro human tissue cross-reactivity study. In the tissue cross-reactivity study, there was no unexpected binding observed in a panel of human tissues. The rat and monkey studies used weekly SC dosing of 0, 10, and 50 mg/kg and weekly IV dosing of 250 mg/kg. There were no adverse effects in the rat study. In the monkey study, minimal-to-mild vascular/perivascular

inflammation was observed, but was attributed to immune complex deposition and, therefore, not expected to be relevant to human safety. In addition to the vasculitis, which was not evident clinically, a greater incidence of transient neurological effects was observed in treated compared to control monkeys. This included decreased or absent flexor reflexes, proprioceptive positioning, placing reactions of limbs, and locomotor stereotypy all of which were considered nonadverse. More details about the toxicology studies are provided in Section 4 of the Investigator's Brochure (IB 2018).

3.3 Benefit/Risk Assessment

The nonclinical safety and pharmacology information for LY3451838 adequately supports the transition from preclinical status to a clinical, first-in-human study. The risk evaluation of LY3451838 through its properties, nature of the target, non-clinical data in relevant species, target population and dose projections, suggest it not be considered a high risk molecule. LY3451838 is a novel monoclonal antibody against PACAP, a neuropeptide that is expressed in both central nervous system and peripheral tissues. While pharmacology of this mechanism has not been directly evaluated in humans, AMG301, a monoclonal antibody against PAC1 receptor, has successfully completed phase 1 clinical testing, and is being evaluated for migraine prevention in an ongoing phase 2 trial. The study of AMG301 in phase 2 suggests that blocking at least part of the PACAP pathway did not lead to significant toxicity in humans. The dose-limiting toxicity of LY3451838 was minimal-to-mild vasculitis in multiple organs in monkeys assessed after 8 weekly IV doses of 250 mg/kg, similar to the presentation of vasculitis due to immune response in toxicology species observed with other monoclonal antibodies (Kronenberg et al. 2017). Immunohistochemistry studies of tissue samples from the 8-week monkey GLP toxicology study demonstrated that the vasculitis was due to immune complex deposition and complement activation. This type of immune response in a single animal species is considered to translate poorly to human safety (EMEA). For this first in human study, the highest dose is limited to 1500 mg, which is predicted to reach an exposure approximately 15-fold lower than the concentration in which vasculitis was observed in monkeys. In addition, PK data will be reviewed with each dose escalation, and an exposure limit will be implemented in this study so that the predicted mean exposure based on observed PK does not significantly exceed that of the no-observed-adverse-effect-level (NOAEL) exposure observed in monkeys.

Immunogenicity and hypersensitivity reactions, including infusion reactions, acute and delayed (including immune complex disease) hypersensitivity reactions are a potential risk for all monoclonal antibodies, including LY3451838. Hypersensitivity risk mitigation in this study includes the administration of a single dose of LY3451838 IV with subsequent close monitoring.

LY3451838 has not been administered to humans previously and accordingly this study has been designed following the principles outlined in the Guideline on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medicinal Products (EMEA CHMP Jul 2017). Any identified risks are considered to be monitorable and manageable at the planned dose range of 25 mg to 1500 mg single doses of LY3451838 in healthy subjects.

There is no anticipated therapeutic benefit for the subjects.

More information about the known and expected benefits, risks, serious adverse events (SAEs), and reasonably anticipated adverse events (AEs) of LY3451838 are found in the IB.

4 Objectives and Endpoints

Table 4.1 shows the objectives and endpoints of the study.

Table 4.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
Evaluate the safety and tolerability of a single dose of LY3451838 in healthy subjects	• Adverse events • Serious adverse events
Secondary	
Evaluate the pharmacokinetics of LY3451838 in healthy subjects following a single dose of LY3451838.	• AUC • C_{max}
Exploratory	
Assess immunogenicity of LY3451838	TEADA incidence and titers
Assess target engagement	PACAP concentration

Abbreviations: AUC = area under the concentration-time curve; C_{max} = maximum drug concentration; PACAP = pituitary adenylate cyclase-activating polypeptide; TEADA = treatment-emergent anti-drug antibodies

5 Study Design

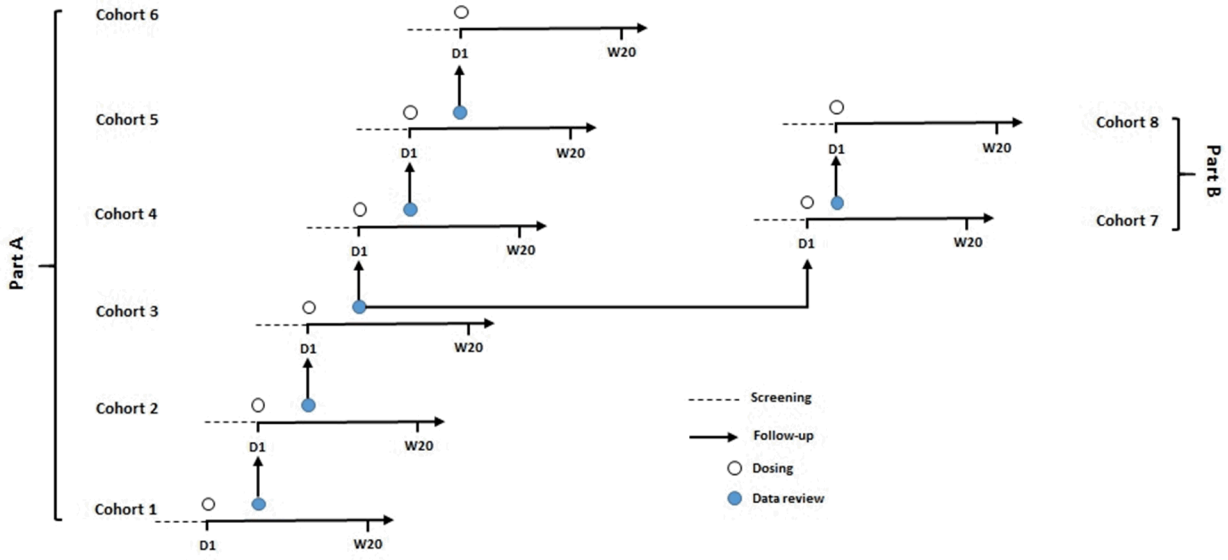
5.1 Overall Design

Study J1H-MC-LAJA is a first-in-human, Investigator- and subject-blind, placebo-controlled, randomized study in healthy subjects to evaluate the safety, tolerability, and pharmacokinetics of LY3451838.

The study will be comprised of 2 parts: Part A (single ascending dose with IV administration), and Part B (single dose SC administration). Part B of the study will only be initiated if the review of safety and tolerability data from Part A are supportive.

Screening will occur in the 28 days prior to Day 1. Eligible subjects will be assigned sequentially into up to 8 cohorts, and randomly assigned within each cohort to receive LY3451838 or placebo in a 6:2 ratio. Subjects will be followed for safety / tolerability, PK and immunogenicity, and will be discharged from the study approximately 20 weeks after dosing. If the investigator decides not to administer the first dose to a subject or not to enroll a subject on a particular day, the subject may be rescheduled to participate in the study and any procedures performed up to that point may be repeated. Subjects who discontinue from the study (Section 8.2) before its completion are required to complete the early discontinuation (ED) procedures (Section 2) before their discharge from the study.

Figure 5.1. Illustration of study design for Protocol J1H-MC-LAJA.



Abbreviations: D = day; W = week

5.1.1 Part A (Single Ascending Dose IV Administration)

Part A of the study is designed to assess the safety and tolerability of a single IV dose of LY3451838 compared to placebo in 6 cohorts of healthy subjects. Up to 6 doses of LY3451838 at a planned dose range of 25 to 1500 mg will be evaluated. The planned dose levels for the 6 cohorts are: 25, 75, 250, 500, 1000 and 1500 mg single dose via IV infusion.

Eligible subjects will be admitted to the clinical research unit (CRU) on Day -1 and eligibility will be confirmed prior to dosing on Day 1. Subjects will be confined for a minimum of 48 hours postdose and may be discharged on Day 3 after all study procedures have been completed, at the discretion of the investigator. Subjects will return to the CRU as outpatients at predetermined visits up to approximately 20 weeks postdose for safety assessment and collection of PK and immunogenicity samples, and will be discharged from the study if deemed appropriate by the investigator. Subjects who discontinue from the study before its completion will be requested to attend an ED visit according to the schedule of activities (Section 2).

Safety will be assessed by monitoring of AEs, immunogenicity, electrocardiograms (ECGs), vital signs (blood pressure, pulse rate, body temperature, and respiratory rate), and physical and clinical laboratory tests.

Sentinel dosing for the first 2 subjects of each cohort will be performed in a blinded manner, with 1 subject receiving LY3451838 and the other receiving placebo. All safety data through Day 5 for these subjects will be evaluated prior to dosing the remaining subjects (5 LY3451838 and 1 placebo), who will be dosed no earlier than 7 days after dosing of the first 2 subjects. All IV infusions will be administered sequentially, with one subject having completed the infusion administration before the next subject is dosed. These precautions enable close monitoring and management of potential for infusion and hypersensitivity reactions.

Subjects who are randomized but not administered treatment may be replaced to ensure that adequate subject data will be available for safety and exposure assessments in this phase of clinical development. The replacement subject should be assigned to the same treatment arm as the discontinued subject.

The dose escalation decision to the next cohort will be made after review of safety data up to Day 15 and PK data from Day 2 of at least 5 subjects who received LY3451838 and 1 subject who receive placebo. Further information on dose escalation is provided in Section 7.4.1.

5.1.2 Part B (Single Dose SC Administration)

Part B is designed to assess safety, tolerability, and PK of LY3451838 after SC administration of LY3451838. A single dose of LY3451838 or placebo will be administered SC in up to 2 cohorts (Cohorts 7 and 8) of 8 subjects each, in a 6:2 ratio. Cohort 7 dosing may be initiated after safety and tolerability data have been reviewed from the first 3 cohorts in Part A as described in Section 7.4.1, and may be conducted in parallel with Cohort 4 dosing in Part A. The planned dose level is 250 mg; however, the dose level may be adjusted based on all available data from the first 3 cohorts of Part A, and will be matched to that used in Cohort 3. Safety, tolerability, and PK data from Cohort 7 will be reviewed to determine if Cohort 8 is necessary to explore additional properties of SC dosing regimen, such as different LY3451838 concentration in the formulation, however, the dose for Cohort 8 will match the dose tested in Cohort 7.

Sentinel dosing will not be implemented for Part B because the dose and exposure is expected to not exceed that of Cohort 3 in Part A.

Eligible subjects will be admitted to the CRU on Day -1. LY3451838 or placebo will be administered SC on Day 1, with maximal number of injections not exceeding 4. Subjects will be discharged after completion of all Day 3 activities; and will return to the CRU for safety, PK, and immunogenicity follow-up and end-of-study visits per Section 2.

Study governance is described in detail in Appendix 3.

5.2 Number of Participants

Up to 80 healthy subjects may be enrolled so that approximately 6 subjects in each dosing group (including that of pooled placebo groups in Part A) complete the study. Subjects who discontinued from the study before study completion may be replaced at the discretion of the sponsor.

A subject completes the study when all scheduled procedures shown in the Schedule of Activities (Section 2) have been finished.

5.3 End of Study Definition

End of the study is the date of the last visit (Visit 16) shown in the Schedule of Activities (Section 2) for the last subject.

5.4 Scientific Rationale for Study Design

This study is designed to evaluate safety, tolerability, and PK of LY3451838 after single IV and SC dose administration in healthy subjects to provide the most unbiased assessment of safety and tolerability in this first-in-human study.

Hypersensitivity reactions, including both acute hypersensitivity reactions and immune complex diseases, are potential risks for all therapeutic antibodies, including LY3451838. Subjects with a history of clinically significant hypersensitivity reactions / conditions, or autoimmune diseases are excluded from the study to minimize risks for hypersensitivity reactions in the subjects in this study, and to avoid confounded interpretation of the safety data. Additional measures will be implemented to monitor and manage infusion reactions (Section 7.4.3.2), immunogenicity, and hypersensitivity reactions (Section 9.6.1). While vasculitis observed in the monkey toxicology studies was attributed to immune complex deposition, additional precautions, such as reviewing PK data before each dose escalation, limiting the dose range and implementing the exposure to that of the monkey NOAEL are designed into the protocol to address the uncertainty of the mechanism for vasculitis.

Because of the distribution of PACAP in the nervous system, and to follow-up on the subtle non-adverse changes in the neurological examination in the 2-month monkey toxicology study, neurological examinations will be performed to detect any early signals on the effects of LY3451838 on the nervous system.

Pharmacokinetic data will be used to guide dose escalation for all cohorts in Part A of the study; dose modification criteria are described in Section 7.4.1. Because the exposure after SC dosing is

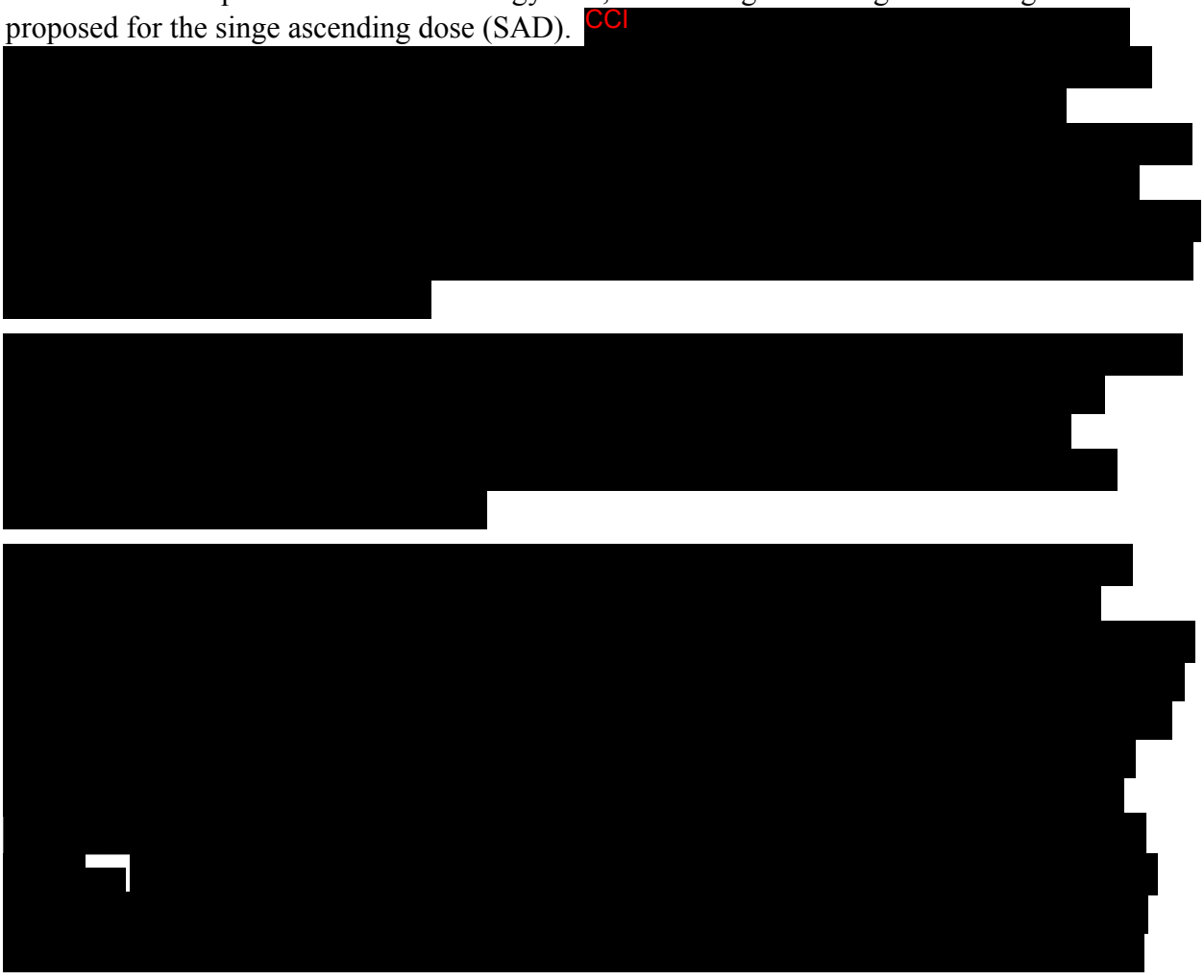
expected to be less than with IV dosing for the same dose, sentinel dosing is not required in Part B of the study.

The predicted half-life of LY3451838 is 12 days, based on the allometric scaling from monkey PK data. A parallel-group design is used in both Part A and Part B of the study to avoid a prolonged washout period between doses and to avoid the potential to confound treatment-emergent antidrug antibody (TEADA) assessment. The monitoring period for this study is approximately 20 weeks after the last dose. This monitoring period duration supports adequate immunogenicity monitoring during the washout of LY3451838.

All parts of the study will be placebo-controlled. Study participants and investigators will be blinded to treatment assignment. This design allows for a more objective assessment of AEs, and enables a comparison of the safety profile between different treatment groups. The sponsor will not be blinded to the treatment assignment to enable prompt management of any emergent safety trend and to perform periodic review of PK and immunogenicity data. Plans to maintain the blind are discussed in Section 7.3.

5.5 Justification for Dose

Based on current preclinical and toxicology data, a dose range of 25 mg to 1500 mg IV is proposed for the singe ascending dose (SAD). CCI



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6 Study Population

Study eligibility will be determined by the history, physical examination, vital signs, clinical laboratory tests and electrocardiogram (ECG) at screening.

The nature of any conditions present at the time of the physical examination and any preexisting conditions will be documented.

Screening may occur up to 28 days prior to enrollment. Subjects who are not enrolled within 28 days of screening may be subjected to an additional medical assessment and/or clinical measurements to confirm their eligibility.

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

6.1 Inclusion Criteria

Subjects are eligible for inclusion in the study only if they meet all of the following criteria at screening as specified in the criteria below:

1. Are healthy male or female subjects, as determined by medical history and physical examination
    a. Male subjects must adhere to contraception restrictions specified in Section 6.3.5:
    b. Female subjects of non-childbearing potential due to:
        i. Menopause: spontaneous amenorrhea for at least 12 months not induced by a medical condition such as anorexia nervosa and not taking medications that induced the amenorrhea (e.g., oral contraceptives, hormones, gonadotropin releasing hormone, anti-estrogens, selective estrogen receptor modulators, or chemotherapy)
        ii. Surgical sterilization
2. Are aged at least 21 to 65 years, inclusive, at screening
3. Have a body mass index of 18 to 35 kg/m^2, inclusive, at screening
4. Have clinical laboratory test results within normal reference range for the population or investigative site, or results with acceptable deviations that are judged to be not clinically significant by the investigator at screening and enrollment
5. Have an estimated glomerular filtration rate ≥60 mL/minute/1.73 m^2 at screening and enrollment;
6. Have venous access sufficient to allow for blood sampling as per the protocol
7. Are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures

8. Are able and willing to give signed informed consent approved by the sponsor and the Institutional Review Board (IRB) governing the site

6.2 Exclusion Criteria

Subjects will be excluded from study enrollment if they meet any of the following criteria at screening and/or enrollment:

9. Are Eli Lilly and Company employees, employees of third-party organizations involved with this study, investigator or site personnel affiliated with this study, or the immediate family of any of these. Immediate family is defined as a spouse, parent, child or sibling, whether biological or legally adopted
10. Are currently enrolled in, or discontinued from, within the last 30 days, a clinical trial involving an investigational drug or device or off-label use of a drug or device, or any other type of medical research judged not to be scientifically or medically compatible with this study
11. Have previously completed or withdrawn from this study or any other study investigating this study drug
12. Have a history or presence of medical illness including, but not limited to, any cardiovascular, hepatic, respiratory, hematological, renal, endocrine, psychiatric or neurological disease, or any clinically significant laboratory abnormality that, in the judgment of the investigator, indicates a medical problem that would preclude study participation
13. Have history (within past 5 years) of, or presence of, uncontrolled asthma, significant atopy, significant rheumatological or autoimmune diseases, including but not limited to systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjogren's Syndrome (SS), or vasculitis; or have positive antinuclear antibody (ANA) that is considered to be clinically significant by the investigator, rheumatoid factor (RF), or anti-neutrophil cytoplasmic antibody (ANCA) at screening; or hereditary angioedema, or common variable immune deficiency.
14. Have had lymphoma, leukemia, or any malignancy within the past 5 years, or have had breast cancer within the past 10 years, except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic diseases for 3 years.
15. Have used or intended to use prescription or over the counter medications, including herbal medications within 14 days prior to dosing. Vitamins/ mineral supplements (not providing more than 100% of the recommended daily amount), occasional paracetamol and stable doses of thyroid hormone replacement are allowed.
16. Have an abnormality in the 12-lead ECG that, in the opinion of the investigator, increases the risks associated with participating in the study. In addition, subjects with the following findings will be excluded:

a. Confirmed Fridericia's corrected QT (QTcF) interval >450 msec for men and >470 msec for women. One additional ECG may be performed if necessary

17. Show evidence of human immunodeficiency virus (HIV) and/or positive human HIV antibodies, hepatitis C and/or positive hepatitis C antibody, or hepatitis B and/or positive hepatitis B surface antigen
18. Have donated blood of more than 450 mL or have participated in a clinical study that required similar blood volume drawn within the past 3 calendar months.
19. Are unwilling to stop alcohol consumption while resident in the CRU.
20. Have an average weekly alcohol intake that exceeds 21 units per week for male subjects and 14 units per week for female subjects (1 unit = 12 oz or 360 mL of beer; 5 oz or 150 mL of wine; 1.5 oz or 45 mL of distilled spirits)
21. Are a current smoker of more than 10 sticks of cigarettes or the equivalent of other tobacco products per day and are unable/unwilling to stop smoking tobacco products while resident in the CRU. Heavy smokers as per judgment of the investigator should be excluded from the study
22. Have an abnormal blood pressure (supine) defined as diastolic blood pressure >90 or <60 mmHg and/or systolic blood pressure >140 or <90 mmHg; or with minor deviation judged to be acceptable by the investigator. Retesting may occur once during the screening visit within 2 hours of the initial abnormal blood pressure measurement at the discretion of the investigator
23. Have clinically significant proteinuria or hematuria at screening and enrollment
24. Regularly use known drugs of abuse
25. Have received treatment with biologic agents (such as monoclonal antibodies, including marketed drugs) within 3 months or 5 half-lives (whichever is longer) prior to dosing.
26. Have significant allergies to monoclonal antibodies, common antihistamines, epinephrine; or have significant allergies or intolerance to methylprednisolone or other systemic corticosteroids.
27. Have clinically significant multiple or severe drug allergies, or intolerance to systemic and topical corticosteroids, or severe post treatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear IgA dermatosis, toxic epidermal necrolysis, or exfoliative dermatitis)
28. In the opinion of the investigator or sponsor, are unsuitable for inclusion in the study

6.3 Lifestyle and/or Dietary Requirements

Throughout the study, subjects may undergo medical assessments and review of compliance with requirements before continuing in the study.

6.3.1 Meals and Dietary Restrictions

Subjects will only consume meals provided by the CRU during inpatient study days. Otherwise, subjects will maintain their own dietary habit during the study.

6.3.2 Caffeine, Alcohol, and Tobacco

Consumption of caffeine- and xanthine-containing products is allowed provided that the subject's consumption has been consistent for the past 30 days. However, during the inpatient days, consumption of caffeinated drinks may be limited to 2 servings each day.

Subjects will not be permitted to consume alcohol from 48 hours before each visit/admission until discharge from the CRU. When not resident in the CRU, male subjects should be advised to limit alcohol consumption to no more than 21 units per week, and female subjects to no more than 14 units per week. All subjects should be advised to limit alcohol consumption to no more than 3 units in a day and not to exceed their habitual alcohol consumption during the study.

Subjects will not be permitted to use tobacco-containing products from 48 hours prior to admission or outpatient visits to the CRU until discharge from the CRU.

6.3.3 Activity

Subjects must refrain from strenuous exercise throughout the study.

6.3.4 Blood Collection

Blood collection via venous catheter during inpatient days.

6.3.5 Male Contraceptive Requirements

Male subjects, regardless of their fertility status, with non-pregnant female partners of childbearing potential 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 90 days after study drug dosing.

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.

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

Male subjects should refrain from sperm donation for the duration of the study and until 90 days following last dose of study drug.

Male subjects who are in exclusively same sex relationships (as their preferred and usual lifestyle) are not required to use contraception.

6.4 Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may not be re-screened, although screening tests such as labs, vital signs / ECGs may be repeated at the discretion of the investigator. Subjects who meet the enrollment criteria, yet are not enrolled within 28 days may be enrolled on a later date, as long as the enrollment criteria are met on Day -1.

7 Treatment

7.1 Treatment Administered

LY3451838 and/or placebo will be administered IV or SC.

Part A: The planned dose levels of LY3451838 are 25 mg, 75 mg, 250 mg, 500 mg, 1000 mg, and 1500 mg. LY3451838 will be administered IV.

After overnight fasting (with water restriction at least 2 hours before dosing), the study drug will be administered as a slow IV infusion over at least 30 minutes for the first 4 cohorts, or over at least 60 minutes for cohorts 5 and 6. Infusion duration may be increased or stopped as deemed necessary based on the standard operation procedure, or if an infusion reaction is observed (Section 7.4.3.2). Sites must have resuscitation equipment, emergency drugs, and appropriately trained medical staff available during the infusion and for at least 6 hours after subjects have completed their infusion. The actual start and stop time of infusion will be recorded in the electronic data capture (EDC). If the infusion is terminated early, this will also be recorded in the EDC. Subject may resume water at least 1 hour after the infusion is completed, and resume meals at least 2 hours after the infusion is completed.

Section 7.4 details dose modifications.

Part B: The planned dose level of LY3451838 in Part B is 250 mg. The dose may be adjusted based on all available data from first 3 cohorts of Part A, the SC dose is intended to match the dose of Cohort 3 in Part A. After overnight fasting (with water restriction at least 2 hours before dosing), the study drug will be administered SC in the abdominal area. Subject may resume water at least 1 hour after the injection is completed, and resume meals at least 2 hours after the injection is completed. Subcutaneous injections should be administered to the abdominal region approximately 5 cm from the umbilicus and the treatment administered with the needle applied at an appropriate angle, with pinching of the skin if necessary. Sites must have resuscitation equipment, emergency drugs, and appropriately trained personnel available for at least 6 hours after subjects have completed their dosing. The actual dosing time will be defined as the time that the injection starts, and will be recorded in the EDC. Only a limited number of individuals will perform SC administration of LY3451838 for consistency reasons. The same type of syringe and needle should be used for all subjects to ensure that injections are delivered to a consistent depth target into the SC space.

LY3451838 Drug Product is a monoclonal antibody formulated for IV or SC administration. LY3451838 for Injection is supplied for clinical trial use as a solution in a single-use glass vial. The vial is manufactured to deliver 200 mg of LY3451838 at 50 mg/mL or 100 mg/mL. In order to ensure complete withdrawal and delivery of the label amount of 200 mg of LY3451838, vials contain an approximate 10% volume overfill. The drug product is filled into a glass vial, and sealed with a stopper and flip-off 2 piece aluminum seal. LY3451838 for Injection vials are stored in refrigerated condition (2ºC to 8ºC).

This study is double-blinded and the placebo prepared at the site by unblinded dispensing personnel will be 0.9% sodium chloride for injection, BP. This solution is indistinguishable in

appearance from the reconstituted active drug solution. Study drug preparation will be conducted and verified by unblinded personnel. Study drug will be administered by blinded personnel.

The unblinded dispensing personnel will receive training and instructions for preparation of each dose of LY3451838 and the preparation of the placebo solutions.

The investigator or designee is responsible for:

- explaining the correct use of the study drug to the subjects
- verifying that instructions are followed properly
- maintaining accurate records of study drug 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.

7.1.1 Packaging and Labeling

The drug product will be manufactured, tested, packaged, and labeled in accordance with all applicable Good Manufacturing Practice (GMP) requirements and country's regulatory requirements. A certificate of analysis confirming the materials are released for human use in clinical trials will be supplied. LY3451838 drug products are for investigational use only and are to be used only within the context of this study.

7.2 Method of Treatment Assignment

In both parts of the study, within each cohort, eligible subjects will be enrolled sequentially, and will be randomly assigned to receive either LY3451838 or placebo in a 6:2 ratio. Treatment assignment will be determined by a computer-generated randomization sequence using an interactive web response system (IWRS).

7.2.1 Selection and Timing of Doses

The single dose of the study drug will be administered at the CRU by a trained staff member.

7.3 Blinding

The study is double-blinded; subjects, investigator, and CRU personnel performing trial-related activities or with the ability to influence study outcomes will be blinded with respect to LY3451838 and placebo treatment. To preserve the blinding, only a minimum number of Lilly personnel may have access to the randomization table and codes or IWRS before the study is complete. Site staff who are responsible for drug preparation will not be blinded; laboratory personnel will also not be blinded.

Emergency unblinding will be performed through the IWRS. This option may be used only if the subject's well-being requires knowledge of the subject's treatment assignment. All unblinding events will be recorded and reported by the IWRS.

In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted for medical management of the event. The subject's 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 Lilly as soon as possible.

If a subject's study treatment assignment is unblinded, the subject must be discontinued from the study, unless the Investigator obtains specific approval from a Lilly medical monitor for the study participant to continue in the study. During the study, emergency unblinding should occur only by accessing the IWRS.

7.4 Dose Modification

Dose levels, sampling schedule, timing of procedures (e.g., time of PK sample collection, ECGs) may be adjusted in view of emerging safety or PK data during the study. If considered appropriate, previous dose levels may be repeated, or lower/intermediate dose levels may be tested. The magnitude of the dose escalation may be reduced after data review. Since these adjustments to timings or dose levels are allowable changes permitted by the protocol, they will not require a protocol amendment.

A Safety Review Panel (SRP), comprising experts in early phase medicine independent of the study team and investigative site, will be established by the sponsor. Any changes to the protocol planned dose levels, together with the supporting data, will be reviewed and approved by the SRP before implementation.

7.4.1 Dose Escalation in Part A

Safety and PK data will be the primary criteria for the dose escalation. In addition, if available at the time of dose escalation decision, antidrug antibody (ADA) data will be used as supporting data for dose escalation, but such data are not required. No dose decision can occur without prior discussion and agreement between the investigator and the Lilly medical monitor.

Six dose levels are planned for Part A. Safety data up to Day 15 and PK data up to Day 2 from at least 5 subjects who received LY3451838 and 1 subject who received placebo will be reviewed before each dose escalation decision can be made.

After review of these data, an agreement on the appropriate dose will be made by the investigator and sponsor for the next cohort/dose level. The magnitude of dose escalations may be adjusted following data review. The dose will not exceed 1500 mg.

7.4.1.1 Stopping Rules

If any of the following occur, dosing at the current level and further dose escalation will be discontinued:

1. A single subject experiences an SAE that is related to LY3451838

a. If an SAE occurs during the infusion of study drug, irrespective of causality, the study drug is discontinued immediately in that subject. No redosing or completion of dosing is considered for that subject regardless of causality. If the infusion SAE is considered related to LY3451838, then the remaining subjects in that cohort are not dosed.

2. Two or more cumulative subjects develop clinically significant acute infusion AEs considered related to LY3451838 during or within 6 hours of completing the infusion that do not resolve with a reduced infusion rate and/or supportive care.
3. Two or more cumulative subjects develop clinically significant hypersensitivity AEs considered related to LY3451838
4. Two or more cumulative subjects experience similar clinically significant events (CSEs) considered related to LY3451838. A CSE will be defined as a moderate-to-severe AE, abnormal clinical sign, or clinical laboratory finding that may pose a risk to the well-being of the subject.
5. 50% or more subjects at a dose level experience moderate or severe AEs that impair normal activities, but do not meet the CSE criteria, and are considered related to LY3451838.

Two or more subjects experience severe adverse reactions, irrespective of their nature.

7.4.2 Decision to Initiate Part B

No dose escalations are planned in Part B. The dosing will begin only after review of safety data from the first 3 cohorts of Part A indicates no stopping rules (specified in Section 7.4.1.1) are met. The dose for Part B will be the same as that of Cohort 3 of Part A, unless adjustment is required based on the review of available safety and PK data.

7.4.3 Special Treatment Considerations

7.4.3.1 Premedication for Infusions

Premedication for the infusions is not planned. However, if an infusion reaction occurs, appropriate medication may be used as determined by the study investigator(s). If infusion reactions are observed, but review of the data suggests that dose escalation may continue, administration of acetaminophen, 500 to 1000 mg, and/or an antihistamine (such as chlorpheniramine or its equivalent) may be administered orally 30 to 60 minutes prior to the start of infusion for subsequent subjects.

The decision to implement premedication for infusions in subsequent cohorts will be made by the investigator and sponsor and recorded in the study documentation, along with the dose-escalation decision.

Any premedications given will be documented as a concomitant therapy (see Section 7.7).

7.4.3.2 Management of Infusion Reactions

There is a risk of infusion reaction with any biological agent; therefore, all subjects should be monitored closely. Symptoms and signs that may occur as part of an infusion reaction include, but are not limited to: fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash, pruritus, myalgia, and dizziness. In the event that a significant infusion reaction occurs, the following guidance should be followed:

- The drug product infusion should be slowed (for example, reduce infusion rate by 50% [for example, an infusion rate of 12 mL/hr becomes 6 mL/hr or slower]) or stopped based on severity and in accordance with the investigator's assessment:
    - if slowed, the infusion should be completed at the slower rate, as tolerated
    - if determined by the investigator that the infusion should no longer continue, no further attempts to dose the subject should be made
- Supportive care will be administered as required
- If it is determined the subject should not receive further doses of study drug, the subject should complete adverse event and other follow-up procedures per Section 2 of this protocol.

Storage samples should be collected for possible immune safety laboratory testing (Section 9.4.5.2).

7.5 Preparation/Handling/Storage/Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained, as communicated by Sponsor, during transit for all study drug received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive study drug or study materials, and only authorized site staff may supply or administer study drug. All study drug should be stored in an environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (such as receipt, reconciliation and final disposition records).

Detailed instructions for the preparation and handling of LY3451838 will be provided to the unblinded site pharmacy personnel by the Sponsor.

Vials of LY3451838 are stable and must be stored refrigerated (2ºC to 8ºC).

7.6 Treatment Compliance

The study drug will be administered at the CRU, and documentation of treatment administration will occur at the site.

7.7 Concomitant Therapy

Subjects on stable concomitant medication at the time of study entry should continue their regular, unchanged dose throughout the study. These medications will be reviewed by the investigator at screening and eligibility will be determined.

Occasional acetaminophen (<2 g/ 24 hours), stool softeners, or medication of topical use without prior consultation with Lilly medical monitor is allowed. Additional drugs are to be avoided during the study unless required to treat an AE, or if used as a premedication prior to infusion.

If the need for other concomitant medication arises, inclusion or continuation of the subject may be at the discretion of the investigator preferably after consultation with a Lilly medical monitor. Any medication used during the course of the study must be documented.

7.8 Treatment after the End of the Study

Not applicable.

8 Discontinuation Criteria

Subjects discontinuing from the study prematurely for any reason must complete adverse event and follow-up procedures per Section 9.2 of this protocol.

8.1 Discontinuation from Study Treatment

Subjects may be discontinued from the study treatment if an SAE occurs during the study drug infusion, or injections irrespective of causality.

Subjects in Part A who discontinue from treatment before infusion end for any reason should complete ED procedures per Section 2 of this protocol, after AE follow up is completed.

Subjects in Part B who discontinue from the treatment before all injections have been completed may be allowed to complete the rest of the study activities (according to the planned Schedule of Activities in Section 2). The decision to allow a subject to complete the study activities should be made jointly by both sponsor and investigator, and only if the reason for discontinuation does not affect the interpretation of the safety and PK/PD data, and continuation of the study activities does not increase risks for the subject. If it is decided that the subject should be discontinued from the study, subject should complete ED procedures according to Schedule of Activities.

8.1.1 Discontinuation of Inadvertently Enrolled Subjects

If the Sponsor or investigator identifies a subject who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the Lilly medical monitor and the investigator to determine if the subject may continue in the study. If both agree it is medically appropriate to continue, the investigator must obtain documented approval from the Lilly medical monitor to allow the inadvertently enrolled subject to continue in the study with or without continued treatment with study drug.

8.2 Discontinuation from the Study

Subjects will be discontinued in the following circumstances:

- Enrollment in any other clinical study involving any study drug 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 subject should be discontinued from the study
    - if the subject, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent
- Subject Decision

  - The subject requests to be withdrawn from the study.

- Termination of the study by the Sponsor or regulatory authorities

8.3 Subjects Lost to Follow-up

A subject 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 CRU. The CRU personnel are expected to make diligent attempts to contact subjects who fail to return for a scheduled visit or were otherwise unable to be followed up by the CRU.

Subjects who withdraw from the study before completion of all study activities may be replaced at the discretion of the Sponsor.

9 Study Assessments and Procedures

Section 2 lists the Schedule of Activities, detailing the study procedures and their timing (including tolerance limits for timing).

Appendix 2 lists the laboratory tests that will be performed for this study.

Appendix 5 provides a summary of the maximum number and volume of invasive samples, for all sampling, during the study.

The specifications in this protocol for the timings of safety and sample collections are given as targets to be achieved within reasonable limits. Modifications may be made to the time points based upon emerging clinical information. The scheduled time points may be subject to minor alterations; however, the actual time must be recorded correctly in the EDC. Failure or delays (i.e. outside stipulated time allowances) in performing procedures or obtaining samples due to legitimate clinical issues (e.g. equipment technical problems, venous access difficulty, or subject defaulting or turning up late on an agreed scheduled procedure) will not be considered as protocol deviations but the CRU will still be required to notify the sponsor in writing via a file note for data reconciliation purpose.

Unless otherwise stated in subsections below, 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.

9.1 Efficacy Assessments

Not applicable.

9.2 Adverse Events

A clinical trial AE is any untoward medical event associated with the use of a drug or drug delivery system in humans, whether or not it is considered related to that drug or drug delivery system.

Investigators are responsible for monitoring the safety of subjects who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the subject.

The Investigator is responsible for the appropriate medical care of subject during the study.

Investigators must document their review of each laboratory safety report.

The Investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the study drug or the study related procedure, or that caused the subject to discontinue the study drug before completing the study. The subject should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the Investigator.

After the informed consent form (ICF) is signed, the CRU personnel will record, via EDC, the occurrence and nature of each subject's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. Additionally, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs.

Planned surgeries should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

Injection site reactions should be captured as AEs. Additional information including the time of day, time relative to injection, size, amount of erythema, induration, and pruritus will be recorded.

If a subject's study drug is discontinued as a result of an AE, CRU personnel must report this to Lilly or its designee via EDC.

9.2.1 Serious Adverse Events

An SAE is any AE from this study that results in one of the following:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above.

The CRU personnel must alert the Lilly medical monitor, or its designee, of any SAE as soon as practically possible.

Additionally, CRU personnel must alert Lilly Global Patient Safety, or its designee, of any SAE within 24 hours of Investigator awareness of the event via a Sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

Although all AEs are recorded in the case report form or EDC after signing informed consent, SAE reporting to the Sponsor begins after the subject has signed informed consent and has received the study drug. However, if an SAE occurs after signing informed consent, but prior to receiving the study drug, AND is considered Reasonably Possibly Related to a study procedure then it MUST be reported.

Investigators are not obligated to actively seek AEs or SAEs in subjects once they have discontinued from and/or completed the study. Serious adverse events will be collected for

30 days after the last dose of study drug. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the Investigator must promptly notify Lilly.

Pregnancy (maternal or paternal exposure to the study drug) does not meet the definition of an adverse event. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

The designated medical monitor of the Sponsor will monitor safety data throughout the course of the study. The Sponsor and/or its designee will review SAEs within appropriate timeframes to meet reporting obligations imposed by regulatory authorities. All serious and unexpected AEs for this study will be reported to regulatory authorities in accordance with local laws, directives, and regulations.

9.2.1.1 Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator reports as related to study drug. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidance.

9.2.2 Complaint Handling

Lilly collects product complaints on study drugs used in clinical trials in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Subjects should be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the study drug so that the situation can be assessed.

9.3 Treatment of Overdose

An overdose is not anticipated, as the study drug will be administered by a trained staff member.

Refer to the IB for treatment of overdose.

9.4 Safety

9.4.1 Medical Assessment and Neurological Examinations

A complete medical assessment will be performed at times specified in Section 2. Symptom-driven assessments will be performed if deemed clinically necessary.

A directed neurological examination will be performed by a physician at the time points specified in the Study Schedule (Section 2). If abnormalities are noted at these time points, additional examinations should be performed at daily intervals until the subject has returned to baseline. The examiner should be familiar with the subject's baseline examination. Mandated elements of the examination include inspection for cranial nerves, tremor, extraocular movements, brachial and patellar deep tendon reflexes, finger-nose pointing, and Romberg sign.

Work up for subjects with clinically significant changes in neurological examination should be considered.

9.4.2 Vital Signs

For each subject, vital signs, including blood pressure, pulse rate and temperature measurements should be conducted according to the Schedule of Activities (Section 2).

Single measurements will be taken at Screening and CRU admission. Supine triplicate blood pressure and pulse rate will be collected at all other timepoints. Body temperature to be obtained as single measurement. Predose vital signs should be taken approximately 1 hour prior to the schedule dosing.

At time points when orthostatic measurements are obtained, subjects should be supine for at least 5 minutes and stand for approximately 2 minutes. When triplicate blood pressure or pulse rate measurements precede the orthostatic measurement, the last supine blood pressure or pulse rate measurement will be used for orthostatic calculations. If the subject feels unable to stand, supine vital signs only will be recorded.

Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. Additional vital signs may be measured during each study period if warranted.

9.4.3 Laboratory Tests

For each subject, laboratory tests detailed in Appendix 2 should be conducted according to the Schedule of Activities (Section 2).

With the exception of safety laboratory test results that may unblind the study, Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor, if a central vendor is used for the study.

9.4.4 Electrocardiograms

For each subject, a 12-lead digital ECG will be collected in triplicate according to the schedule of activities (Section 2). Electrocardiograms must be recorded before collecting any blood samples. Subjects must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. Consecutive replicate ECGs will be obtained at approximately 1-minute intervals. Electrocardiograms may be obtained at additional times, when deemed clinically necessary.

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

If a clinically significant quantitative or qualitative change from baseline is identified after enrollment, the investigator will assess the subject for symptoms (for example, palpitations, near syncope, syncope) to determine whether the subject can continue in the study. The investigator

or qualified designee is responsible for determining if any change in subject management is needed and must document his/her review of the ECG printed at the time of evaluation from at least 1 of the replicate ECGs from each time point.

9.4.4.1 Digital Electrocardiogram Storage

Digital ECGs collected from both parts of the study will be electronically transmitted to a central ECG laboratory designated by Lilly. The central ECG laboratory will perform a basic quality control check (for example, demographics and study details) then store the ECGs in a database. At a future time, the stored ECG data may be overread at the central ECG laboratory for further evaluation of machine-read measurements or to meet regulatory requirements.

The machine-read ECG intervals and heart rate will be used for data analysis and report writing purposes unless a cardiologist overread of the ECGs is conducted prior to completion of the final study report, in which case the overread data would be used.

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

9.4.5 Safety Monitoring

The Lilly medical monitor will monitor safety data throughout the course of the study.

9.4.5.1 Hepatic Safety

If a study subject experiences elevated alanine aminotransferase (ALT) ≥3X upper limit of normal (ULN), alkaline phosphatase (ALP) ≥2X ULN, or elevated total bilirubin (TBL) ≥2X ULN, liver tests (Appendix 4) should be repeated within 3 to 5 days including ALT, aspartate aminotransferase (AST), ALP, TBL, direct bilirubin, gamma-glutamyl transferase (GGT), and creatinine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator based on consultation with the Lilly medical monitor. Monitoring should continue until levels normalize and/or are returning to approximate baseline levels.

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

- elevation of serum ALT to ≥ 5X ULN on two or more consecutive blood tests
- elevated serum TBL to ≥ 2X ULN (except for cases of known Gilbert's syndrome)
- elevation of serum ALP to ≥ 2X ULN on 2 or more consecutive blood tests
- subject discontinued from treatment due to a hepatic event or abnormality of liver tests
- hepatic event considered to be a SAE.

9.4.5.2 Hypersensitivity reactions

Acute and serious hypersensitivity reactions will be assessed and managed as clinically indicated. The clinical information, including examination findings, laboratory testing and treatment for all serious adverse events, including hypersensitivity reactions, will be captured in the EDC.

Non-acute hypersensitivity reactions, including type 3 hypersensitivity reaction will be assessed by clinical presentation. Routine monitoring of vital signs with regular physical examinations, and laboratory testing (including hematology, liver and renal testing, complements C3 and C4, c-reactive protein [CRP] and erythrocyte sedimentation rate [ESR], and urine analysis) will be undertaken to assess for the development of vasculitis, serum sickness and other manifestations of type 3 hypersensitivity reactions.

Stored serum samples for possible immune safety laboratory testing (including, but not limited to: β-tryptase, total IgE, immune-complex testing, and cytokine panel) will be collected for all subjects before study drug administration (Section 2). Additional, unscheduled, stored serum samples for possible immune safety laboratory testing should also be collected approximately 60 to 120 minutes and 4 to 6 weeks after moderate or severe infusion reactions or hypersensitivity reactions.

9.5 Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples of approximately 2 mL each will be collected to determine the serum concentrations of LY3451838. The sampling times may be modified at the discretion of the sponsor, based on review of interim PK data as they become available.

The actual date and time of each sampling must be recorded.

9.5.1 Bioanalysis

Samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor.

Serum concentrations of LY3451838 will be assayed using a validated ELISA (enzyme linked immunosorbent assay). Placebo samples are not planned to be analyzed.

Bioanalytical samples collected to measure study drug concentrations will be retained for a maximum of 1 year following last subject visit for the study.

9.6 Pharmacodynamics

9.6.1 Immunogenicity Assessments

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples of approximately 10 mL each will be collected to determine antibody production against LY3451838. In the event of drug hypersensitivity reactions (immediate or non-immediate), additional samples will be collected as close to the onset of the event as possible, at the resolution of the event, and 30 days following the event. Blood samples for LY3451838 and PACAP concentration will be collected concurrently with these unscheduled immunogenicity

samples. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time of each sampling will be recorded.

Immunogenicity will be assessed by a validated assay designed to detect ADAs in the presence of the study drug at a laboratory approved by the sponsor. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study drug.

Samples will be retained for a maximum of 15 years after the last subject visit, or for a shorter period if local regulations and Ethical Review Boards (ERBs) allow, at a facility selected by the sponsor. The duration allows the sponsor to respond to future regulatory requests related to the study drug. Any samples remaining after 15 years will be destroyed.

9.6.2 Exploratory Assessment of PACAP Concentration

At the visits and times specified in the Schedule of Activities (Section 2), blood samples of approximately 10 mL each will be collected to determine the PACAP plasma concentration.

Blood samples for PACAP concentration measurement will be stored for up to 5 years, and may be used to explore the effects of LY3451838 on other biomarkers related to target engagement and/or migraine / cluster headache pathology.

9.7 Genetics

A blood sample will be collected for pharmacogenetic analysis as specified in the Schedule of Activities (Section 2), where local regulations allow.

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 study drug. Assessment of variable response may include evaluation of AEs or differences in efficacy.

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

Samples will be retained for a maximum of 15 years after the last subject visit, or for a shorter period if local regulations and/or IRBs impose shorter time limits, for the study at a facility selected by Lilly or its designee.

Molecular technologies are expected to improve during the 15 year storage period and therefore cannot be specifically named. However, existing approaches include whole genome or exome sequencing, genome wide association studies, multiplex assays, and candidate gene studies. Regardless of technology utilized, data generated will be used only for the specific research scope described in this section.

9.8 Biomarkers

Biomarker samples relevant to drug disposition, target engagement, PD, mechanism of action, variability of patient response (including safety), and clinical outcome will be collected. This may include genetic testing (DNA, RNA), proteins, lipids, and other cellular elements as well as metabolic assays.

Serum and plasma samples for non-pharmacogenetic biomarker research will be collected at the times specified in the schedule of activities (Section 2) where local regulations allow.

Samples will be used for research on the drug target, disease process, variable response to LY3451838, pathways associated with migraine, mechanisms of action of LY3451838, research methods, or for validating diagnostic tools or assays related to migraine or other primary headaches.

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

Samples will be retained for a maximum of 15 years after the last subject visit, or for a shorter period if local regulations and/or IRBs impose shorter time limits, at a facility selected by Lilly or its designee. This retention period 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 LY3451838 or after LY3451838 is commercially available.

9.9 Health Economics

This section is not applicable for this study.

10 Statistical Considerations and Data Analysis

10.1 Sample Size Determination

The sample size is customary for Phase 1 studies evaluating safety and PK, and is not powered on the basis of statistical hypothesis testing.

Subjects who are randomized but not administered treatment may be replaced to ensure that enough subjects may complete the study.

10.2 Populations for Analyses

10.2.1 Study Participant Disposition

A detailed description of subject disposition will be provided at the end of the study. All subjects who discontinue from the study will be identified, and the extent of their participation in the study will be summarized by treatment. If known, a reason for their discontinuation will be given.

10.2.2 Study Participant Characteristics

Subject demographics (age, gender, race, ethnicity, height, weight, and body-mass index [BMI]) will be summarized by treatment.

10.3 Statistical Analyses

Statistical analysis of this study will be the responsibility of Eli Lilly and Company or its designee. Statistical analyses will be detailed in the statistical analysis plan.

Pharmacokinetic analyses will be conducted on data from all subjects who receive at least one dose of the study drug and have evaluable PK.

Safety analyses will be conducted for all enrolled subjects, whether or not they completed all protocol requirements.

Additional exploratory analyses of the data will be conducted as deemed appropriate. Study results may be pooled with the results of other studies for population PK analysis purposes to avoid issues with post-hoc analyses and incomplete disclosures of analyses.

For continuous variables, summary statistics will include number of subjects, mean, median, standard deviation, minimum, and maximum. Categorical endpoints will be summarized using number of subjects, frequency, and percentages.

10.3.1 Safety Analyses

All treatment and protocol procedure AEs will be listed, and if the frequency of events allows, safety data will be summarized using descriptive methodology. Summary statistics for AE and SAE will be provided by dose level and for all placebo subjects combined.

Safety assessments include laboratory tests, vital signs, ECGs, injection site reactions, and physical examination. The parameters will be listed, and summarized using standard descriptive statistics. Additional analysis will be performed as required.

10.3.2 Pharmacokinetic Analyses

10.3.2.1 Pharmacokinetic Parameter Estimation

All subjects dosed with LY3451838 who have evaluable concentrations will be included in the PK analyses. Pharmacokinetic parameter estimates for LY3451838 will be computed by standard non-compartmental methods.

The primary PK endpoints for analysis will be C_{max} and AUC of LY3451838. Other PK endpoints such as half-life, apparent clearance, apparent volume of distribution, and absolute bioavailability may be reported.

Mean and individual LY3451838 plasma concentration-time curves will be graphically presented. The PK endpoints will be summarized using descriptive statistics.

The relationship between LY3451838 PK and PD and/or safety measures may be evaluated. Other analyses may be performed as needed.

10.3.2.2 Pharmacokinetic Statistical Inference

Dose proportionality for exposure (AUC, C_{max}) may be assessed using the power model approach, as appropriate. Additional analyses may be performed if deemed necessary.

10.3.3 Exploratory Pharmacodynamic Analyses

Summary statistics for each exploratory endpoint may be provided by dose level and time for subjects randomized to LY3451838 and for all placebo subjects combined. Additional analyses may be conducted as appropriate.

10.3.4 Evaluation of Immunogenicity

The frequency and percentage of subjects with preexisting ADA and with TEADA+ to LY3451838 will be tabulated. 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 to baseline if ADAs were detected at baseline (treatment-boosted ADA). For the TEADA+ subjects, the distribution of maximum titers will be described. The frequency of neutralizing antibodies may also be tabulated in TEADA+ subjects.

The relationship between the presence of antibodies and the PK parameters and PD response including safety and efficacy to LY3451838 may be assessed.

10.3.5 Data Review During the Study

Interim access to safety data is scheduled to occur throughout the study. The investigator and the Lilly medical monitor will make the determination regarding dose escalation based on their review of the blinded safety, tolerability and PK data. Review of ADA data is scheduled on a

rolling basis throughout the study to guide dose selections. Individual PK/PD/ADA data will not be reviewed by the investigator until the study is complete to avoid unblinding. A small number of individuals from Lilly sponsor team will be unblinded during these reviews.

10.3.6 Interim Analyses

At least 1 interim analysis is planned for this study. It will be conducted after the 12-week ADA data from the first two cohorts are available. All available safety, tolerability, PK and ADA data up to that point will be reviewed by the sponsor. The interim analysis will be used to guide the design of this and subsequent studies.

Additional interim analyses may be conducted without protocol amendment, as the primary objective for this study is not based on inferential statistical analyses. No adjustments for multiple comparisons will be made.

11 References

[EMEA CHMP] European Medicines Agency. Guidance on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal product. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2017/07/WC500232186.pdf. Accessed on 27 Aug 2018.

[IB] Eli Lilly and Company. Investigator's Brochure for LY3451838, Sep 2018.

Kronenberg S, Husar E, Schubert C, Freichel C, Emrich T, Lechmann M, et al. Comparative assessment of immune complex-mediated hypersensitivity reactions with biotherapeutics in the non-human primate: Critical parameters, safety and lessons for future studies. *Regulatory Toxicology and Pharmacology*. 2017;88:125-137.

Zagami AS, Edvinsson L, Goadsby PJ. Pituitary adenylate cyclase activating polypeptide and migraine. *Annals of Clinical and Translational Neurology*. 2014;1(12):1036-1040.

Appendix 1. Abbreviations and Definitions

Term	Definition
ADA	antidrug 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 AE 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.
ANA	antinuclear antibody
ANCA	Anti-cytoplasmic antibody
AUC	area under the concentration-time curve
blinding	A procedure in which one or more parties to the study are kept unaware of the treatment assignment(s). Unless otherwise specified, blinding will remain in effect until final database lock. A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the subject is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the subject are not. A double-blind study is one in which neither the subject nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received
BP	blood pressure
CGRP	calcitonin gene-related peptide
C_{max}	maximum drug concentration
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.
CRP	C-reactive protein
CRU	clinical research unit
CSE	clinically significant event
ED	early discontinuation
enroll	The act of assigning a subject to a treatment. Subjects who are enrolled in the study are those who have been assigned to a treatment.
enter	Subjects entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.

IRB	institutional review board
ESR	erythrocyte sedimentation rate
GCP	good clinical practice
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
informed consent	A process by which a subject 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 subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
IV	Intravenous
MABEL	minimal anticipated biological effect level
MTD	maximum tolerated dose
NOAEL	no observed adverse effect level
randomize	the process of assigning subjects to an experimental group on a random basis
PACAP	pituitary adenylate cyclase-activating polypeptide
PK/PD	pharmacokinetic/pharmacodynamic
RA	rheumatoid arthritis
RF	rheumatoid factor
SAE	serious adverse event
SC	Subcutaneous
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SLE	systemic lupus erythematosus
SUSARs	suspected unexpected serious adverse reactions
SS	Sjogren's Syndrome

SRP	Safety Review Panel
TEADA	treatment-emergent anti-drug antibodies
TEAE	treatment-emergent adverse event: Any 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
t_{max}	time to C_{max}
VPAC	vasoactive intestinal polypeptide receptor
VIP	vasoactive intestinal peptide

Appendix 2. Clinical Laboratory Tests

Safety Laboratory Tests

Hematology	Clinical Chemistry[b]
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count (RBC)	Bicarbonate
Mean cell volume	Chloride
Mean cell hemoglobin	Calcium
Mean cell hemoglobin concentration	Glucose[a]
Leukocytes (WBC)	Blood urea
Platelets	Total cholesterol
Differential WBC [Absolute counts] of:	Total protein
Neutrophils	Albumin
Lymphocytes	Total bilirubin/direct bilirubin
Monocytes	Alkaline phosphatase (ALP)
Eosinophils	Aspartate aminotransferase (AST)
Basophils	Alanine aminotransferase (ALT)
Erythrocyte sedimentation rate (ESR)	Creatinine
	C-reactive protein (CRP)
	Total complement C3 (C3)
	Total complement C4 (C4)
Urinalysis	
Specific gravity	
pH	Hepatitis B surface antigen[c]
Protein	Hepatitis C antibody[c]
Glucose	HIV[c]
Ketones	Pregnancy test (urine)
Bilirubin	
Urobilinogen	
Blood	
Nitrite	
Leukocytes	
Microscopy[d]	
Antinuclear antibody (ANA)[c]	
Rheumatoid factor (RF)[c]	
Anti-neutrophil cytoplasmic antibody (ANCA)[c]	

Abbreviations: FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; RBC = red blood cells; WBC = white blood cells; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; C3 = Total complement C3; C4 = Total complement C4.

a Fasting glucose performed at Screening, Predose and 24 h (postdose) only

b Results of these assays will be validated by the local laboratory at the time of testing. Additional tests may be performed or auto-calculated by the laboratory as part of its standard panel that cannot be removed. Some of the above parameters are calculated from measured values. Omission of calculated values will not be considered as a protocol violation.

c Performed at screening only
d If clinically indicated, per investigator's discretion.

Appendix 3. Study Governance, Regulatory and Ethical Considerations

Informed Consent

The investigator is responsible for:

- ensuring that the subject understands the nature of the study, the potential risks and benefits of participating in the study, and that their participation is voluntary.
- ensuring that informed consent is given by each subject. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of investigational product.
- answering any questions the subject may have throughout the study and sharing in a timely manner any new information that may be relevant to the subject's willingness to continue his or her participation in the study.
- providing a copy of the ICF to the participant or the participant's legal representative and retaining a copy on file.

Recruitment

Lilly or its designee is responsible for the central recruitment strategy for subjects. Individual investigators may have additional local requirements or processes. Study specific recruitment material should be approved by Lilly.

Ethical Review

The investigator must give assurance that the ethical review board (ERB) was properly constituted and convened as required by ICH guidelines and other applicable laws and regulations.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the CRU. Lilly or its representatives must approve the ICF before it is used at the CRU. All ICFs must be compliant with the ICH guideline on GCP.

The CRU's ERB(s) should be provided with the following:

- the current IB
- ICF
- relevant curricula vitae

Regulatory Considerations

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

1) consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
2) applicable ICH GCP Guidelines
3) applicable laws and regulations

Some of the obligations of the sponsor will be assigned to a third party organization.

Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

Final Report Signature

The Sponsor's responsible medical officer and statistician will sign/approve the final clinical study report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- provide instructional material to the CRU, as appropriate.
- provide training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the CRFs, and study procedures.
- make periodic visits to the CRU.
- be available for consultation and stay in contact with the CRU personnel by mail, telephone, and/or fax.
- review and evaluate CRF data and/or use standard computer edits to detect errors in data collection.
- conduct a quality review of the database.

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

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to the original source documents.

Data Collection Tools/Source Data

An electronic data capture system will be used in this study. The site must define and retain all source records and must maintain a record of any data where source data are directly entered into the data capture system.

Data Protection

Data systems used for the study will have controls and requirements in accordance with local data protection law.

The purpose and use of subject personal information collected will be provided in a written document to the subject by the Sponsor.

Study and Site Closure

Discontinuation of Study Sites

Study site participation may be discontinued if Lilly or its designee, the investigator, or the ERB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Discontinuation of the Study

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

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with subjects in consultation with Lilly medical monitor or its designee.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	
WBC	Prothrombin Time INR
Neutrophils	
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, total
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Conjugated bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody[a]**
AST	**Alkaline Phosphatase Isoenzymes[a]**
GGT	**Anti-smooth muscle antibody (or anti-actin**
CPK	**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 Lilly-designated or local laboratory.

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

Appendix 5. Blood Sampling Summary

This table summarizes the approximate number of venipunctures and blood volumes for all blood sampling (screening, safety laboratories, and bioanalytical assays) during the study.

Protocol J1H-MC-LAJA Sampling Summary – Part A and B

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	21	1	21
Hematology and chemistry - laboratory tests (fasting)[a]	10	2	20
Hematology and chemistry - laboratory tests (non-fasting)[a]	8	13	104
Pharmacokinetics	2	19	38
Blood discard for cannula patency	0.3	8	2.4
Pharmacodynamics (PACAP)	10	12	120
Immunogenicity	10	7	70
Pharmacogenetics	10	1	10
Non-pharmacogenetics	10	2	20
Infusion/Hypersensitivity reactions[a]	8.5	1	8.5
Total			413.9
Total for clinical purposes [rounded up to nearest 10 mL]			420

[a] CRP, ESR, C3 and C4 will be tested using chemistry and/or hematology samples. Additional samples, including for hypersensitivity analyses, may be drawn if needed for safety purposes.

Appendix 6. Protocol Amendment J1H-MC-LAJA(a) Summary

Protocol J1H-MC-LAJA, A Safety, Tolerability, and Pharmacokinetics Study of LY3451838 in Healthy Subjects, has been amended in response to queries raised by Health Science Authorities (HSA), Singapore. Additional minor amendments to the protocol are made to add tests for early detection of hypersensitivity reactions and to ensure consistency of the randomization and unblinding procedures. The new protocol is indicated by Amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are as follows:

Section # and Name	Description of Change	Brief Rationale
2. Schedule of Activities 9.4.5.2 Hypersensitivity Reactions	Total complement C3 and total complement C4 tests will be performed at screening and Visits 4, 7, 9, and 11.	C3 and C4 tests can aid in the early detection of type III hypersensitivity reactions.
5.1 Overall Design 5.1.1 Part A (Single Ascending Dose IV Administration) 7.1 Treatment Administered	The planned dose levels in Part A updated to: 25, 75, 250, 500, 1000 and 1500 mg single dose via IV infusion. The second planned dose level is updated from 125 mg to 75 mg.	To address HSA query about dose increment between Cohort 1 and Cohort 2.
6.2 Exclusion Criteria	Criterion #22 updated to exclude subjects with hypertension (diastolic blood pressure >90 or <60 mmHg and/or systolic blood pressure >140 or<90 mmHg)	Criteria updated to enroll only normotensive subjects in the study, in response to HSA query.
7.2 Method of Treatment Assignment 7.3 Blinding	Randomized method updated from paper based method to interactive web response system (IWRS)	The randomization and unblinding will be implemented via IWRS, rather than randomization table.

Revised Protocol Sections

Note:	All deletions have been identified by ~~strikethroughs~~. All additions have been identified by the use of underscore.

Section 2 Schedule of Activities

Total complement C3 and total complement C4 tests added to Screening and Visits 4, 7, 9, and 11.

Section 5 Study Design

Section 5.1 Overall Design

Section 5.1.1 Part A (Single Ascending Dose IV Administration)

Part A of the study is designed to assess the safety and tolerability of a single IV dose of LY3451838 compared to placebo in 6 cohorts of healthy subjects. Up to 6 doses of LY3451838 at a planned dose range of 25 to 1500 mg will be evaluated. The planned dose levels for the 6 cohorts are: 25, 75~~125~~, 250, 500, 1000 and 1500 mg single dose via IV infusion.

Section 6 Study Population

Section 6.2 Exclusion Criteria

22. Have an abnormal blood pressure (supine) defined as diastolic blood pressure >90~~95~~ or <60~~50~~ mmHg and/or systolic blood pressure >140~~160~~ or <90 mmHg; or with minor deviation judged to be acceptable by the investigator. Retesting may occur once during the screening visit within 2 hours of the initial abnormal blood pressure measurement at the discretion of the investigator

Section 7 Treatment

Section 7.1 Treatment Administered

Part A: The planned dose levels of LY3451838 are 25 mg, 75~~125~~ mg, 250 mg, 500 mg, 1000 mg, and 1500 mg. LY3451838 will be administered IV.

Section 7.2 Method of Treatment Assignment

In both parts of the study, within each cohort, eligible subjects will be enrolled sequentially, and will be randomly assigned to receive either LY3451838 or placebo in a 6:2 ratio. Treatment assignment will be determined by a computer-generated randomization sequence using an interactive web response system (IWRS). ~~A randomization table will be created by a computer software program. The randomization list will be provided to the designated unblinded site staff for subject randomization and dispensing purposes and kept in a secure location, accessible to the designated unblinded site staff only.~~

Section 7.3 Blinding

The study is double-blinded; subjects, investigator, and CRU personnel performing trial related activities or with the ability to influence study outcomes will be blinded with respect to LY3451838 and placebo treatment. To preserve the blinding, only a minimum number of Lilly personnel may have access to the randomization table and codes or IWRS before the study is complete. Site staff who are responsible for drug preparation will not be blinded; laboratory personnel will also not be blinded.

Emergency unblinding will be performed through the IWRS. This option may be used only if the subject's well-being requires knowledge of the subject's treatment assignment. All unblinding events will be recorded and reported by the IWRS. ~~One set of sealed envelopes containing the randomization code will be made available to the Investigator at the start of the trial. A code envelope, which reveals the treatment for a specific study subject, may be opened during the study only if the subject's well-being requires knowledge of the subject's treatment assignment.~~

If a subject's study treatment assignment is unblinded, the subject must be discontinued from the study, unless the Investigator obtains specific approval from a Lilly medical monitor for the study participant to continue in the study. During the study, emergency unblinding should occur only by accessing the ~~study subject's emergency code~~IWRS.

~~At the end of the study, unopened envelopes will be returned to Lilly or its designee, or destroyed according to site procedures.~~

Section 9 Study Assessments and Procedures

Section 9.4.5.2 Hypersensitivity Reactions

Non-acute hypersensitivity reactions, including type 3 hypersensitivity reaction will be assessed by clinical presentation. Routine monitoring of vital signs with regular physical examinations, and laboratory testing (including hematology, liver and renal testing, complements C3 and C4, c-reactive protein [CRP] and erythrocyte sedimentation rate [ESR], and urine analysis) will be undertaken to assess for the development of vasculitis, serum sickness and other manifestations of type 3 hypersensitivity reactions.

Appendix 2 Clinical Laboratory Test

Total complement C3 and total complement C4 tests added to the list of Safety Laboratory Tests.

Appendix 5 Blood Sampling Summary

Footnote 'a' updated to indicate that C3 and C4 will be tested using chemistry and/or hematology samples.

Appendix 7. Protocol Amendment J1H-MC-LAJA(b) Summary

Protocol J1H-MC-LAJA, A Safety, Tolerability, and Pharmacokinetics Study of LY3451838 in Healthy Subjects, has been amended in response to address issues identified during the implementation of the study. The new protocol is indicated by Amendment (b) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are as follows:

Section # and Name	Description of Change	Brief Rationale
2. Schedule of Activities	Window for Visits 8 to 12 increased	To improve flexibility of subject scheduling
2. Schedule of Activities	Optimized Day -1 procedures as follows: • The medical assessments, neurological examination, and eligibility review may be performed pre-dose on Day 1. • If screening is within 1 week of day -1, neurological examinations, ECGs, hematology and chemistry does not need to be repeated; • C3, C4, CRP and ESR are moved to predose on Day 1	To reduce subject burden
2. Schedule of Activities	Window for Visit 8 changed to -1 up to +2	To prevent overlap in PK draw days
6.1 Inclusion Criteria	Inclusion #3 updated to allow subjects with BMI between 18 to 35 kg/m^2 to be enrolled.	To improve enrollment, and increase BMI up to 35 Kg/m^2 is not expected to affect safety of LY3451838.
6.2 Exclusion Criteria	Criterion #13 updated to allow subjects with non-clinically significant positive ANA titer to be enrolled	The observed prevalence of ANA in subjects during the screening for Study LAJA is significantly higher than the reported ANA prevalence in healthy population in literature. In healthy subjects without any history or symptoms or signs of connective tissue disease, an ANA titer is considered clinically significant only if the titer exceeds 1:160.

Revised Protocol Sections

Note:	All deletions have been identified by ~~strikethroughs~~. All additions have been identified by the use of underscore.

Section 2 Schedule of Activities

Study Schedule Protocol JAH-MC-LAJA – Part A (Intravenous Administration) and Part B (Subcutaneous Administration)

Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16[a]**
Study Day	**-28**	**-1**	**1**	**2**	**3**	**5**	**7**	**9 (-1 ±up to +2)**	**15 (±2)**	**22 (±3~~2~~)**	**29 (±3~~2~~)**	**43 (±3~~2~~)**	**57 (±4)**	**71 (±4)**	**85 (±7)**	**141 / ED (±7)**
Visit Type	S	A	I	I	D	O	O	O	O	O	O	O	O	O	O	O
Informed consent	X															
Medical history	X															
Height/weight[b]	X		X								X		X		X	X
Medical Assessment[c]	X	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Neurological examination	X	X[d]		X			X				X					X
Electrocardiogram[e]	X	X[d]	Predose, 1, 3 h	24 h (± 90 m)	X	X	X	X	X	X	X		X		X	X
Vital signs[f, g]	X	X[d]	Predose, EOI[h], 1, 3 h	24 h (± 90 m)	X	X	X	X	X	X	X	X	X	X	X	X
Orthostatic BP and pulse rate			Predose, 1 h	24 h			X		X		X					X
Pregnancy test (urine)	X	X[d]									X		X			X
Screening tests	X															
Eligibility review		X[d]														
Study drug administration			X													
Hematology and chemistry[i]		X[d]	Predose	X	X	X	X	X	X	X	X	X	X	X	X	X
C3, C4, CRP and ESR	X	~~X~~[d]	Predose	X			X		X		X					
Urine analysis		X[d]		X			X		X		X					
PK sample[i]			EOI[h], 3, 6, 8, 12 h	24 h (± 60 m), 36 h (± 60 m)	48 h (±60 m)	X	X	X	X	X	X	X	X	X	X	X
PACAP sample[i]			Predose, EOI[h] 6, 12 h	24 h	48 h		X		X		X		X		X	X

Immunogenicity sample			Predose				X		X		X		X		X	X
Samples for infusion and hypersensitivity reactions[j]			Predose													
Non-genetic biomarker sample			Predose				X									
PGx sample[k]			Predose													
Adverse events		← X →														
Concomitant medications	← X →															

Abbreviations: A = CRU admission; BP = blood pressure; CRU = clinical research unit; D = CRU discharge; ED = early discontinuation; EOI = end of infusion; h = hour; I = inpatient stay; m = minute; O = outpatient; C3 = total complement C3; C4 = total complement C4; CRP = C reactive Protein; ESR = erythrocyte sediment rate; PACAP = pituitary adenylate cyclase-activating polypeptide; PGx = pharmacogenomics; S = screening.

Note: if multiple procedures take place at the same time point, the following order of the procedure should be used: electrocardiogram, vital signs, and venipuncture. Unless otherwise specified, predose samples may be taken at any time prior to dosing, based on CRU activity schedule.

a in case of early discontinuation/withdrawal, the subject should undergo all Visit 16 activities.

b Height will be collected at Screening only.

c Full medical assessment prior to first dose (on Day -1 or Day 1), discharge, and discontinuation visits. Symptom-driven medical assessment as deemed necessary by the Investigator.

d Day -1 samples/activities could be collected/performed up to 5 days before the scheduled day of dosing. The medical assessment, neurological examination and eligibility review may be performed pre-dose on Day 1. If screening visit is within 1 week (inclusive) of Day -1, neurological examination, ECG, hematology and chemistry do not need to be repeated..

e Single electrocardiogram will be collected at Screening and CRU admission only. Triplicate electrocardiograms will be collected at all other timepoints.

f Vital signs include blood pressure, pulse rate, and body temperature. Single measurements at Screening and CRU admission. Supine triplicate blood pressure and pulse rate at all other timepoints.

g Body temperature to be obtained as single measurement.

h End of infusion procedures are only required for Part A of the study – to be performed within 10 minutes from infusion completion..

i Predose and 24 h (postdose) samples to be collected after at least 8 hours of fasting. PK samples on day 5 and beyond should be obtained at approximately (± 2 hr) the same time of day as the dosing time on day 1.

j Samples for infusion reactions and hypersensitivity reactions will be collected and stored for all subjects. Post treatment samples (up to 3) will only be collected in subjects who experience moderate to severe infusion reactions or hypersensitivity reactions (as defined in Section 9.4.5.2).

k If sample not collected as indicated in Study Schedule table, it may be collected a following visit.

Section 6.1 Inclusion Criteria

3. Have a body mass index of 18 to 35~~32~~ kg/m^2, inclusive, at screening

Section 6.2 Exclusion Criteria

13. Have history (within past 5 years) of, or presence of, uncontrolled asthma, significant atopy, significant rheumatological or autoimmune diseases, including but not limited to systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjogren's Syndrome (SS), or vasculitis; or have positive antinuclear antibody (ANA) that is considered to be clinically significant by the investigator, rheumatoid factor (RF), or anti-neutrophil cytoplasmic antibody (ANCA) at screening; or hereditary angioedema, or common variable immune deficiency.

Appendix 8. Protocol Amendment J1H-MC-LAJA(c) Summary

Protocol J1H-MC-LAJA, A Safety, Tolerability, and Pharmacokinetics Study of LY3451838 in Healthy Subjects, has been amended in response to address issues identified during the implementation of the study. The new protocol is indicated by Amendment (c) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are as follows:

Section # and Name	Description of Change	Brief Rationale
7.1 Treatment Administered	Additional vial capacity that can deliver LY3451838 at 100 mg/mL was added.	Availability of additional vials that can deliver LY3451838 at 100 mg/mL.

Revised Protocol Sections

Note:	All deletions have been identified by ~~strikethroughs~~. All additions have been identified by the use of <u>underscore</u>.

Section 7.1 Treatment Administered

LY3451838 Drug Product is a monoclonal antibody formulated for IV or SC administration. LY3451838 for Injection is supplied for clinical trial use as a solution in a single use glass vial. The vial is manufactured to deliver 200 mg of LY3451838 at 50 mg/mL <u>or 100 mg/mL</u>. In order to ensure complete withdrawal and delivery of the label amount of 200 mg of LY3451838, vials contain an approximate 10% volume overfill. The drug product is filled into a glass vial, and sealed with a stopper and flip-off 2 piece aluminum seal. LY3451838 for Injection vials are stored in refrigerated condition (2ºC to 8ºC).

Appendix 9. Protocol Amendment J1H-MC-LAJA(d) Summary

Protocol J1H-MC-LAJA, A Safety, Tolerability, and Pharmacokinetics Study of LY3451838 in Healthy Subjects, has been amended in response to address issues identified during the implementation of the study. The new protocol is indicated by Amendment (d) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are as follows:

Section # and Name	Description of Change	Brief Rationale
3.3 Benefit/Risk Assessment 5.4 Scientific Rationale for Study Design	Vasculitis seen in monkey tox data was confirmed to be due to immune complex deposition and complement activation.	Confirmed by IHC studies conducted on tissue samples from the 8-week monkey GLP tox study.
5.5 Justification for Dose 7.4.1. Dose Escalation in Part A	PK information updated due to current prediction based on observed human PK and discussion of 3 points of justification added.	Human PK, safety, and immunogenicity data suggest that dosing slightly beyond the NOAEL exposure should pose little additional risks to participants.

Revised Protocol Sections

Note:	All deletions have been identified by ~~strikethroughs~~. All additions have been identified by the use of underscore.

3.2 Background

The toxicity of LY3451838 was assessed in 2-month rat and monkey studies and in an in vitro human tissue cross-reactivity study. In the tissue cross-reactivity study, there was no unexpected binding observed in a panel of human tissues. The rat and monkey studies used weekly SC dosing of 0, 10, and 50 mg/kg and weekly IV dosing of 250 mg/kg. There were no adverse effects in the rat study. In the monkey study, minimal-to-mild vascular/perivascular inflammation ~~most suggestive of~~ was observed, but was attributed to immune complex deposition and, therefore, not expected to be relevant to human safety. In addition to the vasculitis, which was not evident clinically, a greater incidence of transient neurological effects was observed in treated compared to control monkeys. This included decreased or absent flexor reflexes, proprioceptive positioning, placing reactions of limbs, and locomotor stereotypy all of which were considered nonadverse. More details about the toxicology studies are provided in Section 4 of the Investigator's Brochure (IB 2018).

3.3 Benefit Risk Assessment

The nonclinical safety and pharmacology information for LY3451838 adequately supports the transition from preclinical status to a clinical, first-in-human study. The risk evaluation of

LY3451838 through its properties, nature of the target, non-clinical data in relevant species, target population and dose projections, suggest it not be considered a high risk molecule. LY3451838 is a novel monoclonal antibody against PACAP, a neuropeptide that is expressed in both central nervous system and peripheral tissues. While pharmacology of this mechanism has not been directly evaluated in humans, AMG301, a monoclonal antibody against PAC1 receptor, has successfully completed phase 1 clinical testing, and is being evaluated for migraine prevention in an ongoing phase 2 trial. The study of AMG301 in phase 2 suggests that blocking at least part of the PACAP pathway did not lead to significant toxicity in humans. The dose-limiting toxicity of LY3451838 was minimal-to-mild vasculitis in multiple organs in monkeys assessed after 8 weekly IV doses of 250 mg/kg, similar to the presentation of vasculitis due to immune response in toxicology species observed with other monoclonal antibodies (Kronenberg et al. 2017). Immunohistochemistry studies of tissue samples from the 8-week monkey GLP toxicology study demonstrated that the vasculitis was due to immune complex deposition and complement activation. This type of immune response in a single animal species is considered to translate poorly to human safety (EMEA). ~~The weight of evidence suggests that the most likely mechanism of vasculitis was immune complex deposition, rather than an excessive on target pharmacology.~~ For this first in human study, the highest dose is limited to 1500 mg, which is predicted to reach an exposure approximately ~~16~~15-fold lower than the concentration in which vasculitis was observed in monkeys. In addition, PK data will be reviewed with each dose escalation, and an exposure limit will be implemented in this study so that the predicted mean exposure based on observed PK does not significantly exceed that of the no-observed-adverse-effect-level (NOAEL) exposure observed in monkeys ~~significantly~~.

Immunogenicity and hypersensitivity reactions, including infusion reactions, acute and delayed (including immune complex disease) hypersensitivity reactions are a potential risk for all monoclonal antibodies, including LY3451838. Hypersensitivity risk mitigation in this study includes the administration of a single dose of LY3451838 IV with subsequent close monitoring.

LY3451838 has not been administered to humans previously and accordingly this study has been designed following the principles outlined in the Guideline on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medicinal Products (EMEA CHMP Jul 2017). Any identified risks are considered to be monitorable and manageable at the planned dose range of 25 mg to 1500 mg single doses of LY3451838 in healthy subjects.

There is no anticipated therapeutic benefit for the subjects.

More information about the known and expected benefits, risks, serious adverse events (SAEs), and reasonably anticipated adverse events (AEs) of LY3451838 are found in the IB.

5.4 Scientific Rationale for Study Design

Hypersensitivity reactions, including both acute hypersensitivity reactions and immune complex diseases, are potential risks for all therapeutic antibodies, including LY3451838. Subjects with a history of clinically significant hypersensitivity reactions / conditions, or autoimmune diseases are excluded from the study to minimize risks for hypersensitivity reactions in the subjects in this study, and to avoid confounded interpretation of the safety data. Additional measures will be

implemented to monitor and manage infusion reactions (Section 7.4.3.2), immunogenicity, and hypersensitivity reactions (Section 9.6.1). While vasculitis observed in the monkey toxicology studies ~~were suggestive of~~ was attributed to immune complex ~~disease~~ deposition, additional precautions, such as reviewing PK data before each dose escalation, limiting the dose range and implementing the exposure to that of the monkey NOAEL are designed into the protocol to address the uncertainty of the mechanism for vasculitis.

Because of the distribution of PACAP in the nervous system, and to follow-up on the subtle non-adverse changes in the neurological examination in the 2-month monkey toxicology study, neurological examinations will be performed to detect any early signals on the effects of LY3451838 on the nervous system.

5.5 Justification for Dose

Based on current preclinical and toxicology data, a dose range of 25 mg to 1500 mg IV is proposed for the singe ascending dose (SAD). The predicted efficacious dose is 500 mg IV based on allometric scaling of PK parameters from monkey and the ability to achieve a target concentration of 15 µg/mL at 30 days post-dose. The target concentration selected for LY3451838 is the galcanezumab trough concentration at an effective dose of 120 mg monthly in migraine patients. The rationale for selecting this target concentration for LY3451838 is the overlap in PACAP and calcitonin gene-related peptide (CGRP) expression profile, potency of the neuropeptides for their target(s) in the same concentration range, and similarity in the potency of the antibodies against their targets.

The proposed starting dose of 25 mg is 20-fold lower than the predicted efficacious dose, which is expected to be a minimal anticipated biological effect level (MABEL). In addition, the starting dose has a margin of safety of more than 50-fold based on dose, area under the concentration-time curve (AUC), and maximum drug concentration (C_{max}) for both rat and monkey toxicology studies (Table 5.1Table 5.1).

The highest planned dose for this study is 1500 mg IV. This dose is predicted to achieve an exposure approximately 3-times higher than the predicted efficacious exposure. A single 1500 mg IV dose has a margin of safety of 2 based on dose and ~~0.9~~0.8 based on AUC relative to the monkey NOAEL. While margin of safety (MOS) based on monkey AUC is slightly less than 1, this is deemed acceptable because the predicted exposure after a single 1500-mg dose based on the observed human PK in the first 3 cohorts of this study is >~~16~~15-fold lower than the dose in which toxicity was observed (i.e., 250 mg/kg IV). ~~Furthermore, it is planned to limit the predicted mean exposure to that observed at the monkey NOAEL, such that the mean predicted $AUC_{0-\infty}$ at a given dose level will not exceed 98,000 µg/mL*h based on the observed PK from prior cohorts.~~ Furthermore, the mean predicted human $AUC_{0-\infty}$ of approximately 122,500 µg/mL*h, is only slightly higher (1.25x) than the monkey NOAEL AUC_{0-168h} (i.e., 50 mg/kg SC). Based on the available toxicology and clinical data, the risk of reaching this exposure is acceptable in this single dose study. Firstly, the NOAEL defining toxicity in monkeys was wide-spread vasculitis. The immunohistochemistry results confirmed the initial hypothesis that the vasculitis observed in monkeys was due to immune-complex deposition. In general,

translation of immune-related responses between a single toxicology species and humans has been poor (EMEA CHMP Jul 2017). Secondly, LY3451838 has been administered to 40 healthy subjects at up to 1000 mg dose. No subjects experienced any SAEs, or discontinued from study due to an AE. The immunogenicity data from the first 2 cohorts have been reviewed, and only 1 subject developed treatment-emergent antidrug antibody at fairly low titer. Thirdly, the vasculitis was observed in a 2-month (8 weekly doses) monkey study, while current clinical study involves single doses. The risk for developing immune-complex disease is low after a single dose.

The planned SC dose for Part B is 250 mg. This dose is feasible with the current formulation (Section 7.1) and will allow for an adequate safety, tolerability and PK evaluation following SC administration. It may be adjusted to match the dose administered to subjects in Cohort 3 Part A.

Table 5.1 Margin of Safety for Intravenous Administration of LY3451838 Based on Administered Dose and Predicted Exposure

	IV Reference Dose (mg)	Dose (mg/kg)	Dose Multiple[a]	AUC (µg•hr/mL)[b]	C_{max} (µg/mL)	Exposure Multiple (AUC)[a]	Exposure Multiple (C_{max})[a]
Human	1500	25	–	~~110,000~~ 122,500[c]	~~510~~ 450[c]	–	–
	25	0.4	–	1,800[d]	8.5[d]	–	–
Rat NOAEL[d][e]	1500	250 (IV)	10	430,000	14,000	~~3.9~~3.5	~~28~~31
	25		600			240	1,600
Monkey NOAEL[e][f]	1500	50 (SC)	2	98,000	740	~~0.9~~0.8	1.~~5~~6
	25		120			54	87

Abbreviations: AUC = area under the concentration-time curve; C_{max} = maximum drug concentration; IV = intravenous; NOAEL = no-observed-adverse-effect level; SC = subcutaneous.

[a] Dose multiple is the dose in animals/dose in humans based on mg/kg. Exposure multiple is the calculated exposure in animals / predicted exposure in humans. (Refer to Section 4 of the IB.)
(Note: route of administration is IV in humans and rat and SC in monkey).

[b] The AUCs are $AUC_{0-\infty}$ after a single dose in human; AUC_{0-96h} on Day 50 after weekly dosing in rat; AUC_{0-168h} on day 50 after weekly dosing in monkey.

[c] Plasma pharmacokinetics at the 1500 mg dose were predicted based on the observed human PK at doses of 25, 75, and 250 mg LY3451838

[d] Based on allometric scaling from monkey PK (8363751), plasma pharmacokinetics were estimated following single dose of LY3451838 in humans

~~[d]~~[e] NOAEL determined in a 2-month repeat dose toxicity study (5002638).

~~[e]~~[f] NOAEL determined in a 2-month repeat dose toxicity study (5002639).

7.4.1 Dose Escalation in Part A

After review of these data, an agreement on the appropriate dose will be made by the investigator and sponsor for the next cohort/dose level. The magnitude of dose escalations may be adjusted following data review. The dose will not exceed 1500 mg. ~~and the mean $AUC_{0-\infty}$ at a given dose will not exceed that observed in the monkey NOAEL (i.e., 98000 µg/mL*h).~~

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