Protocol I9H-MC-FFAB (c)

A Phase 1 Randomized, Placebo-Controlled Study to Determine the Effect of LY3316531 on Capsaicin-Induced Dermal Blood Flow in Healthy Male Subjects

NCT03611608

Approval Date: 06-Feb-2019

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EudraCT Number 2018-000710-38

Confidential Information

IL-23/CGRP Bispecific Antibody (LY3316531)

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Clinical Pharmacology Protocol Approved by Lilly:
18 June 2018
Amendment (a) Approved by Lilly: 25 October 2018
Amendment (b) Approved by Lilly: 21 December 2018
Amendment (c) Electronically Signed and Approved by Lilly on approval date provided below.

Approval Date: 06-Feb-2019 GMT

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1. Protocol Synopsis

Title of Study:
A Phase 1 Randomized, Placebo-Controlled Study to Determine the Effect of LY3316531 on Capsaicin-Induced Dermal Blood Flow in Healthy Male Subjects

Rationale:
LY3316531 is a humanized bispecific antibody that selectively binds to interleukin-23 (IL-23) and calcitonin gene-related peptide (CGRP). This dual inhibitor is an innovative attempt to target pathways that affect the pathology associated with auto-inflammatory conditions.

This study will assess the activity of LY3316531 on CGRP neutralization via capsaicin-induced dermal blood flow (DBF) as measured using laser Doppler imaging (LDI) in healthy male subjects.

Objective(s)/Endpoints:

Objectives	Endpoints
Primary	
To assess target neutralization of CGRP following a single IV dose of LY3316531 versus placebo in healthy male subjects via capsaicin-induced DBF as measured using LDI	Decrease from baseline within 30 days, relative to placebo, in capsaicin-induced DBF (by blocking CGRP) following at least 1 dose level of a single IV dose of LY3316531
Secondary	
To assess the safety and tolerability of a single dose of LY3316531 in healthy male subjects	Incidence of adverse events, treatment-emergent adverse events, and serious adverse events
To characterize the pharmacokinetics of LY3316531 following IV administration in healthy male subjects	C_{max} and AUC

Abbreviations: AUC = area under the concentration versus time curve; CGRP = calcitonin gene-related peptide; C_{max} = maximum observed drug concentration; DBF = dermal blood flow; IV = intravenous; LDI = laser Doppler imaging.

Summary of Study Design:

Study I9H-MC-FFAB is a Phase 1 single-site, randomized, subject- and investigator-blind, placebo (Pbo)-controlled, parallel-dose group, single-dose study of LY3316531 (LY) in healthy male subjects. The study will evaluate 1 cohort (Cohort 1) of 16 subjects (12 LY:4 Pbo) with a planned single dose of 300-mg LY3316531 via intravenous (IV) administration. Should an effect not be observed at this starting dose, an optional cohort (Cohort 2) of 12 subjects (9 LY:3 Pbo) may be evaluated with a dose not to exceed 2000-mg IV or the highest tolerable and safe dose evaluated in the single-ascending dose Study I9H-MC-FFAA. All subjects will be invited to attend a follow-up assessment of capsaicin-induced blood flow approximately 160 days post treatment administration.

Treatment Arms and Planned Duration for an Individual Subject:
After a screening period up to 28 days, eligible subjects will be randomized to receive the planned single IV dose of

300-mg LY3316531 or Pbo on the morning of Day 1. Subjects will remain in the CRU for up to 32 hours after study drug administration and attend scheduled visits at the CRU for up to160 days to assess DBF and measurements for safety, tolerability, and pharmacokinetics (PK). The decision to implement the optional Cohort 2 will be made after reviewing the change in DBF from baseline (relative to placebo) in subjects of Cohort 1 on Day 10 (Figure FFAB.1). The dose to be administered in Cohort 2 will not exceed 2000-mg IV or the highest tolerable dose determined to be safe in Study FFAA.

Number of Subjects:
Cohort 1 is planned to enroll 16 subjects (12 LY:4 Pbo). Optional Cohort 2 is planned to enroll 12 subjects (9 LY:3 Pbo). It is not planned to replace subjects; however, subjects may be replaced if necessary to meet study objectives or at the discretion of the Sponsor.

Statistical Analysis:

Safety: All investigational product (IP) and related protocol procedure adverse events will be listed and, if the frequency of events allows, safety data will be summarized using descriptive methodology. The incidence of treatment-emergent adverse events and serious adverse events will be presented by severity and by association with treatment as perceived by the investigator. Symptoms reported to occur prior to treatment with the study drug will be distinguished from those reported as new or increased in severity during the trial. Safety parameters that will be assessed include laboratory tests, vital signs, electrocardiogram, body weight, immunogenicity, and infusion reactions.

Pharmacokinetics: PK parameter estimates for LY3316531 will be calculated using standard noncompartmental methods of analysis. The primary parameters for analysis will be maximum observed drug concentration (C_{max}) and AUC of LY3316531. Other noncompartmental parameters, such as half-life, apparent clearance, and apparent volume of distribution may be reported. Mean and individual plasma concentration versus time profiles and individual and summary statistics of PK parameter estimates will be generated. Population PK analysis methods may be utilized if necessary.

Pharmacodynamics: Relationships between LY3316531 exposure and capsaicin-induced DBF (absolute and percentage changes), between LY3316531 exposure and total CGRP plasma levels, and between total CGRP plasma levels and capsaicin-induced DBF (absolute and percentage changes) may be explored using graphical- and model-based approaches. Absolute and percentage change in DBF from baseline over all subjects will be summarized by providing the mean, standard deviation, median, minimum, and maximum for plasma drug concentration for each cohort and overall for each sample day and time combination, and maximum over the entire study. Data may be log-transformed prior to summarizing if necessary. The inter-subject and intra-subject variabilities in human pharmacodynamic (PD) responses may also be assessed if appropriate.

Statistical: PK/PD analyses will be conducted on data from all subjects who receive at least 1 dose of LY3316531 and have evaluable PK. If Cohort 2 is conducted, data from like treatment arms across cohorts will be pooled for the purpose of analysis. Pharmacodynamic parameters, and their change from baseline, will be summarized at each applicable visit using descriptive statistics. No statistical inferences will be made and no control for multiplicity is planned. Additional analyses may be performed.

2. Schedule of Activities

Study Schedule Protocol I9H-MC-FFAB

	Screening	Baseline		Postdose								
Visit No.	**V1**	**V2**		**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**ED**
Study Day	**-28 d from Day -2**	**-1**	**1**	**2**	**10 ± 1 d**	**24 ± 1 d**	**38 ± 2 d**	**52 ± 2 d**	**66 ± 4 d**	**80 ± 4 d**	**120 ± 7 d**	**160 ± 7 d**	
Admission to CRU		X											
Discharge from CRU				X									
Informed consent	X												
Review/confirm I/E criteria	X	X											
Complete medical history	X												
Complete physical examination	X		Predose	X						X			X
Weight	X									X			X
Height	X												
Symptom-directed physical examination			When needed										
Concomitant medications	X		X[a]	X	X	X	X	X	X	X			X
Vital signs (pulse rate, blood pressure, and temperature)[b,c]	X	X	Predose, EOI, 2 h, 6 h, and 12 h after SOI	24 h after SOI	X	X	X	X	X	X			X
Review preexisting conditions/AEs	X		X[a]	X	X	X	X	X	X	X			X
ECGs[c,d]	X		Predose, EOI, and 6 h after SOI	24 h after SOI	X	X		X		X			X
QuantiFERON®-TB Gold test or TST	X												

	Screening	Baseline		Postdose								
Visit No.	**V1**	**V2**		**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**ED**
Study Day	**-28 d from Day -2**	**-1**	**1**	**2**	**10 ± 1 d**	**24 ± 1 d**	**38 ± 2 d**	**52 ± 2 d**	**66 ± 4 d**	**80 ± 4 d**	**120 ± 7 d**	**160 ± 7 d**	
Read TST (if applicable)	X[e]												
Chest X-ray (PA)	X[f]												
HIV/HBV/HCV	X												
Serum chemistry and hematology	X	X		X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X			X	X	X	X	X	X	X	X	X
Ethanol test and urine drug screen	X	X											
Pharmacogenetics (exploratory storage samples for DNA)			Predose										
LY3316531 or placebo administration (IV)			X										
Immunogenicity[g,h]			Predose		X	X				X	X	X	X
LY3316531 concentration (PK)[g,h]			Predose, EOI, 2 h and 6 h after SOI	24 h after SOI	X	X	X	X	X	X	X	X	X
Target engagement assay (total CGRP)			Predose	24 h after SOI	X	X	X	X	X	X	X	X	X
Capsaicin challenge and LDI[i]	X			24-32 h after SOI	X	X	X	X	X	X	X	X	X[j]

Abbreviations: AE = adverse event; CGRP = calcitonin gene-related peptide; CRU = clinical research unit; d = study day; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ED = early discontinuation; EOI = end of infusion; h = hour(s); HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; I/E = inclusion/exclusion; IV = intravenous; LDI = laser Doppler imaging; No. = number; PA = posterior to anterior; PK = pharmacokinetics; SOI = start of infusion; TB = tuberculosis; TST = tuberculin skin test; V = visit.

[a] At the discretion of the CRU, the baseline measurement for this assessment can be collected at any time after subject admission to the CRU up until just prior to LY3316531 or placebo administration on Day 1.

[b] Additional vital sign measurements may be obtained when clinically indicated. Vital signs should be taken following an approximate 5-minute rest in supine position. Temperature measurement is required only at screening and baseline.

[c] ECG, vital sign, and PK sampling should occur at approximately the same time. ECG recording and vital sign measurements should occur prior to the blood draw.

[d] ECG should be taken following an approximate 5-minute rest in supine position. ECGs are requested to be taken at the specified time; however, aberrations to specified recording times will not be considered protocol deviations as long as the ECGs are taken and the actual recording time is documented. All ECGs will be collected as local safety single ECGs.

[e] The follow-up TST reading should occur 2 to 3 days after V1.

[f] Not required if chest X-ray was performed within the last 1 year, found to be normal, and report is available. A lateral chest X-ray may be performed if clinically or radiologically indicated.

[g] Samples are requested to be taken at the specified time; however, aberrations to specified sampling times will not be considered protocol deviations as long as the samples are taken and the actual sampling time is recorded. It is essential that the actual times of doses and samples are recorded accurately on the appropriate forms.

[h] In the event of drug hypersensitivity reactions (immediate or non-immediate), up to 3 additional samples will be collected each for PK and immunogenicity at the following times: 1) as close to the onset of the reaction event as possible, 2) at the resolution of the event, and 3) 30 days following the event.

[i] All subjects will have the capsaicin challenge and LDI procedure (pre-challenge and 30 and 40 minutes post-challenge) during a second screening day, V2, and subsequent postdose visits resulting in up to10 total capsaicin challenges per subject. For each subject, DBF will be measured consistently on the same arm at all study visits.

[j] If a subject discontinues from the study early, capsaicin challenge and LDI measurements may be performed at ED if possible, if deemed appropriate by the investigator, and if the most recent capsaicin challenge and LDI measurements for that subject were conducted 7 or more days prior to the ED visit.

3. Introduction

3.1. Study Rationale

LY3316531 is a humanized bispecific antibody that selectively binds to interleukin-23 (IL-23) and calcitonin gene-related peptide (CGRP). This dual inhibitor is an innovative attempt to target pathways involving IL-23 and CGRP that affect the pathology associated with auto-inflammatory conditions. Each molecule of LY3316531 can bind a maximum of one molecule of IL-23 and one molecule of CGRP.

Study I9H-MC-FFAB (FFAB) is a Phase 1 study being conducted to assess target neutralization of CGRP following a single IV dose of LY3316531 in healthy male subjects via capsaicin-induced dermal blood flow (DBF) as measured using laser Doppler imaging (LDI). LDI is the imaging technique generally used in the capsaicin-induced DBF model and studies with CGRP antagonists.

In addition, the safety, tolerability, and pharmacokinetics (PK) of a single dose of LY3316531 in healthy subjects will be evaluated.

3.2. Background

A typical organ-specific, T-cell-driven inflammatory disease, psoriasis had been considered a T helper (Th) 1-type skin disease for decades until a new Th population, Th17, was identified (Lew et al. 2004; Steinman 2007; Weaver et al. 2007). However, substantial clinical and basic research observations now suggest that the IL-23/Th17 axis is essential in the pathogenesis of psoriasis (Di Cesare et al. 2009). IL-23, a member of the IL-12 family of cytokines, is a heterodimeric protein comprised of 2 subunits; the p40 subunit, which it shares with IL-12, and the p19 subunit, believed to be specific to IL-23. IL-23 is produced by antigen-presenting cells, such as dendritic cells and macrophages, and plays an important role in maintenance and amplification of Th17 cells (Lee et al. 2004; Piskin et al. 2004). In addition, Th17 cells and their downstream effector molecules, including IL-17A, IL-17F, IL-21, IL-22, and tumor necrosis factor alpha (TNF-α), are found at increased levels in human psoriatic skin lesions and circulation (Boniface et al. 2007; Lowes et al. 2008; Caruso et al. 2009; Kagami et al. 2010).

Treatment of psoriasis with biologic therapy, particularly with those agents targeting the IL-23/Th17 axis, has demonstrated clinical activity in patients with psoriasis (Crow 2012). Agents specifically targeting the IL-23 p19 subunit have demonstrated clinical activity in psoriasis (including LY3074828 in Study I6T-MC-AMAA) (Krueger et al. 2015; Papp et al. 2015; Gordon et al. 2015; Kopp et al. 2015; Sofen et al. 2014) and Crohn's disease (Sands et al. 2015).

The calcitonin gene-related peptide (CGRP) is a 37-amino acid neuropeptide member of a family of peptides that includes amylin, adrenomedullin, and calcitonin. The predominant form of CGRP is known as α-CGRP, with a second isoform, β-CGRP, being produced from a separate gene but having high sequence homology (Steenbergh et al. 1985). Both isoforms have similar biological activities, but differ in their expression patterns; α-CGRP is expressed mainly in the peripheral and central nervous system while β-CGRP is expressed mostly in the enteric nervous

system (Mulderry et al. 1988). The CGRP is a potent vasodilator (Brain et al. 1985). While CGRP antagonists seem to restore normal tonus in CGRP-induced dilation of isolated arterial rings, the evidence to date suggests that CGRP antagonists do not alter basal vascular tone (Chaitman et al. 2012; Verheggen et al. 2002). The CGRP has a well-established role in neurogenic inflammation and nociception (Hirsch et al. 2013). It is able to facilitate the production and secretion of numerous pro-inflammatory mediators that lead to hyperemia, edema, and pain in inflamed tissues (Cady et al. 2011). The CGRP pathway may play a specific role in inflammatory skin disorders having direct effects on immune cells (ie, dermal dendritic cells), cytokine production, and itch and pain pathologies in various dermatoses (Lotti et al. 2014; Kashem et al. 2015). Interestingly, CGRP regulates sensory neurons through the IL-23/IL-17 axis as well (Riol-Blanco et al. 2014; Ding et al. 2016). In addition to its involvement in inflammation and nociception, it is believed that CGRP can increase the production of IL-23 (Kashem et al. 2015).

Several nonclinical studies were performed to support the use of LY3316531 in humans. Weekly administration of LY3316531 to cynomolgus monkeys in a general toxicology study resulted in no adverse drug-related findings at doses of 20 or 60 mg/kg (subcutaneous [SC]), or 200 mg/kg (intravenous [IV]) for 3 months. The exposure multiple and dose multiple to the highest human dose, based on this monkey study, are 5× and 28×, respectively. Additionally, a tissue cross-reactivity study was performed with LY3316531 in human and monkey tissues, which produced no toxicologically important difference in tissue binding between the species.

Study I9H-MC-FFAA (FFAA) is an ongoing Phase 1, first-in-human clinical study to explore the safety, tolerability, and PK of single and multiple doses of LY3316531 in healthy subjects and the safety, tolerability, PK, and pharmacodynamics (PD) of a single dose of LY3316531 in patients with psoriasis.

Study FFAB will test the ability of LY3316531 to neutralize CGRP in capsaicin-induced dermal blood flow (DBF). Capsaicin (the active compound in hot peppers) applied to human skin activates nociceptor neurons via the environmental sensor TRPV1 (“Capsaicin Receptor”) and releases inflammatory mediators (Caterina et al. 1997) including CGRP, a potent vasodilator. The inhibition of CGRP can reduce capsaicin-induced DBF as measured using LDI (Van der Schueren et al. 2008). Thus, capsaicin-induced DBF has been used as a CGRP-dependent PD biomarker, with the PD effect measured using LDI (Sinclair et al. 2010; Vermeersch et al. 2015).

LY3316531 is a bispecific antibody that contains the binding regions from the IL-23 monoclonal antibody, LY3074828 (mirikizumab), and the CGRP monoclonal antibody, LY2951742 (galcanezumab). A galcanezumab study (Study CGAA) of capsaicin-induced DBF in healthy subjects following a single dose showed DBF was reduced at all measurements from 3 to 42 days postdose for the 75-, 200-, and 600-mg doses, while doses of 1, 5, and 25 mg showed no effect on DBF (Vermeersch et al. 2015).

3.3. Benefit/Risk Assessment

On the basis of the nonclinical data, LY3316531 is not considered to be a high-uncertainty compound. No drug-related changes occurred in safety pharmacology, immunotoxicology, or

clinical and anatomic pathology assessments as part of the 3-month toxicology study in cynomolgus monkeys. In the clinical and anatomic pathology assessments following the end of the treatment phase, there were no adverse drug-related effects observed in cynomolgus monkeys receiving LY3316531, including at IV or SC injection sites. In a tissue cross-reactivity study examining the binding of LY3316531 to a panel of normal human and cynomolgus monkey tissues, there was low-grade cytoplasmic immunoreactive binding detected in cells of most tissues, including some mutually-exclusive tissues, which was considered not biologically or toxicologically important due to the cytoplasmic pattern of immunoreactivity.

The 2 antibody binding regions in LY3316531 are the same as the respective binding regions in mirikizumab and galcanezumab. Although it is too early in the clinical development of LY3316531 to understand how it will compare to mirikizumab and galcanezumab, clinical exposure, efficacy, and safety for mirikizumab and galcanezumab are briefly summarized as follows.

- For mirikizumab, as of February 2018, 819 clinical trial participants (245 patients with psoriasis, 248 patients with ulcerative colitis, 85 patients with Crohn's disease, and 241 healthy subjects) have been exposed to either placebo or mirikizumab. Mirikizumab single doses ranged from 5 to 1200 mg and multiple doses were up to a maximum of 1000-mg IV and 300-mg SC. Improvement of psoriasis after a single dose of mirikizumab has been observed in the higher-dose cohorts. No dose-related safety or tolerability issues were observed in completed and ongoing clinical pharmacology studies and in the unblinded safety data from the 2 ongoing Phase-2 studies. A total of 1 serious adverse reaction (anaphylaxis) has been reported.

- For galcanezumab, as of November 2017, 3156 clinical trial participants (419 healthy subjects, 2586 patients with migraine, and 151 patients with osteoarthritis) have been exposed to galcanezumab. Galcanezumab single doses ranged from 1 to 600 mg and multiple doses were up to 300 mg. The Phase 3 clinical studies in patients with migraine demonstrated clinically meaningful reductions in migraine headache days and a favorable safety profile that includes a low incidence of serious adverse events (SAEs) and discontinuations due to adverse events (AEs). Treatment-emergent adverse events (TEAEs) were generally mild to moderate. A total of 1 serious adverse reaction (urticaria) has been reported.

Because LY3316531 has been administered only as single doses to relatively few human subjects and only 6 of these subjects were dosed as high as 300 mg (Study FFAA), Study FFAB has been designed to be conducted in accordance with principles outlined in the Guideline on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medicinal Products (EMEA/CHMP/SWP/28367/07 Rev. 1).

No clinically significant adverse events or changes in laboratory safety parameters (hematology, clinical chemistry urinalysis), vital signs, or ECGs occurred in the ongoing Study FFAA. LY3316531 was administered as single IV ascending doses (3, 15, 75 and 300 mg) in a total of 18 healthy male and female subjects (Part A, Cohorts 1 through 4). Safety data from the 300-mg

IV Cohort 4 (6 subjects) in Study FFAA were reviewed and found acceptable for dosing at 300-mg IV in Study FFAB.

Study FFAA has additional cohorts planned for a single 300-mg SC dose and up to 2000-mg IV doses in healthy subjects (Part A) and multiple IV doses in healthy subjects (Part B), with each subject evaluated over a 3-month period. Also planned are a single-dose 300-mg cohort and 2 optional single-dose cohorts (dosage to be determined) in patients with psoriasis (Part C) pending analysis of safety data across all previous cohorts.

Because LY3316531 affects the immune system, there is a potential risk it could reactivate an infection such as tuberculosis (TB) or hepatitis B, and could raise the risk that an infection could become more serious than it otherwise would. This risk will be mitigated by screening potential subjects for TB (using QuantiFERON®-TB Gold test and chest X-ray), hepatitis, and human immunodeficiency virus (HIV); and anyone who tests positive in any of these tests will be excluded from the study.

More information about the known and expected benefits, risks, and reasonably anticipated adverse events (AEs) of LY3316531 can be found in the Investigator's Brochure (IB).

There is no anticipated therapeutic benefit for healthy subjects.

4. Objectives and Endpoints

Table FFAB.4.1 shows the objectives and endpoints of the study.

Table FFAB.4.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess target neutralization of CGRP following a single IV dose of LY3316531 versus placebo in healthy subjects via capsaicin-induced DBF as measured using LDI	Decrease from baseline within 30 days, relative to placebo, in capsaicin-induced DBF (by blocking CGRP) following at least 1 dose level of a single IV dose of LY3316531
Secondary	
To assess the safety and tolerability of a single dose of LY3316531 in healthy subjects	Incidence of adverse events, treatment-emergent adverse events, and serious adverse events
To characterize the PK of LY3316531 following a single dose IV administration in healthy subjects	C_{max} and AUC
Tertiary/Exploratory	
To evaluate the formation of ADA to LY3316531	Presence of ADA against LY3316531
To evaluate the relationship between LY3316531 exposure and total CGRP plasma levels	E_{max} and EC_{50} for relationship between LY3316531 exposure and CGRP plasma level
To evaluate the relationship between LY3316531 exposure and capsaicin-induced DBF	E_{max} and EC_{50} for relationship between LY3316531 exposure and capsaicin-induced DBF
To evaluate the relationship between capsaicin-induced DBF and total CGRP plasma levels	Correlation between capsaicin-induced DBF and total CGRP plasma levels

Abbreviations: ADA = antidrug antibody; AUC = area under the concentration versus time curve; CGRP = calcitonin gene-related peptide; C_{max} = maximum observed drug concentration; DBF = dermal blood flow; E_{max} = maximum effect; EC_{50} = effective concentration of LY3316531 that gives half-maximum effect; IV = intravenous; LDI = laser Doppler imaging; PK = pharmacokinetics.

5. Study Design

5.1. Overall Design

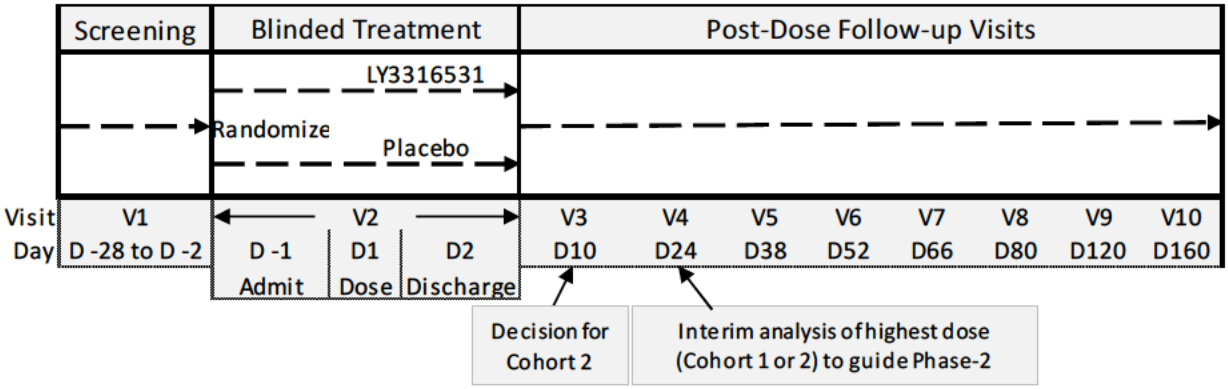
Study FFAB is a Phase 1 single-site, randomized, subject- and investigator-blind, placebo (Pbo)-controlled, parallel-dose group, single-dose study of LY3316531 in healthy subjects.

After a screening period up to 28 days, subjects will be admitted to the clinical research unit (CRU) on Day -1 and will fast overnight. Subjects will receive a single dose of study drug or Pbo on Day 1 and will undergo the study assessments specified in the Schedule of Activities (Section 2). Subjects may be discharged on Day 2, up to 32 hours after dose administration. In case of safety concerns, subjects will be required to stay in the CRU for a longer period at the discretion of the investigator. Subjects will return to the CRU during the postdose follow-up period (Visits 3 through 10) for a total of 8 follow-up visits through Day 160. For each follow-up visit, subjects will attend the CRU to have the capsaicin challenge and LDI measurement performed along with any other scheduled procedures. These visits are specified in the Schedule of Activities (Section 2) and Figure FFAB.1.

The study will evaluate 1 cohort of 16 subjects (12 LY:4 Pbo) with a planned single dose of 300-mg LY3316531 via IV administration. If no treatment effect on DBF is detected in Cohort 1, an optional Cohort 2 (12 subjects; 9 LY:3 Pbo) may be evaluated with a dose not to exceed 2000-mg IV or the highest tolerable dose determined to be safe in the single-ascending dose (SAD) Study FFAA. The decision to implement the optional Cohort 2 will be made if a sufficiently large decrease from baseline, relative to placebo, in capsaicin-induced DBF is not seen with 300 mg (Cohort 1) within 9 days of the dose (on Day 10). Both cohorts will follow the same admission, treatment, and assessment schedule.

Subjects enrolled will be followed for up to 160 days post treatment administration. It is not planned to replace subjects; however, subjects may be replaced if necessary to meet study objectives or at the discretion of the Sponsor.

Study governance considerations are described in detail in Appendix 3.



Abbreviations: D = day; V = visit.

Figure FFAB.1. Protocol I9H-MC-FFAB study design for Cohort 1 and optional Cohort 2.

5.2. Number of Participants

Up to 40 subjects may be screened to enroll 16 subjects in Cohort 1, and up to 30 subjects may be screened to enroll 12 subjects in optional Cohort 2. It is not planned to replace subjects; however, subjects may be replaced if necessary to meet study objectives or at the discretion of the Sponsor. Subjects enrolled will be followed for up to 160 days post treatment administration.

5.3. End of Study Definition

End of the study is the date of the last visit or last scheduled procedure shown in the Schedule of Activities (Section 2) for the last subject.

5.4. Scientific Rationale for Study Design

This study will assess the pharmacodynamic effects of LY3316531 using capsaicin challenge and LDI over 160 days following the single dose. In addition, the PK, safety, and tolerability of a single dose of LY3316531 will be evaluated.

A parallel-group design (drug versus Pbo) was selected based on the expected long half-life of the molecule in humans.

For operational reasons, dosing may be conducted in smaller groups, for example, 4 subjects (3 LY, 1 Pbo) per day.

Subjects will remain in the CRU for up to 32 hours after the single dose of LY3316531 or Pbo at Visit 2 to provide adequate and close safety monitoring and to allow for a 24-hour postdose capsaicin challenge and LDI measurement.

Follow-up visits will occur on Day 10 (Visit 3) and approximately every 14 days thereafter for Visits 4 through 8. Visits 9 and 10 will occur at Day 120 and Day 160, respectively. LDI measurements and follow-up visits will continue up to Day 160 based on the long duration of the PD effect noted in this study (see Schedule of Activities in Section 2).

5.5. Justification for Dose

LY3316531 is a bispecific antibody that contains the binding regions from the IL-23 monoclonal antibody, mirikizumab, and the CGRP monoclonal antibody, galcanezumab. The initial 300-mg dose selected for this study (safety to be confirmed first in Study FFAA) is based on LDI measurements of DBF following galcanezumab administration in human subjects; on PK, safety, and efficacy data available from clinical studies with mirikizumab and galcanezumab; and on PK and safety information for LY3316531 in cynomolgus monkeys.

- **Galcanezumab (CGRP antibody), DBF, and LDI in humans:** following a single dose of galcanezumab in human subjects, capsaicin-induced DBF was reduced at all measurements using LDI from 3 to 42 days post-LY2951742 doses of 75-, 200-, and 600-mg SC, while doses of 1-, 5-, and 25-mg SC showed no effect on DBF (Vermeersch et al. 2015). The 600-mg SC dose appeared to produce maximal effect. Because the primary objective of the current study is to confirm the ability of LY3316531 to neutralize CGRP, a comparably high dose to produce maximal effect was chosen. The effect of 300-mg IV dose of LY3316531 is hypothesized to be similar to that of 600-mg SC dose of galcanezumab on capsaicin-induced DBF, assuming similar PK and in-vivo potency.
- **Mirikizumab and galcanezumab safety in humans:** the highest single doses evaluated for mirikizumab (1200-mg IV) and galcanezumab (600-mg SC) were found safe in healthy subjects.
- **LY3316531 safety in cynomolgus monkeys:** the 300-mg and 2000-mg IV doses are expected to produce area under the concentration versus time curves (AUCs) that are 8.5- and 1.3-fold lower, respectively, than the AUC observed at the no-observed-adverse-effect level dose in toxicology studies in cynomolgus monkeys (Table FFAB.5.2).

If data from the 300-mg IV dose is not sufficient to conclude that LY3316531 was able to reduce CGRP activity, a dose of up to 2000-mg IV or the highest tolerable dose determined to be safe in Study FFAA may be evaluated.

Table FFAB.5.2. Margin of Safety for Intravenous Administration of LY3316531 Based on Administered Dose and Predicted Exposure

	Dose (mg)	Dose (mg/kg)	Dose Multiple[a]	AUC (µg•hr/mL)	AUC Exposure Multiple[a]	C_{max} (µg/mL)	C_{max} Exposure Multiple[a]
Cohort-1 Single Dose[b]	300	6	–	43600	–	180	
Non-Human Primates NOAEL[c]		200 QW	33	371250	8.5	6358	35
Cohort-2 Maximum Dose[b]	2000	40.0		291000		1200	
Non-Human Primates NOAEL[c]		200 QW	5	371250	1.3	6358	5.3

Abbreviations: AUC = area under the plasma concentration versus time curve; C_{max} = maximal observed drug plasma concentration; NOAEL = no-observed-adverse-effect level; PK = pharmacokinetics; QW = once per week.

[a] Dose multiple is the dose in animals/dose in humans based on mg/kg. AUC exposure multiple = mean AUC_{tau} observed after the last dose in monkeys/predicted mean AUC(0-∞) after a single dose in humans. C_{max} exposure multiple = mean C_{max} observed after the last dose in monkeys/predicted mean C_{max} after a single dose in humans.

[b] Body weight of human is based on the lowest permitted body weight (50 kg) for Study FFAB. Human PK parameters were predicted using allometric scaling methods based on data collected following a single dose of LY3316531 in monkeys (Study 8340704).

[c] NOAEL determined in a 3-month repeat-dose toxicity study in monkeys (Study #20108516).

6. Study Population

Eligibility of subjects for the study will be based on the results of screening medical history, physical examination, vital signs, chest x-ray, clinical laboratory tests, and electrocardiogram (ECG).

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, is 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 and/or enrollment:

[1] are overtly healthy males, as determined through medical history and physical examination

[2] agree to either remain abstinent (if this is their preferred and usual lifestyle) or use condoms with spermicide as well as 1 additional highly effective method of contraception or effective method of contraception during the study and for 5 months following the last dose of study drug

[3] are between 18 and 55 years of age, inclusive, at the time of screening

[4] have a body mass index of 18 to 32.0 kg/m^2, inclusive, and a minimum body weight of 50 kg

[5] 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

[6] have venous access sufficient to allow for blood sampling and administration of the investigational product (IP) for IV administration as per the protocol

[7] have suitable skin characteristics for the dermal capsaicin challenge (as determined by clinical-staff judgment) and have demonstrated at least a 100% increase in dermal flow following capsaicin challenge as part of the screening procedures and measured through LDI

[8] are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures

[9] are able and willing to give signed informed consent

6.2. Exclusion Criteria

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

[10] female subjects

[11] are investigative site personnel directly affiliated with this study and their immediate families. Immediate family is defined as a spouse, biological or legal guardian, child, or sibling

[12] are Lilly employees or employees of any third-party organization involved with the study

[13] are currently enrolled in a clinical study involving an IP (active drug or placebo) or any other type of medical research judged not to be scientifically or medically compatible with this study or have received any nonbiologic IP within 30 days or 5 half-lives (whichever is longer) of their initial screening visit

[14] have previously completed or withdrawn from investigating mirikizumab (IL-23 antibody), galcanezumab (CGRP antibody), or LY3316531 (IL-23/CGRP bispecific antibody) and have previously received any of these IPs

[15] have an abnormality in the 12-lead ECG that, in the opinion of the investigator, increases the risks associated with participating in the study including QTc >450 msec (male), history of congenital long QT syndrome or other conduction abnormality

[16] have a history of or current psychiatric disorders

[17] have evidence of clinically significant active infection, fever of 100.5°F (38°C) or above, at baseline (Day 1); however, if deemed appropriate by the investigator because of potential error or other unusual circumstance, re-assessment of laboratory parameters including drug screen, vital signs, and intercurrent illness is allowed once

[18] had any surgical procedure (except for minor surgery requiring local or no anesthesia and without any complications or sequelae) within 12 weeks prior to screening, or any planned surgical procedure scheduled to occur during the study

[19] have received live, attenuated live, or non-live vaccine(s) within 28 days of screening or intend to receive during the study

[20] have a history of multiple or severe allergies or has had an anaphylactic reaction to prescription or nonprescription drugs or food

[21] have a history of allergy to humanized monoclonal antibodies or to the drug excipients, or have clinically significant multiple or severe drug allergies, intolerance to topical corticosteroids, or a history of severe posttreatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, or exfoliative dermatitis)

[22] have had serious, opportunistic, or chronic/recurring infection within 6 months prior to screening. Examples include but are not limited to infections requiring IV antibiotics, hospitalization, or prolonged anti-infective treatment

[23] had any malignancy within the past 5 years except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of recurrence for at least 3 years prior to screening and cervical carcinoma in situ, with no evidence of recurrence within the 5 years prior to baseline

[24] have used cigarettes or other tobacco products within the previous 3 months or will not agree to refrain from use during the study

[25] have used caffeine-containing products and/or alcohol from 24 hours prior to all study visits and during in-clinic stays. At all other times, alcohol consumption and caffeine intake are limited to no more than 2 alcoholic beverages or equivalent (beer [284 mL/10 ounces], wine [125 mL/4 ounces], or distilled spirits [25 mL/1 ounce]) per day and caffeinated beverages will be limited to no more than 2 units per day amounts (1 unit=120 mg of caffeine)

[26] have had strenuous activity within 48 hours prior to admission or will not agree to avoid strenuous activity within 48 hours prior to each visit through the final follow-up visit

[27] are regular users of known drugs of abuse and/or have positive findings on urinary drug tests at screening; OR an average weekly alcohol intake that exceeds 21 units per week OR are unwilling to stop alcohol consumption during study visits/time in the research unit (1 unit of alcohol = 12 oz or 360 mL of beer; 5 oz or 150 mL of wine; 1.5 oz or 45 mL of distilled spirits)

[28] have donated blood of more than 500 mL within the previous 30 days of study screening

[29] show evidence of active or latent TB, as documented through medical history and examination, chest x-rays (posterior to anterior; a lateral chest X-ray may be performed if clinically or radiologically indicated), and TB testing: either a positive tuberculin skin test (TST; defined as a skin induration >5 mm at 48 to 72 hours, regardless of Bacillus Calmette–Guérin or other vaccination history) or a positive (not indeterminate) QuantiFERON-TB Gold test. In the event of an indeterminate test result, 1 repeat test is allowed. The choice to perform a TST or a QuantiFERON-TB Gold test will be made by the investigator according to local licensing and standard of care. The QuantiFERON-TB Gold test can only be used in countries where it is licensed, and the use of this test is dependent on previous treatment(s). This test may not be suitable if previous treatment(s) produce significant immunosuppression

[30] are immunocompromised

[31] have a history or current cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk when taking the IP; or of interfering with the interpretation of data

[32] intend to use herbal, over-the-counter, or prescription medication within 14 days prior to dosing and during the study. Certain medications, for example vitamin supplements, may be permitted at the discretion of the investigator

[33] 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

[34] have an abnormal blood pressure, pulse rate, and/or temperature as determined by the investigator

[35] have evidence of chronic viral infection:

[35a] show evidence of hepatitis C and/or positive hepatitis C antibody with confirmed presence of hepatitis C virus ribonucleic acid at screening.

[35b] show evidence of hepatitis B and/or positive hepatitis B surface antigen at screening

[35c] show evidence of HIV infection and/or positive for HIV antibodies at screening

[35d] have had symptomatic herpes zoster within 3 months prior to screening that constitutes (per investigator's judgment) a risk to the subject when taking the study medication or that may interfere with the interpretation of study data

[36] have a history of significant allergies, in particular to ethanol or sensitivity to the fruits of capsicum plants (for example, chili peppers)

[37] have eczema, scleroderma, psoriasis, dermatitis, keloids, tumors, ulcers, burns, flaps, or grafts on their forearm or other abnormality of the skin that may interfere with the study assessments

[38] cannot avoid excess tanning (any exposure to sunlight or a tanning bed that would cause a sunburn reaction) throughout the study and cannot cover forearms for 24 hours prior to each treatment period

[39] have excessive hair growth on the volar surface of the forearm or subjects currently using lotions, oils, depilatory preparations, or other topical treatments on a regular basis that cannot be discontinued for the duration of the study; subject has used any topical treatments within 7 days of the start of the study

[40] in the opinion of the investigator or sponsor, are unsuitable for inclusion in the study

6.2.1. Rationale for Exclusion of Certain Study Candidates

The safety, tolerability, and PK of LY3316531 are being assessed in female subjects as part of Study FFAA. As Study FFAB is focused only on the ability of LY3316531 to neutralize CGRP, the evaluation specifically in female subjects is not needed. Female subjects are being excluded from Study FFAB to avoid the demonstrated hormone-dependent variations in CGRP-mediated DBF previously found in healthy females (Ibrahimi et al. 2017).

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 should not eat after midnight during the night before study drug administration. Water is permitted. Subjects may eat breakfast approximately 2 hours postdose. A normal diet may be consumed at all other times during the study.

6.3.2. Caffeine, Alcohol, and Tobacco

6.3.2.1. Caffeine and Alcohol

The use of caffeine-containing products and/or alcohol is not allowed from 24 hours prior to all study visits and during in-clinic stays. At all other times, alcohol consumption is limited to no more than 2 alcoholic beverages or equivalent (beer [284 mL/10 ounces], wine [125 mL/4 ounces], or distilled spirits [25 mL/1 ounce]) per day and caffeinated beverages will be limited to no more than 2 units (1 unit = 120 mg of caffeine) per day.

6.3.2.2. Tobacco

Subjects will be excluded if they have used cigarettes or other tobacco products within 3 months prior to the start of this study.

6.3.3. Activity

Strenuous activity is not allowed within 48 hours prior to admission on Day -1 and 48 hours prior to each visit.

6.3.4. Contraception

All subjects and their partners should agree to use a reliable method of birth control during the study and for 5 months following dosing of the study drug (see Inclusion Criterion [2]).

6.4. Screen Failures

Healthy subjects who do not meet the criteria for participation in this study (screen failure) may not be re-screened. However, if, for example, a subject had an intercurrent illness around the time of initial screening or there are issues with the quality of the laboratory safety samples (eg, hemolysis), re-assessment of laboratory parameters including drug screen and vital signs will be allowed.

In addition, participants who were eligible for inclusion in previous cohorts, but were not randomized for nonmedical reasons, may be reassessed, following a discussion with the sponsor.

7. Treatment

7.1. Treatment Administered

LY3316531 is supplied for clinical trial use as solution formulation in glass vials. Further dilution may be needed for IV administration. See Pharmacy Instructions for more information.

Placebo will be sterile saline (0.9% NaCl). Placebo doses should be held in the pharmacy for an equivalent amount of time as is required to prepare doses of LY3316531.

The IP will be administered as a slow IV infusion over at least 30 minutes. Sites must have resuscitation equipment, emergency drugs, and appropriately trained staff available during the infusion and for at least 6 hours after subjects have completed receiving their infusion.

All clinical trial materials provided to the investigator will be stored in a secure place, assigned using the interactive web response system, and dispensed by appropriately trained persons. The dispensing of the IPs will be fully documented. Detailed records of the amounts of the IP received, dispensed, and remaining at the end of the study will be maintained.

The investigator or designee is responsible for

- explaining the correct use of the IP(s) to the site personnel
- verifying that instructions are followed properly
- maintaining accurate records of dispensing and collecting IP, and
- returning all unused IP 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.

The products for the capsaicin and the vehicle solutions required for the capsaicin-induced DBF assessment will be supplied by the investigative site. Pharmacy instructions for the preparation of these capsaicin and vehicle solutions will be provided by the investigative site.

7.1.1. Packaging and Labeling

LY3316531 and Pbo will be supplied to the investigative site by Lilly or its designee in accordance with current good manufacturing practices, and will be supplied with lot numbers, expiry dates, and certificates of analysis, as applicable.

Clinical trial materials will be labeled according to the country's regulatory requirements. All IPs will be stored, inventoried, reconciled, and destroyed according to applicable regulations. Clinical trial materials are manufactured in accordance with current good manufacturing practices.

LY3316531 is supplied for clinical trial use as solution in vial with study-specific labels. The 2-mL vial is manufactured to contain 150 mg of LY3316531 (75 mg/mL). Vials will be supplied in cartons, with the appropriate quantity specific to the planned dispensing schedule of the IP.

Placebo for all cohorts is 0.9% sodium chloride (sterile saline).

When prepared for dosing according to instructions, it will not be possible to distinguish between LY3316531 and Pbo.

The IP must be prepared by an unblinded pharmacist who is not involved in any other study-related procedures.

7.2. Method of Treatment Assignment

Randomization tables for allocation of LY3316531 or Pbo will be prepared by the statistician or designee for the study and provided to the site pharmacists involved in dose preparation.
The allocation and dispensation of the IP will be fully documented and verified by a second person. Detailed records of the amounts of the IP received, dispensed, and remained at the end of the study will be maintained by the site pharmacy.

7.2.1. Selection and Timing of Doses

The dose in Cohort 1 will be 300 mg of LY3316531 administered through IV infusion. The actual time of the single dose administered to each subject will be determined by the site and recorded in each subject's case report form (CRF).

A decision to implement the optional Cohort 2 will be made if a statistically significant decrease in capsaicin-induced DBF (relative to placebo) is not seen with 300 mg (Cohort 1) within 9 days of the dose (Day 10). If Cohort 2 is conducted, the single dose not to exceed 2000 mg or the highest tolerable dose determined to be safe in Study FFAA will be administered through IV infusion over the same time period as used in Cohort 1.

7.3. Blinding

Study FFAB will be subject- and investigator-blind. Pharmacy staff who prepare and dispense study medication are required to be unblinded to treatment allocation and are not allowed to participate in any other procedure of this study. Subject treatment assignments and drug accountability records will be held in a secure location accessible only by individuals involved with study drug preparation or dispensation. Blinding will be maintained throughout the conduct of the study as described in the separate Blinding Plan.

In case of an emergency, appropriate site personnel per the site's standard operating procedure have 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.

Upon completion of the study, all codes must be returned to Lilly or its designee.

7.4. Dose Modification

7.4.1. Special Treatment Considerations

7.4.1.1. Management of Infusion Reactions

Infusion-related reaction (IRR) is a risk with any biological agent; therefore, all subjects should be monitored closely for IRR. Symptoms and signs that may occur as part of an IRR 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 IRR occurs, the following guidance should be followed:

- The infusion should be slowed (for example, reduce infusion rate by 50% [for example, an infusion rate of 12 mL/hour becomes 6 mL/hour or slower]) or stopped, depending on the symptoms/signs present:
    - 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 should be employed in accordance with the symptoms/signs
- Premedication for the infusions is not planned. However, if an IRR occurs in previously-dosed subjects, appropriate pre-medication (for example, acetaminophen 500 to 1000 mg and/or an antihistamine administered orally 30 to 60 minutes prior to the start of infusion) may be administered to subsequently-dose subjects as determined by the study investigator(s). The decision to premedicate for infusions will be made by the investigator and sponsor and recorded in the study documentation. Any premedications given will be documented as a concomitant therapy (see Section 7.7).

7.5. Preparation/Handling/Storage/Accountability

LY3316531 vials should be stored at 2°C to 8°C (36°F to 46°F) in the original carton to protect it from light. LY3316531 vials should not be frozen.

Sterile saline vials (0.9% sodium chloride) should be stored at room temperature (15°C to 25°C [59°F to 77°F]). The investigator or designee must confirm appropriate temperature conditions have been maintained, as communicated by Sponsor, during transit for all IPs received and any discrepancies are reported and resolved before use of the study treatment.

All clinical trial materials provided to the investigator will be stored in a secure place and allocated and dispensed by appropriately trained personnel. The allocation and dispensation of the IP will be fully documented and verified by a second person. Detailed records of the amounts of the IP received, dispensed, and remaining at the end of the study will be maintained.

Only participants enrolled in the study may receive IPs or study materials, and only authorized site staff may supply or administer IP. All IPs 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.

Detailed instructions for the preparation and handling of LY3316531 will be provided by the sponsor.

The IP must be prepared by an unblinded pharmacist who is not involved in any other study related procedures.

All IPs will be stored, inventoried, reconciled, and destroyed according to applicable regulations. Clinical trial materials are manufactured in accordance with current good manufacturing practices.

Detailed records of the amounts of the IP received, dispensed, and remained at the end of the study will be maintained by the site pharmacy.

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).

The investigative site will be responsible for obtaining United States Pharmacopeia (USP) and The National Formulary-grade capsaicin, performing analysis to demonstrate compliance with USP, and handling and storing the capsaicin powder in accordance with the manufacturer instructions. The site will be responsible for preparing, handling, and storing the capsaicin solution to be used in the capsaicin challenges in accordance with the manufacturer instructions.

7.6. Treatment Compliance

The IP will be administered at the clinical site, and documentation of treatment administration will occur at the site.

7.7. Concomitant Therapy

In general, concomitant medication should be avoided unless required to treat an AE.

The use of chronic, stable doses of thyroxine is allowed. The use of multivitamins and vitamin C is allowed until 2 days prior to entrance into the CRU. The use of acetaminophen (paracetamol), up to 2 grams per day, is allowed up to 3 days before entrance into the CRU. Thereafter and during the study the investigator may permit a limited amount of acetaminophen for the treatment of headache or any other pain.

Other medication to treat AEs will be prescribed according to the circumstances and guided by the investigator's judgment. If the need for concomitant medication (other than acetaminophen) arises, inclusion or continuation of the subject will be at the discretion of the investigator and Lilly clinical pharmacologist or CRP. In the event medication is used, the name of the drug, the dose and dosage regimen will be recorded in the CRF.

7.8. Treatment after the End of the Study

This section is not applicable to this study.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

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, the subject must be discontinued from the study.

8.2. Discontinuation from the Study

Subjects will be discontinued in the following circumstances:

- Enrollment in any other clinical study involving an IP or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- Participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- Investigator Decision
    - the investigator decides that the 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, or legal representative, requests to be withdrawn from the study.
- Sponsor Decision
    - Lilly stops the study or stops the subject's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP
- Adverse event
    - A clinically significant systemic hypersensitivity reaction occurs following administration of the IP (for example, drug-related symptomatic bronchospasm, allergy-related edema/angioedema, or hypotension) that requires parenteral medication, does not respond to symptomatic medication, or results in clinical sequelae or an anaphylactic reaction.

The nature of any conditions, clinical signs or symptoms, or abnormal laboratory values present at the time of discontinuation and any applicable follow-up procedures will be documented.

Refer to the Schedule of Activities (Section 2) for data to be collected at the time of discontinuation and follow-up.

8.3. Subjects Lost to Follow-up

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

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.

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

This section is not applicable for this study.

9.2. Adverse Events

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 subjects 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 IP or the study, or that caused the subject to discontinue the IP 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, study site personnel will record, via electronic case report form (eCRF), 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.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment or a study procedure, taking into account the disease, concomitant treatment or pathologies.

A "reasonable possibility" means that there is a potential cause and effect relationship between the IP, study device and/or study procedure and the AE.

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

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 patient or may require intervention to prevent one of the other outcomes listed in the definition above.

Study site personnel must alert the Lilly CRP/clinical pharmacologist, or its designee, of any SAE as soon as practically possible.

Additionally, study site 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.

Investigators are not obligated to follow subjects for AEs or SAEs once they have discontinued from and/or completed the study (the subject summary CRF has been completed). 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 IP) does not meet the definition of an AE. 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.

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 IP or procedure. 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 guidances.

9.2.2. Complaint Handling

Lilly collects product complaints on IPs and drug delivery systems 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 has a complaint or problem with the IP so that the situation can be assessed.

9.3. Treatment of Overdose

For the purposes of this study, an overdose of LY3316531 is considered any dose higher than the dose assigned through randomization.

Refer to the IB (LY3316531).

9.4. Safety

9.4.1. 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.

9.4.2. Vital Signs

For each subject, vital sign measurements should be conducted according to the Schedule of Activities (Section 2) and as clinically indicated.

Blood pressure and pulse rate should be measured after at least 5 minutes supine (or semi-recumbent if subject is unable to lie supine).

If orthostatic measurements are required, subjects should be supine for at least 5 minutes and subsequently stand for at least 3 minutes.

If the subject feels unable to stand, only supine vital signs 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.

Body temperature will be measured as specified in the Schedule of Activities (Section 2) and as clinically indicated.

Body weight will be recorded as specified in the Schedule of Activities (Section 2) and as clinically indicated.

9.4.3. Electrocardiograms

For each subject, ECGs should be collected according to the Schedule of Activities (Section 2) and as clinically indicated.

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

For each subject, a single 12-lead digital ECG will be collected according to the Schedule of Activities. 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. Electrocardiograms may be obtained at additional times, when deemed clinically necessary. All ECGs recorded should be stored at the investigative site.

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 visit(s) and for immediate subject management, should any clinically relevant findings be identified.

If a clinically significant finding is identified (including, but not limited to, changes in QT/corrected QT interval from baseline) after enrollment, the investigator will determine if 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 review of the ECG printed at the time of collection. Any new clinically relevant finding should be reported as an AE.

9.4.4. Safety Monitoring

The Lilly clinical pharmacologist or CRP/scientist will monitor safety data throughout the course of the study.

Lilly will review SAEs within time frames mandated by company procedures. The Lilly clinical pharmacologist or CRP will periodically review the following data:

- trends in safety data
- laboratory analytes
- adverse events including monitoring of incidence and nature of any infections, and infusion reactions.

When appropriate, the Lilly clinical pharmacologist or CRP will consult with the functionally independent Global Patient Safety therapeutic area physician or clinical research scientist.

9.4.4.1. 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, and creatine phosphokinase 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 clinical pharmacologist or CRP. 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 2 or more consecutive blood tests
- elevation of 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 an SAE.

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples of approximately 5 mL each will be collected to determine the serum concentrations of LY3316531. A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

Drug concentration information that may unblind the study will not be reported to the investigative site or blinded personnel until the study has been unblinded.

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 LY3316531 will be assayed using a validated enzyme-linked immunosorbent assay method. Analyses of samples collected from subjects who received Pbo are not planned.

Bioanalytical samples collected to measure study drug concentrations will be retained for a maximum of 1 year following last subject visit for the study. During this time, samples remaining after the bioanalyses may be used for exploratory metabolism studies or exploratory analyses such as bioanalytical assay validation or cross-validation exercises.

9.6. Pharmacodynamics

9.6.1. Total CGRP

Target engagement for the CGRP part of the molecule will be assessed by measuring total CGRP concentrations before and after LY3316531 or Pbo administration. CGRP concentration is expected to increase with target engagement as CGRP is bound to LY3316531 and takes on the longer half-life of the antibody.

At visits specified in the Schedule of Activities, venous blood samples of approximately 2 mL each will be collected for measurement of total plasma CGRP concentration. Samples for CGRP measurements will be analyzed in a validated assay at a laboratory approved by the sponsor and stored at a facility designated by the sponsor.

The sample(s) will be stored for up to a maximum of 15 years after the last subject visit for the study at a facility selected by the sponsor.

9.6.2. Measurement of Dermal Blood Flow

Capsaicin-induced DBF will be measured at visits specified in the Schedule of Activities. All measurements for assessment of capsaicin-induced response should be performed while the subjects are resting in a supine position on a comfortable bed in a quiet, temperature-controlled room (ambient temperature).

During each visit (screening and study periods), after at least 30 minutes acclimatization, 3 rubber O-rings will be placed on the volar surface of the forearm. After placement of the O-rings, a baseline DBF measurement will be performed of the areas defined by the rings within 10 minutes before capsaicin application. DBF will be measured with LDI (PeriScan PIM 3 system, Perimed, Stockholm, Sweden). After the baseline measurement, 2 topical doses of 20 µL capsaicin (1000 µg/20 µL) will be applied in the 2 proximal O-rings of the subject's forearm. A 20 µL topical dose of the vehicle solution will be applied in the distal ring. LDI measurements will again be performed at 30 and 40 minutes after the capsaicin and vehicle application. For each subject, DBF will be measured consistently on the same arm at all study visits.

A detailed description of the procedure will be provided by the investigator.

9.6.3. Immunogenicity Assessments

At the visits and times specified in the Schedule of Activities, venous blood samples will be collected to determine antibody production against LY3316531. To interpret the results of immunogenicity, a PK sample will be collected at the same time points. All samples for immunogenicity should be taken predose on Day 1 and pre-capsaicin challenge at each postdose follow-up visit. In the event of drug hypersensitivity reactions (immediate or nonimmediate), additional samples will be collected as close to the onset of the event as possible, at the resolution of the event, and approximately 30 days following the event. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

Immunogenicity will be assessed by a validated assay designed to detect antidrug antibodies (ADAs) in the presence of LY3316531 at a laboratory approved by the sponsor. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of LY3316531.

Treatment-emergent ADAs are defined in Section 10.3.5. If the immunogenicity titer at the last scheduled assessment or discontinuation visit is increasing (compared to previous measurements) or remains high, additional samples may be collected (approximately every 3 months for up to 1 year after Day 160) until the titer reaches a plateau/decreases (if increasing) or remains the same/decreases (if high). A PK sample will be collected at each time point. Additional samples may also be collected if there is a possibility that an AE is immunologically mediated.

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 LY3316531. Any samples remaining after 15 years will be destroyed.

9.7. Genetics

A blood sample will be collected for pharmacogenetic analysis as specified in the Schedule of Activities, 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 potential reasons for variable exposure or response to LY3316531 and to investigate genetic variants thought to play a role in inflammatory diseases. 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 ERBs/institutional review boards impose shorter time limits, for the study 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 LY3316531 or after LY3316531 is commercially available.

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

This section is not applicable for this study.

9.9. Health Economics

This section is not applicable for this study.

10. Statistical Considerations and Data Analysis

10.1. Sample Size Determination

The choice of sample size was based on the statistical power to meet the primary endpoint for a single cohort. CCI [redacted]

CCI [redacted] A 1-sided significance level of $\alpha = 0.10$ and a standard deviation of 1.322 are assumed. CCI [redacted] A 2-sample t-test with unpooled variance estimates (using Satterthwaite's approximation to the degrees of freedom) is used to compute the power CCI [redacted] CCI [redacted]

CCI [redacted]

Statistical power may be increased for the LY3316531 dose used in Cohort 1 if a like dose is used in the optional Cohort 2 and the data are combined across cohorts.

In addition to statistical power, 12 LY and 4 Pbo subjects were chosen to be enrolled in Cohort 1 and 9 LY and 3 Pbo subjects were chosen to be enrolled in the optional Cohort 2 for operational reasons and to ensure a satisfactory number of evaluable subjects, reducing the need to replace subjects.

CCI

CCI

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 reported. If known, a reason for their discontinuation will be given. A disposition table for all enrolled subjects will be provided.

10.2.2. Study Participant Characteristics

The subject's age, sex, weight, height, racial designation, or other demographic and study disease characteristics will be recorded and summarized.

10.3. Statistical Analyses

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

Pharmacokinetic/Pharmacodynamic analyses will be conducted on data from all subjects who receive a dose of LY3316531 and have evaluable PK, total CGRP, or LDI data.

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

All protocol deviations that occur during the study will be considered for their severity and impact, and will be taken into consideration when subjects are assigned to analysis populations prior to database lock and unblinding. Details of subject assignment to the analysis populations will be listed.

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.

10.3.1. Safety Analyses

10.3.1.1. Clinical Evaluation of Safety

All IP and protocol procedure AEs will be listed, and if the frequency of events allows, safety data will be summarized using descriptive methodology.

The incidence of symptoms for each treatment will be presented by severity and by association with IP as perceived by the investigator. Symptoms reported to occur prior to treatment with the study drug will be distinguished from those reported as new or increased in severity during the study. Each symptom will be classified by the most suitable term from the medical regulatory dictionary.

The number of IP-related SAEs will be reported and summarized by preferred term.

10.3.1.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include safety laboratory parameters, vital signs, and ECG parameters. The parameters will be listed, and summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data. Baseline for safety parameters will be defined as the last evaluable value before the first dose for each subject.

10.3.2. Pharmacokinetic Analyses

10.3.2.1. Pharmacokinetic Parameter Estimation

Pharmacokinetic parameter estimates for LY3316531 will be calculated using standard noncompartmental methods of analysis.

The primary parameters for analysis will be maximum observed drug concentration (C_{max}) and AUC of LY3316531. Other noncompartmental parameters, such as half-life, clearance, and

volume of distribution may be reported. Mean and individual plasma concentration versus time profiles and individual and summary statistics of PK parameter estimates will be generated.

Population-based methods of analyses may also be performed.

10.3.3. Pharmacodynamic Analyses

Raw DBF, capsaicin-induced changes from baseline in DBF (both absolute and percentage changes) relative to Pbo, and plasma CGRP concentrations will be measured. Descriptive statistics will summarize these quantities at each dose administered. Additional exploratory analyses may be conducted as deemed appropriate.

10.3.4. Pharmacokinetic/Pharmacodynamic Analyses

Analyses of the relationship between LY3316531 exposure and total CGRP plasma concentrations and DBF will be conducted using graphical- and model-based approaches. Additional exploratory analyses may be performed if warranted by the data.

10.3.5. Evaluation of Immunogenicity

The frequency and percentage of subjects with preexisting ADA and/or with treatment-emergent (TE) ADA to LY3316531 will be tabulated. For subjects who are ADA negative at baseline, TE ADAs are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution of the assay. For subjects who are ADA positive at baseline, TE ADAs are defined as those with a 4-fold (2 dilutions) increase in titer compared to baseline. For subjects with TE ADA, the distribution of maximum titers will be described. The frequency and percentage of subjects with neutralizing antibodies, if measured, may also be tabulated for subjects with TE ADA.

The relationship between the presence of antibodies and the PK parameters and PD response, including safety related to LY3316531, may be assessed.

10.3.6. Data Review During Cohort 1

Available safety and LDI data through 9 days postdose (Day 10) of Cohort 1 will be reviewed to determine if the optional Cohort 2 will be implemented. The minimum number of evaluable subjects needed for this decision to advance to a higher dose will be 9 LY and 3 Pbo. The decision to implement the optional Cohort 2 will be made if a sufficiently large decrease from baseline, relative to placebo, in capsaicin-induced DBF is not seen in Cohort 1 with 300 mg through 9 days postdose (Day 10 data review) or within 23 days postdose (Day 24 interim analyses). The dose to be administered in Cohort 2 will not exceed 2000-mg IV or the highest tolerable dose determined to be safe in Study FFAA. The investigator will remain blinded, and the Lilly sponsor team will be unblinded during these reviews.

10.3.7. Interim Analyses

A single interim analysis that includes all safety and LDI data, and may include PK data, through 23 days postdose (Day 24) will inform the decision to proceed to Phase 2. The interim analysis

will be based on the highest dose level evaluated (either Cohort 1 or optional Cohort 2, if implemented).

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Appendix 1. Abbreviations and Definitions

Term	Definition
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.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AUC	area under the concentration versus time curve
blinding	A procedure in which 1 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
CGRP	calcitonin gene-related peptide
C_{max}	maximum observed 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.
compliance	Adherence to all the study-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
CRF	case report form
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CRU	clinical research unit
DBF	dermal blood flow
ECG	electrocardiogram
eCRF	electronic case report form

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.
ERB	ethical review board
GCP	good clinical practice
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IL	interleukin
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.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product (IP)	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
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
LDI	laser Doppler imaging
legal representative	An individual or judicial or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study.
Pbo	Placebo
PK/PD	pharmacokinetic(s)/pharmacodynamic(s)
QTcF	corrected QT interval by Fridericia's formula
randomize	the process of assigning subjects/patients to an experimental group on a random basis
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.
SUSARs	suspected unexpected serious adverse reactions
TB	tuberculosis
TBL	total bilirubin
TE	treatment-emergent
Th	T helper
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
TST	tuberculin skin test
ULN	upper limit of normal
USP	United States Pharmacopeia and The National Formulary

Appendix 2. Clinical Laboratory Tests

Safety Laboratory Tests

Hematology
- Hematocrit
- Hemoglobin
- Erythrocyte count (RBC)
- Mean cell volume
- Mean cell hemoglobin
- Mean cell hemoglobin concentration
- Leukocytes (WBC)
- Platelets

Absolute counts of:
- Neutrophils
- Lymphocytes
- Monocytes
- Eosinophils
- Basophils

Urinalysis
- Specific gravity
- pH
- Protein
- Glucose
- Ketones
- Bilirubin
- Urobilinogen
- Blood
- Nitrite
- Microscopy[d]

Clinical Chemistry
- Sodium
- Potassium
- Bicarbonate
- Chloride
- Calcium
- Phosphorus
- Glucose, random
- Urea
- Total protein
- Albumin
- Total bilirubin
- Alkaline phosphatase (ALP)
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Creatinine
- Gamma-glutamyl transferase (GGT)

Serology
- Hepatitis B surface antigen[a]
- Hepatitis C antibody[a,b]
- HIV[a]

Other
- Ethanol test[c]
- Urine drug screen[c]
- The QuantiFERON-TB Gold test or TST[a]
- Immunogenicity (anti-LY3316531 antibodies)

Abbreviations: HIV = human immunodeficiency virus; RBC = red blood cell; TST = tuberculin skin test; WBC = white blood cell.

[a] Performed at screening only

[b] A positive hepatitis C antibody laboratory assessment will be confirmed with a test for hepatitis C virus (HCV) ribonucleic acid (RNA).

[c] Ethanol test and urine drug screen will be performed at screening and repeated prior to admission to the clinical research unit (Day -1), and when clinically indicated.

[d] Performed if Dipstick test abnormal or at discretion of investigator

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 or legal representative. 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 IP.
- 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 study subjects. Individual investigators may have additional local requirements or processes. Study-specific recruitment material should be approved by Lilly.

Ethical Review

The investigator or appropriate local representative must give assurance that the ERB was properly constituted and convened as required by International Council for Harmonisation (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 investigative site(s). Lilly or its representatives must approve the ICF before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on GCP.

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

- the current IB and updates during the course of the study
- 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 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.

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

Final Report Signature

The investigator or designee will sign the clinical study report for this study, indicating agreement with the analyses, results, and conclusions of the report.

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 study sites, 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 study site.
- be available for consultation and stay in contact with the study site 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 study site. 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/patient personal information collected will be provided in a written document to the subject/patient 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 or its designee CRP.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin time
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
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Conjugated bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody**
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 cell; WBC = white blood cell.

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 I9H-MC-FFAB Sampling Summary

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	30	1	30
Clinical laboratory tests[a]	12.5	10	125
Pharmacokinetics	5	13	65
Blood discard for cannula patency	2	5	10
Pharmacodynamics (total CGRP)	2	10	20
Immunogenicity	7.5	8	60
Pharmacogenetics	6	1	6
Total			316
Total for clinical purposes (rounded up to the nearest 10 mL)			320

[a] Additional samples may be drawn if needed for safety purposes.

Appendix 6. Protocol Amendment I9H-MC-FFAB(c) Summary
A Phase 1 Randomized, Placebo-Controlled Study to Determine the Effect of LY3316531 on Capsaicin-Induced Dermal Blood Flow in Healthy Male Subjects

Overview

Protocol I9H-MC-FFAB, A Phase 1 Randomized, Placebo-Controlled Study to Determine the Effect of LY3316531 on Capsaicin-Induced Dermal Blood Flow in Healthy Male Subjects, has been amended. 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:

- Assessments will be performed for all subjects on Day 160 (visit 10) as emerging data from Day 120 assessments showed that many subjects continued to show inhibition of capsaicin induced blood flow.

Revised Protocol Sections

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

1. Protocol Synopsis

Summary of Study Design:

Study I9H-MC-FFAB is a Phase 1 single-site, randomized, subject- and investigator-blind, placebo (Pbo)-controlled, parallel-dose group, single-dose study of LY3316531 (LY) in healthy male subjects. The study will evaluate 1 cohort (Cohort 1) of 16 subjects (12 LY:4 Pbo) with a planned single dose of 300-mg LY3316531 via intravenous (IV) administration. Should an effect not be observed at this starting dose, an optional cohort (Cohort 2) of 12 subjects (9 LY:3 Pbo) may be evaluated with a dose not to exceed 2000-mg IV or the highest tolerable and safe dose evaluated in the single-ascending dose Study I9H-MC-FFAA. ~~S~~All subjects will be invited to attend a follow~~ed for~~-up assessment of capsaicin-induced blood flow approximately~~to~~ 160 days post treatment administration. ~~Assessments at Day 160 will be performed only in subjects with significant inhibition of capsaicin-induced blood flow at Day 120. Significant inhibition of capsaicin-induced blood flow is defined as an individual decrease (within a subject) of 50% ± 10% or more compared to the screening response to capsaicin (i.e. response to capsaicin at screening (pre-administration) versus response on Day 120).~~

2. Schedule of Activities

	Screening	Baseline			Postdose								
Visit No.	**V1**	**V2**			**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10~~*~~**	**ED**
Study Day	**-28 d from Day -2**	**-1**	**1**	**2**	**10 ± 1 d**	**24 ± 1 d**	**38 ± 2 d**	**52 ± 2 d**	**66 ± 4 d**	**80 ± 4 d**	**120 ± 7 d**	**160 ± 7 d**	

[…]

Abbreviations:…

~~* This visit will only be performed in subjects with significant inhibition of capsaicin-induced blood flow at Visit 9, as defined in Section 5.1.~~

[…]

5.1. Overall Design

Study FFAB is a Phase 1 single-site, randomized, subject- and investigator-blind, placebo (Pbo)-controlled, parallel-dose group, single-dose study of LY3316531 in healthy subjects.

After a screening period up to 28 days, subjects will be admitted to the clinical research unit (CRU) on Day -1 and will fast overnight. Subjects will receive a single dose of study drug or Pbo on Day 1 and will undergo the study assessments specified in the Schedule of Activities

(Section 2). Subjects may be discharged on Day 2, up to 32 hours after dose administration. In case of safety concerns, subjects will be required to stay in the CRU for a longer period at the discretion of the investigator. Subjects will return to the CRU during the postdose follow-up period (Visits 3 through 10~~9~~) for a total of 8~~7~~ follow-up visits through Day 160~~120., with an additional visit on Day 160 if required for subjects with significant inhibition of capsaicin-induced blood flow at Day 120. Significant inhibition of capsaicin-induced blood flow is defined as an individual decrease (within a subject) of 50% ± 10% or more compared to the screening response to capsaicin (i.e. response to capsaicin at screening (pre-administration) versus response on Day 120).~~ For each follow-up visit, subjects will attend the CRU to have the capsaicin challenge and LDI measurement performed along with any other scheduled procedures. These visits are specified in the Schedule of Activities (Section 2) and Figure FFAB.1.

[…]

Subjects enrolled will be followed for up to160 days post treatment administration. ~~Assessments at Day 160 will be performed only in subjects with significant inhibition of capsaicin-induced blood flow at Day 120, as defined above.~~ It is not planned to replace subjects; however, subjects may be replaced if necessary to meet study objectives or at the discretion of the Sponsor.

5.4. Scientific Rationale for Study Design

This study will assess the pharmacodynamic effects of LY3316531 using capsaicin challenge and LDI over 160~~120~~ days following the single dose. ~~An additional LDI measurement may be performed on Day 160, depending on emerging data, in subjects with significant inhibition of capsaicin-induced blood flow as defined in Section 5.1.~~ In addition, the PK, safety, and tolerability of a single dose of LY3316531 will be evaluated.

9.6.3 Immunogenicity Assessments

[…]

Treatment-emergent ADAs are defined in Section 10.3.5. If the immunogenicity titer at the last scheduled assessment or discontinuation visit is increasing (compared to previous measurements) or remains high, additional samples may be collected (approximately every 3 months for up to 1 year after ~~Day 120/~~Day 160) until the titer reaches a plateau/decreases (if increasing) or remains the same/decreases (if high). A PK sample will be collected at each time point. Additional samples may also be collected if there is a possibility that an AE is immunologically mediated.

Leo Document ID = 3a6dde68-4dbc-40fe-9f9d-4d7f1ba85215

Approver: PPD
Approval Date & Time: 06-Feb-2019 18:52:11 GMT
Signature meaning: Approved

Approver: PPD
Approval Date & Time: 06-Feb-2019 20:28:44 GMT
Signature meaning: Approved