Protocol J2F-MC-OHAA(a)
A Single Ascending Dose Study to Evaluate Safety, Tolerability, and Pharmacokinetics of LY3478006 in Healthy Subjects

LY3478006

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1. Protocol Synopsis

Title of Study:
A Single Ascending Dose Study to Evaluate Safety, Tolerability, and Pharmacokinetics of LY3478006 in Healthy Subjects

Rationale:
This first-in-human study will investigate the safety, tolerability, and pharmacokinetics (PK) of LY3478006 after single escalating intravenous (IV) doses and a single subcutaneous (SC) dose of LY3478006 in healthy subjects. The data generated in this study will be used to guide the design of future clinical studies.

Objective(s)/Endpoints:

Objectives	Endpoints
Primary	
To assess the safety and tolerability following single doses of LY3478006 in healthy subjects, including those of Japanese origin.	Frequency of serious adverse events (SAEs) and treatment-emergent adverse events (TEAEs)
Secondary	
To assess the serum PK of LY3478006 following single IV or SC doses of LY3478006 in healthy subjects.	Maximum observed drug concentration (C_{max}) and area under the concentration versus time curve from zero to infinity ($AUC_{0-\infty}$)
To estimate the absolute bioavailability of LY3478006 following a single SC dose relative to a single IV dose in healthy subjects.	Absolute bioavailability

Summary of Study Design:

Study J2F-MC-OHAA is a Phase 1, subject- and investigator-blind, placebo-controlled, randomized, parallel, single ascending dose study in healthy subjects.

Treatment Cohorts and Planned Duration:

Seven cohorts (Cohorts 1 to 7) of healthy subjects will be studied. In each cohort, 8 subjects will be randomized (3:1 ratio) to receive LY3478006 or placebo (6 LY3478006 subjects and 2 placebo subjects). Four of the 8 healthy subjects enrolled in Cohorts 3, 4, 5, and 6 are planned to be of Japanese origin (first generation; randomized [3:1 ratio] to receive LY3478006 or placebo).

Cohorts 1 through 6 will be sequentially enrolled to test 6 single ascending dose levels of LY3478006 (planned dose levels of 10 mg, 30 mg, 100 mg, 300 mg, 600 mg, and 1000 mg) or placebo administered intravenously (IV). Subjects in Cohorts 1 through 6 may be dosed in at least 2 dosing groups (approximately 4 subjects in each group) on separate days. Study drug will be administered to 1 subject at a time (study drug infusion can start for a given subject after the end of infusion of the previous subject). Safety data through Day 15 postdose must be evaluated

from at least 6 of 8 subjects prior to the decision to dose escalate to the subsequent cohort. Cohort 7 will be enrolled to test 1 dose level of LY3478006 (planned dose level of 100 mg, a higher dose level may be administered but not to exceed 300 mg) or placebo administered subcutaneously (SC). All subjects in Cohort 7 may be dosed on a single day.

Subjects will have up to a 4-week screening period, will be admitted to the clinical research unit (CRU) on Day -1, and their eligibility will be confirmed prior to dosing on Day 1. Subjects will remain resident in the CRU and may be discharged on Day 5 after all study procedures have been completed, at the discretion of the investigator. Subjects will return to the CRU as outpatients at predetermined visits up to approximately 12 weeks postdose for safety assessment and collection of PK, pharmacodynamic (PD) biomarker, and immunogenicity samples. The follow-up period may be extended by adding up to 3 outpatient visits if necessary based on the emerging PK data. Subjects who do not develop treatment-emergent antidrug antibodies (TE-ADA), or whose ADA at the end of the follow-up period do not meet TE-ADA criteria, may be discharged from the study at the end of the follow-up period if deemed appropriate by the investigator. Subjects whose ADA meets the TE-ADA criteria at the end of the follow-up period will continue outpatient visits to monitor ADA until the signal returns to baseline or for up to 12 months after the end of the follow-up period (or early termination), whichever is sooner.

Number of Subjects:
Up to 70 healthy subjects may be enrolled so that approximately 56 subjects complete the study. It is planned that 16 of these 56 subjects will be of Japanese origin (first generation).

Statistical Analysis:

Summary statistics data tabulations and data graphs by ethnicity (Japanese and non-Japanese) will be provided as appropriate.

Adverse events 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 the study drug as perceived by the investigator. The number of IP-related SAEs will be reported. Safety parameters, including safety laboratory, vital signs, neurologic examination, and pupillometry, will be listed and summarized using standard descriptive statistics.

Pharmacokinetic parameters for LY3478006 will be calculated by standard noncompartmental methods of analysis (NCA). The primary parameters for analysis will be C_{max} and $AUC_{0-\infty}$. Pharmacokinetic parameter estimates from the NCA will be evaluated to delineate effects of dose proportionality. Log-transformed C_{max} and AUC estimates will be evaluated in a linear model with log-transformed IV dose for healthy subjects as explanatory variable. The treatment differences will be back-transformed to present the ratios of geometric means and the corresponding 90% confidence intervals. For the SC dose, the bioavailability relative to IV infusion at the same dose will be evaluated via a log-transformed model.

2. Schedule of Activities

Study Schedule Protocol J2F-MC-OHAA

		Study Day													
Procedure	**Screening ≤28 days prior to Day 1**	**-1**	**1**	**2**	**3**	**5**	**8**	**10 (±1)**	**15 (±1)**	**22 (±1)**	**29 (±1)**	**43 (±2)**	**57 (±2)**	**71 (±4)**	**Day 85 (±4)[m] or E/T**
Informed Consent	X														
Outpatient Visit	X						X	X	X	X	X	X	X	X	X
CRU Admission		X													
CRU Discharge						X									
Medical History	X														
Height	X														
Weight	X	X													X
Physical Examination[a]	X	X	Predose	24 hr	X	X	X	X	X	X	X	X	X	X	X
Directed Neurological Examination	X	X		24 hr	X	X	X		X		X		X		X
Pupillometry		X				X		X			X				
ECG[b]	X		Predose (1, -0.5, 0 hr), end of infusion[c], 3, 6, 12 hr	24 hr	48 hr	X	X	X	X	X	X	X	X		X
AE[d] and Medication Review		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug Administration[e]			0 hr												
Vital Signs[f]	X		Predose, end of infusion[c], 3, 6, 12 hr	24 hr	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test[g]	X	X													X
Serology (Hepatitis B Surface Antigen, HIV, Hepatitis C Antibody)	X														

Study Schedule Protocol J2F-MC-OHAA

		Study Day													
Procedure	**Screening ≤28 days prior to Day 1**	**-1**	**1**	**2**	**3**	**5**	**8**	**10 (±1)**	**15 (±1)**	**22 (±1)**	**29 (±1)**	**43 (±2)**	**57 (±2)**	**71 (±4)**	**Day 85 (±4)[m] or E/T**
Clinical Laboratory Tests	X	X	Predose[g]	24 hr	X		X		X	X	X	X	X	X	X
Urinalysis	X		Predose				X				X		X		X
Urine Drug Screen, Ethanol Breath Test	X	X													
PK Sample[h]			Predose, end of infusion[c], 3, 6, 12 hr	24 hr	48 hr	X	X	X	X	X	X	X	X	X	X
NGF Sample			Predose, end of infusion[c], 3, 6, 12 hr	24 hr	48 hr	X	X	X	X	X	X	X	X	X	X
Immunogenicity[i]			Predose						X		X				X
Skin Punch Biopsies[j]			Predose				X								
Non-Pharmacogenetic Storage Samples[k]			Predose		X						X				
Storage Pharmacogenetic Samples[l]			Predose												

Abbreviations: ADA = antidrug antibody; AE = adverse event; CRU = clinical research unit; ECG = electrocardiogram; E/T = early termination; HIV = human immunodeficiency virus; hr = hour; IV = intravenous; NGF = nerve growth factor, PK = pharmacokinetics; SC = subcutaneous; TE-ADA = treatment-emergent antidrug antibody.

Note: Study procedures scheduled relative to IV dosing time are to occur from the time of the start of infusion; e.g., 3 hours postdose would be 3 hours after the start of the IV infusion.

[a] Full physical examination on Day -1 and Day 85 or E/T (may include body temperature and respiratory rate). At all other time points, the examination will include at a minimum, an assessment of skin, injection site, and oral cavity.

[b] Single safety ECGs.

[c] End of infusion procedures are only applicable for subjects enrolled in IV cohorts (Cohorts 1 through 6), and are not required for subjects enrolled in SC Cohort 7.

[d] Post-treatment blood samples will be collected in subjects who experience generalized urticaria or if anaphylaxis is suspected following infusion (Section 9.4.5.2).

Study Schedule Protocol J2F-MC-OHAA

[e] For Cohorts 1 through 6, IV infusion duration must be at least 30 minutes, and infusion duration may be increased further as deemed necessary if infusion reaction is observed.

[f] Supine and orthostatic (standing) blood pressure and pulse rate at all time points. Predose vital signs can be taken on Day 1 at any time prior to the scheduled dosing; at other times, vital signs should be taken as close to the scheduled time as possible. Body temperature and respiratory rate may be measured at the times of the full physical examination, or at any other time if clinically indicated.

[g] Serum hCG pregnancy test performed at screening. Urine pregnancy test performed at all other time points, and at the investigator's discretion.

[h] PK sampling times are given as targets to be achieved within reasonable limits.

[i] For subjects who develop TE-ADA, additional outpatient visits may be required to monitor ADA until they return to baseline. Additional safety assessments and samples for immunogenicity and PK should be taken at these additional visits, as described in Section 9.7.

[j] Two skin biopsies (6-mm punches) taken from the abdomen at each time point for each subject. The "Predose" biopsy samples may be taken on Day -1 or predose on Day 1.

[k] Serum and plasma storage samples will be collected.

[l] Pharmacogenomic sample may be taken on Day -1 or any time prior to dosing on Day 1.

[m] If 12 weeks is shorter than 5 half-lives of LY3478006 based on the emerging PK data, up to 3 additional visits will be added to ensure a follow-up period of approximately 5 half-lives after study drug dosing. Study activities for these additional visits will be the same as for the Day 85 visit.

3. Introduction

3.1. Study Rationale

LY3478006 is an antibody being developed as a treatment for chronic pain conditions. The antibody binds selectively to the TrkA receptor and inhibits nerve growth factor (NGF)-dependent receptor activation.

LY3478006 has not been administered to humans. This first-in-human study will investigate the safety, tolerability, and pharmacokinetics (PK) of LY3478006 after single escalating intravenous (IV) doses and a single subcutaneous (SC) dose of LY3478006 in healthy subjects. The data generated in this study will be used to guide the design of future clinical studies.

3.2. Background

Adequate treatment of acute and chronic pain is severely hindered by the continued broad utilization of medications with either limited efficacy and/or significant safety concerns, such as nonsteroidal anti-inflammatory drugs and opioids. Novel, preferably non-opioid, therapeutic options for pain management are desperately needed to address this unmet medical need.

Nerve growth factor has a clear role in the development of the central and peripheral nervous system, but its primary role in adulthood appears to be as a sensitizing agent in a variety of chronic pain conditions. Nerve growth factor has been reported to be elevated in the plasma of patients with chronic pain (Hefti et al. 2006), and antibodies targeting NGF have shown clinical efficacy in a wide range of chronic pain conditions including osteoarthritis, chronic low back pain, and painful diabetic neuropathy (Chang et al. 2016). Anti-NGF antibodies, including tanezumab, have been shown to bind NGF and prevent engagement with both NGF receptors, TrkA and p75 (La Porte et al. 2014).

The 140 kDa TrkA receptor (encoded by the *NTRK1* gene) is the high affinity receptor for NGF and is expressed in central nervous system (CNS), sensory, and sympathetic neurons as well as several subtypes of circulating immune cells. The p75 receptor (encoded by the *NGFR* gene) is the low affinity receptor for NGF that also binds other members of the neurotrophin family (BDNF and NT3, among others). The p75 receptor is widely expressed in the peripheral nervous system (PNS) and CNS, as well as many other tissues, and is often found in cells expressing other neurotrophin receptors (TrkA, TrkB, and TrkC). While the p75 receptor may play a role in NGF-dependent sensitization, key transcriptional mechanisms thought to support long-term chronic pain states are more closely linked to NGF signaling through TrkA, via the formation of the NGF/TrkA signaling endosome (Mantyh et al. 2011; Wasner et al. 2003).

Elevated tissue and/or plasma levels of NGF play a key role in NGF-dependent sensitization, but NGF may also be released by tissues directly adjacent to neuronal receptors. It remains unclear what role these local circuit effects may play in overall NGF sensitization, but direct receptor inhibition may more efficiently inhibit these interactions versus the NGF sequestration strategy employed by the existing clinical anti-NGF antibodies. LY3478006 is an antibody that binds the TrkA receptor and blocks the interaction of NGF with TrkA. LY3478006 has shown efficacy in a preclinical model of gait impairment, an assay that is sensitive to NGF-dependent mechanisms

(Adams et al. 2016). Clinical studies with LY3478006 will examine the potential for a selective TrkA therapeutic to achieve long-lasting efficacy in chronic pain conditions, offering a significant improvement over existing standards of care.

3.3. Benefit/Risk Assessment

There is no anticipated therapeutic benefit for subjects in this study.

Two safety topics emerged during the development of anti-NGF antibodies: atrophy of sympathetic neurons in animal studies, and an increased incidence of rapidly progressing osteoarthritis (RPOA) in human clinical trials. Sympathetic neuronal atrophy was not associated with demonstrable deficits in sympathetic function, and recovered with drug washout in adult animals (Angeletti et al. 1971; Bjerre et al. 1975; Belanger et al. 2017). Further, no major effects on sympathetic function have been reported in clinical trials to date in patients dosed with tanezumab (Brown et al. 2014; Brown et al. 2015) or in tanezumab-treated monkeys subjected to head-up tilt challenge (Belanger et al. 2017). In nonclinical repeat dose studies in rats (1-month) and non-human primates (3 months) minimal neuronal hypertrophy rather than atrophy was observed with LY3478006. No neuronal necrosis clinical sequelae were observed. Given the potential for compounds acting along this pathway to affect sympathetic function, this study will monitor for evidence of sub-clinical effects on autonomic function using pupillometry, which has been shown to detect dysfunction of both sympathetic and parasympathetic systems (Ferrari et al. 2010; Muppidi et al. 2013). While the likely mechanisms are unknown, RPOA in humans remains a potential risk for anti-TrkA inhibitors.

The nonclinical safety information for LY3478006 adequately supports the transition from preclinical status to a clinical, single-dose study. LY3478006 has not been administered to humans previously, thus the study is 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 (EMA 2017). Any identified risks are considered to be monitorable and manageable at the planned single ascending dose range of 10 mg to 1000 mg for LY3478006 in healthy subjects.

More information about the known and expected benefits, risks, serious adverse events (SAEs) and reasonably anticipated adverse events (AEs) of LY3478006 are to be found in the Investigator's Brochure (IB).

4. Objectives and Endpoints

Table OHAA.1 shows the objectives and endpoints of the study.

Table OHAA.1. Objectives and Endpoints

Objectives	Endpoints
Primary To assess the safety and tolerability following single doses of LY3478006 in healthy subjects, including those of Japanese origin.	Frequency of SAEs and TEAEs
Secondary To assess the serum PK of LY3478006 following single IV or SC doses of LY3478006 in healthy subjects.	C_{max} and $AUC_{0-\infty}$
To estimate the absolute bioavailability of LY3478006 following a single SC dose relative to a single IV dose in healthy subjects.	Absolute bioavailability
Exploratory To assess the changes in serum NGF levels following single IV and SC doses of LY3478006 in healthy subjects.	Serum NGF levels over time
To assess the changes in skin pTrkA and tTrkA levels following single IV and SC doses of LY3478006 in healthy subjects.	Pre and postdose pTrkA and tTrkA levels
To assess the serum PK of LY3478006 following single IV doses of LY3478006 in healthy Japanese subjects.	C_{max} and $AUC_{0-\infty}$

Abbreviations: $AUC_{0-\infty}$ = area under the concentration versus time curve (AUC) from zero to infinity; C_{max} = maximum observed drug concentration; IV = intravenous; NGF = nerve growth factor; PK = pharmacokinetics; SAEs = serious adverse events; SC = subcutaneous; TEAEs = treatment-emergent adverse events.

5. Study Design

5.1. Overall Design

Study J2F-MC-OHAA is Phase 1, subject- and investigator-blind, placebo-controlled, randomized, parallel, single-ascending dose study in healthy subjects.

Seven cohorts (Cohorts 1 to 7) of healthy subjects will be studied. In each cohort, 8 subjects will be randomized (3:1 ratio) to receive LY3478006 or placebo (6 LY3478006 subjects and 2 placebo subjects). Four of the 8 healthy subjects enrolled in Cohorts 3, 4, 5, and 6 are planned to be of Japanese origin (first generation; randomized [3:1 ratio] to receive LY3478006 or placebo). If the recruitment of Japanese subjects becomes limiting for a particular cohort, then additional non-Japanese subjects may be entered into a cohort to allow for dose escalation. Japanese subjects will subsequently be enrolled so that at least 3 Japanese subjects complete placebo and each LY3478006 dose level. In addition, it is preferred that the non-Japanese subjects also be non-Asian.

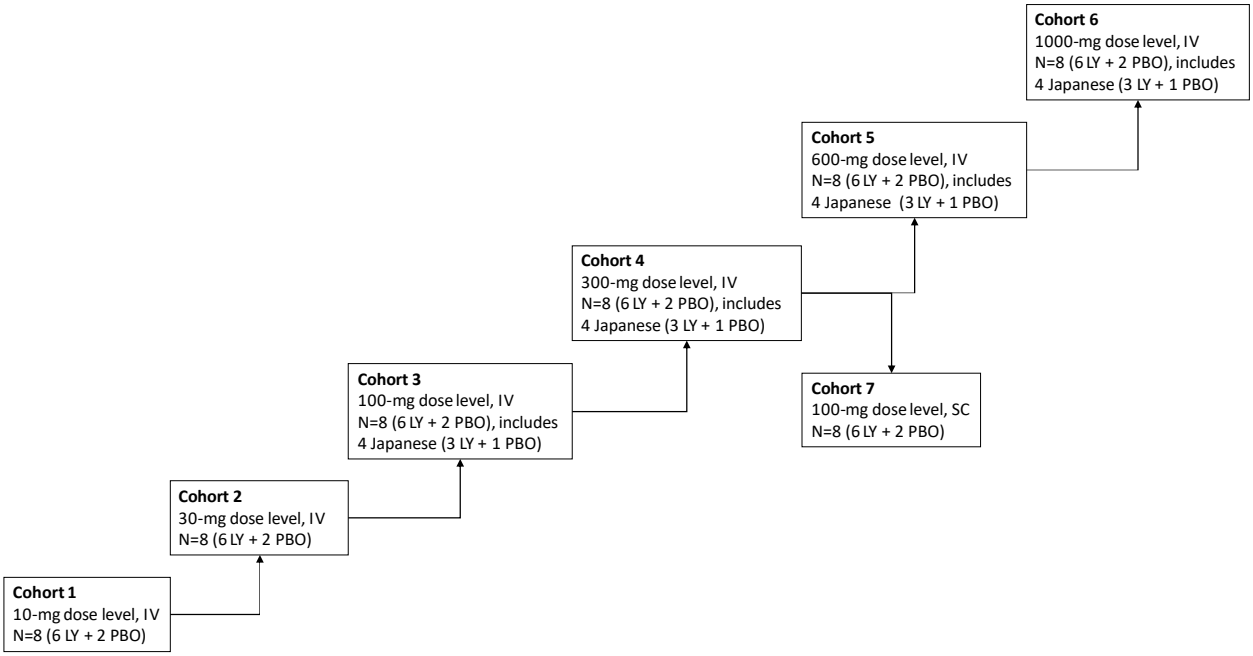
Cohorts 1 through 6 will be sequentially enrolled to test 6 single ascending dose levels of LY3478006 (planned dose levels of 10 mg, 30 mg, 100 mg, 300 mg, 600 mg, and 1000 mg) or placebo administered intravenously (IV). Subjects in Cohorts 1 through 6 may be dosed in at least 2 dosing groups (approximately 4 subjects in each group) on separate days. Study drug will be administered to 1 subject at a time (study drug infusion can start for a given subject after the end of infusion of the previous subject). Safety data through Day 15 postdose must be evaluated from at least 6 of 8 subjects prior to the decision to dose escalate to the subsequent cohort (dose escalation criteria are described in Section 7.4.1). Cohort 7 will be enrolled to test 1 dose level of LY3478006 (planned dose level of 100 mg, a higher dose level may be administered but not to exceed 300 mg) or placebo administered subcutaneously (SC). All subjects in Cohort 7 may be dosed on a single day. Figure OHAA.1 illustrates the study design.

Subjects will have up to a 4-week screening period, will be admitted to the clinical research unit (CRU) on Day -1, and their eligibility will be confirmed prior to dosing on Day 1. Subjects will remain resident in the CRU and may be discharged on Day 5 after all study procedures have been completed, at the discretion of the investigator. Subjects will return to the CRU as outpatients at predetermined visits up to approximately 12 weeks postdose for safety assessment and collection of PK, pharmacodynamic (PD) biomarker, and immunogenicity samples. Safety will be assessed by monitoring of AEs, clinical laboratory tests, vital signs (blood pressure and pulse rate), electrocardiograms (ECGs), directed neurological examinations, and pupillometry.

Subjects will be followed for 12 weeks based on a projected half-life of approximately 16 days. This follow-up period may be extended by adding up to 3 outpatient visits if necessary based on the emerging PK data, to ensure a follow-up duration of at least 5 half-lives (Section 2). Study activities for these additional visits will be the same as for the Day 85 visit. For subjects who do not develop treatment-emergent antidrug antibodies (TE-ADAs), or whose ADA at the end of the follow-up period do not meet TE-ADA criteria, they may be discharged from the study at the end of the follow-up period if deemed appropriate by the investigator. For subjects whose ADA meets the TE-ADA criteria at the end of the follow-up period, additional outpatient visits may be

required to monitor ADA until the signal returns to baseline (Section 9.7), or for up to 12 months after the end of the follow-up period (or early termination), whichever is sooner. Adverse events and blood samples for LY3478006 concentration should also be collected at these outpatient visits.

Study governance considerations are described in detail in Appendix 3.



Abbreviations: IV = intravenous; LY = LY3478006; N = number of subjects; PBO = placebo; SC = subcutaneous.
Note: Figure is for illustration purposes only. Escalation to next cohort will take place following review of safety data up to Day 15.

Figure OHAA.1. Illustration of study design for Protocol J2F-MC-OHAA.

5.2. Number of Participants

Up to 70 healthy subjects may be enrolled so that approximately 56 subjects complete the study. It is planned that 16 of these 56 subjects will be of Japanese origin (first generation). For purposes of this study, a subject completes the study when all scheduled procedures shown in the Schedule of Activities (Section 2) have been finished. Subjects who discontinue the study following dose administration but before completing may be replaced at the discretion of the sponsor and investigator.

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

A subject- and investigator-blinded, randomized, placebo-controlled design was chosen to minimize bias in the primary objective of the study. A parallel-group design was chosen because a crossover design is impractical for compounds that have long half-lives. Additionally, a crossover design could confound PK data if subjects develop neutralizing ADA.

Conducting the study in healthy subjects mitigates the potential confounding effects of the disease state and concomitant medications in patients, and therefore provides the most unbiased assessment of the safety and tolerability of LY3478006 in this first human dose (FHD) study. It is possible that this study will support further development of LY3478006 in Japanese patients, therefore, it is planned that 4 healthy Japanese subjects will be enrolled in each of Cohorts 3, 4, 5, and 6.

While recently published European Medicines Agency guideline (EMA 2017) recommends use of sentinel dosing in first-in-human studies, it also allows for flexibility in a proposed dosing approach based on the available scientific data and preclinical assessment of a given molecule. The intended and exaggerated pharmacological responses of LY3478006 have been well characterized in multiple preclinical pharmacology models. Results of toxicology studies suggest that non-monitorable or clinically unmanageable concerns after single dose would be unlikely to occur in humans treated with LY3478006. Based on the available data, LY3478006 does not present an uncertainty profile necessitating a sentinel dosing approach. Furthermore, sentinel dosing with non-high uncertainty compounds, such as LY3478006, may lead to inability to interpret data due to false positive AE findings in the absence of data from all cohorts or placebo-treated subjects. However, for the escalating IV cohorts, each cohort may be split so that 4 subjects will only be dosed on a given day to allow sufficient time for study related procedures to be completed in a timely manner.

Periodic safety data reviews will ensure that any subject can be discontinued early, or the dose escalation can be terminated, in case of any AE requiring such a decision.

Safety, tolerability, PK, immunogenicity, and PD biomarker data in healthy subjects will assist in identifying an appropriate dose range for subsequent clinical studies.

5.5. Justification for Dose

Human PK parameters, including clearance (CL, Q) and volume of distribution (V1, V2) were predicted using the allometric scaling from monkey PK parameters, with a fixed exponent of 0.8 and 1 for clearance and volume, respectively (Wang and Prueksaritanont 2010).

The minimal pharmacology active dose (PAD) is determined from the rat DRG pTrkA signaling data, and the biologically effective dose (BED) is defined from an integrated review of the preclinical data package detailed in the IB that included the following measures:

- A prior clinical study with a nonselective small molecule TrkA inhibitor indicated that very high coverage over the TrkA IC_{50} may be required for efficacy (Loudon et al. 2018). The plasma concentration of LY3478006 required to achieve 30-fold coverage

over the human pTrkA IC_{50} in skin is approximately 37.4 µg/mL (human pTrkA in vitro IC_{50} = 0.83 nM, and assumes a typical antibody 10% skin:plasma partition coefficient).

- The plasma concentration at the minimal effect dose (MED) of 10 mg/kg in the rat intra-articular CFA-induced gait deficit model is 46.2 µg/mL after 3 days postdose.
- The plasma concentration required to achieve significant inhibition of DRG pTrkA signaling at 3 days postdose is 5.7 µg/mL.

The predicted BED of 65 mg QW, 150 mg Q2W, and 400 mg Q4W are predicted to achieve a C_{trough} above the minimal 30-µg/mL threshold for the entire dosing interval once steady state is reached. The predicted PAD of 10 mg QW, 30 mg Q2W, and 80 mg Q4W are predicted to achieve C_{trough} above the minimal 5.7-µg/mL threshold for the entire dosing interval once steady state is reached. These predictions apply to both IV and SC administration as they are based upon C_{trough} from a 2-compartment linear PK model with a bioavailability of 83%. Once clinical PK data (including SC bioavailability) become available, the predicted BED will be refined for both the IV and SC dosing regimens. It is currently proposed that future multiple dose studies will start with a monthly (Q4W) dosing regimen

A single-dose monkey PK/PD study was performed at 0.1, 0.5, and 3 mg/kg IV to explore the relationship between dose, exposure, and PD using the same assay and methodology compared to the single ascending dose study: every animal was its own control and 4 postdose skin punch biopsies were collected. These data were useful to establish the time points for the collection of the postdose skin punch biopsies in healthy subjects, but were not informative enough to build a PK/PD model as the 3 doses explored provided similar PD effect.

To establish safety and tolerability of LY3478006 and evaluate the dose/exposure-response relationship (via skin punch biopsies to measure pTrkA and tTrkA), a wide dose range for LY3478006 (10, 30, 100, 300, 600, and 1000 mg, IV) is proposed for the single ascending dose study performed in healthy subjects. In addition, a single 100-mg SC dose is planned to be administered to define the bioavailability of LY3478006. However, based on emerging data a higher dose may be administered but will not exceed 300 mg.

The no-observed-adverse-effect level (NOAEL) for LY3478006 in the monkey 3-month toxicology study is 170 mg/kg IV. In rats, adverse skin lesions consistent with self-trauma (persistent scratching) limited the dosing of LY3478006 to approximately 1 month, and erosion/ulceration of the tongue was present at all doses tested in small numbers of rats (changes which were also consistent with injury/trauma as opposed to direct toxicity of the test article on the tongue). Therefore, no NOAEL was identified in rat although the adverse changes are of questionable human relevance and are clinically monitorable. As shown in Table OHAA.2, the proposed starting dose of 10 mg IV and maximum dose of 1000 mg IV have a sufficiently large margin of safety in the monkey both in terms of dose and exposure. The starting dose of 10 mg is anticipated to be 8-fold lower than the PAD and the top dose of 1000 mg is anticipated to be 2.5-fold higher than the BED. Taking the assumption that the predicted PAD dose of 80 mg Q4W provides 50% of the effect (assuming ED50 value based on 50% TE in DRG): with a hill factor of 1, the 400-mg Q4W projected BED dose is predicted to provide around ED85 and the

top dose of 1000 mg is predicted to be around ED90. The planned maximum dose (1000 mg IV) in humans was selected as 1/10th the repeat dose monkey NOAEL (and highest dose tested in rat) based on dose (mg/kg). Pharmacokinetic projections predict that drug exposures at the maximum dose of 1000 mg IV will remain below 1/7th the exposures at the NOAEL in the monkey GLP toxicology study (dosed for 3 months). Potential treatment-emergent changes in cutaneous sensation are expected to be readily evident to subjects and, in addition, scheduled neurologic exams will include assessments for changes in cutaneous sensation. Scheduled physical examinations will also include inspection of the oral cavity.

Table OHAA.2. Margin of Safety for Intravenous Administration of LY3478006 Based on Administered Dose and Predicted Human Exposure and Actual Animal Exposure

	Dose (mg/kg)	Dose Multiple[a]	AUC (µg•hr/mL)	AUC Exposure Multiple[b]	C_{max} (µg/mL)	C_{max} Exposure Multiple[c]
Human Starting dose (10 mg IV)	0.167	–	1006	–	2.9	–
Rat LOAEL skin/tongue[d]	60 (SC)	359	63600	63.2	824	284
Rat Highest Dose Tested	170 (IV)	1018	269000	267	4470	1541
Monkey NOAEL[e]	170 (IV)	1018	728000	724	7230	2493
Human Maximum dose (1000 mg IV)	16.7	–	100581	–	289.9	–
Rat LOAEL skin/tongue[d]	60 (SC)	3.6	63600	0.63	824	2.8
Rat Highest Dose Tested	170 (IV)	10.2	269000	2.7	4470	15.4
Monkey NOAEL[e]	170 (IV)	10.2	728000	7.2	7230	24.9

Abbreviations: AUC = area under the serum concentration × time curve; C_{max} = maximal serum concentration; IV = intravenous; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; SC = subcutaneous.

a Dose multiple is the dose in animals/dose in humans based on mg/kg and human body weight = 60 kg. Exposure multiple is the calculated $AUC_{tau,ss}$ in animals / predicted $AUC_{0-\infty}$ in humans (see Table 4.10 in the IB for predicted human PK).

b AUC multiple = mean AUC_{tau} observed after the last dose in animal/predicted mean $AUC_{0-\infty}$ after a single dose in human. AUC in rats presented is calculated as 0-96hr. AUC in monkeys presented is calculated as 0-168hr.

c C_{max} multiple = mean C_{max} observed after the last dose in animal/predicted mean C_{max} after a single dose in human.

d Determined in a 1-month repeat dose toxicity study.

e NOAEL determined in a 3-month repeat dose toxicity study.

The margin of safety table presented above is based on predicted exposure following IV administration (100% bioavailability) and therefore provides an appropriate margin for SC dosing, where bioavailability cannot be higher than 100%.

6. Study Population

Eligibility of subjects for the study will be based on the results of screening medical history, physical examination, vital signs, clinical laboratory tests, and 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, are not permitted.

6.1. Inclusion Criteria

Subjects are eligible for inclusion in the study only if they meet all of the following criteria at screening and/or enrollment:

[1] are overtly healthy males or female Japanese or non-Japanese subjects, as determined by medical history and physical examination.

[1a] Male subjects must agree to adhere to contraception restrictions specified in Section 6.3.4.

[1b] Female subjects:

Women not of childbearing potential may participate and include those who are infertile due to surgical sterilization (hysterectomy without bilateral oophorectomy or confirmed tubal occlusion [not tubal ligation]).

[2] Are aged 18 to 55 years (20 to 55 years for Japanese subjects), inclusive, at screening.

[3] Have a body mass index (BMI) of 18.0 to 32.0 kg/m^2, inclusive, at screening.

[4] Have clinical laboratory test results within normal reference range for the investigative site, or results with acceptable deviations that are judged to be not clinically significant by the investigator.

[5] Have venous access sufficient to allow for IV drug delivery and blood sampling as per the protocol.

[6] Are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures and CRU procedures.

[7] Have given signed informed consent.

Additional criteria to qualify as Japanese subjects in this study:

[8] To qualify as a subject of Japanese origin (first-generation Japanese), the subject, the subject's biological parents, and all of the subject's biological grandparents must be of exclusive Japanese descent and have been born in Japan.

6.2. Exclusion Criteria

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

[9] 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.

[10] Are Eli Lilly and Company (Lilly) employees or employees of third-party organizations involved with the study who require exclusion of their employees.

[11] Are currently enrolled in a clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.

[12] Have participated, within the last 30 days, in a clinical study involving an investigational product. If the previous investigational product has a long half-life, 5 half-lives or 30 days, whichever is longer, should have passed.

[13] Have previously completed or withdrawn from this study or any other study investigating LY3478006, and have previously received the investigational product.

[14] Have known allergies to LY3478006, related compounds or any components of the formulation, or history of significant atopy.

[15] Have clinically significant abnormal ECG results constituting a risk when taking the investigational product, as determined by the investigator.

[16] Have persistent abnormal blood pressure and/or pulse rate as determined by the investigator.

[17] Have evidence of orthostatic hypotension defined as decrease in systolic or diastolic of ≥20mmHg or ≥10mmHg, respectively.

[18] Have a history or presence of cardiovascular, respiratory, hepatic, ophthalmological, renal, gastrointestinal, endocrine, hematological, neurological, or psychiatric disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk when taking the investigational product; or of interfering with the interpretation of data.

[19] Have a history or presence of mononeuropathy, polyneuropathy, or autonomic neuropathy.

[20] Subjects who are not suitable for measurement of pupil size by the study specified methodology.

[21] Regularly use known drugs of abuse (including cannabis) and/or show positive findings on urinary drug screening.

[22] Show evidence of human immunodeficiency virus (HIV) infection and/or positive human HIV antibodies.

[23] Have liver function test (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP], total bilirubin [TBL]) above the upper limit of normal (ULN) at screening.

[24] Show evidence of hepatitis C and/or positive hepatitis C antibody.

[25] Show evidence of hepatitis B and/or positive hepatitis B surface antigen.

[26] Are women who are lactating.

[27] Have used or intend to use over-the-counter or prescription medication (including herbal medications) within 7 days prior to dosing or during the study with the exception of: vitamins and mineral supplements (not providing >100% of the recommended daily allowance), hormone replacement, and/or occasional paracetamol/acetaminophen. If this situation arises, inclusion of an otherwise suitable subject may be at the discretion of the sponsor.

[28] Have donated blood of more than 500 mL within the last month.

[29] Have an average weekly alcohol intake that exceeds 21 units per week (males) and 14 units per week (females), or are unwilling to stop alcohol consumption from 48 hours prior to dosing (1 unit = 12 oz or 360 mL of beer; 5 oz or 150 mL of wine; 1.5 oz or 45 mL of distilled spirits).

[30] Consume more than 10 cigarettes per day or the equivalent, and/or are unable or unwilling to refrain from smoking, vaping, or nicotine use (including replacement therapy) during CRU admissions.

[31] 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.

[32] Have significant allergies to humanized monoclonal antibodies.

[33] Have clinically significant multiple or severe drug allergies, or intolerance to topical corticosteroids, or severe post treatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear IgA dermatosis, toxic epidermal necrolysis, or exfoliative dermatitis).

[34] Have had lymphoma, leukemia, or 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 metastatic disease for 3 years.

[35] Have had breast cancer within the past 10 years.

[36] In the opinion of the investigator or sponsor, are unsuitable for inclusion in the study.

6.3. Lifestyle and/or Dietary Requirements

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

6.3.1. Meals and Dietary Restrictions

Subjects should fast for at least 4 hours prior to study drug administration and are required to remain recumbent for approximately 2 hours (unless otherwise required for procedures) after study drug administration and remain sedentary in a bed or chair for the subsequent 4 hours for observation. Subjects are permitted to have a meal approximately 1 hour following the completion of dosing. While resident in the CRU, a standard diet (or a Japanese diet, where appropriate) will be provided. When outpatient, a subject's typical diet may be consumed at all other meal times during the study.

Subjects will not be permitted to consume foods containing poppy seeds from 48 hours prior to attending the CRU on Days -1, 8, 29, and 57.

6.3.2. Caffeine, Alcohol, and Tobacco

Consumption of caffeine- and xanthine-containing products is allowed, provided that the subject's consumption has been consistent for the past 30 days.

Subjects will not be permitted to consume alcohol from 48 hours before each visit until leaving the CRU. Subjects will be advised to abstain from alcohol consumption for the remainder of the trial until their final visit.

Subjects will not be permitted to smoke from CRU admission until discharge from the CRU.

6.3.3. Activity

Subjects should avoid strenuous exercise and/or activity from 48 hours prior to visits until leaving the CRU.

6.3.4. Male Contraceptive Requirements

Male subjects, regardless of their fertility status, with non-pregnant female partners of childbearing potential must agree to either remain abstinent (if this is their preferred and usual lifestyle) or use condoms as well as one additional highly effective (less than 1% failure rate) method of contraception (such as combination oral contraceptives, implanted contraceptives, or intrauterine devices) or effective method of contraception (such as diaphragms with spermicide or cervical sponges) for 90 days after study drug dosing.

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

be noted, however, that the use of male and female condoms as a double barrier method is not considered acceptable due to the high failure rate when these barrier methods are combined.

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

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

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

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may not be re-screened. If subjects have minor deviations in screening assessments (e.g., laboratory safety tests, vital signs) these may be repeated at the investigator's discretion to confirm eligibility.

7. Treatment

7.1. Treatment Administered

This study involves a comparison of LY3478006 administered over a planned single ascending dose range of 10 mg to 1000 mg versus placebo administered by IV infusion, and following a single 100 mg dose versus placebo administered by SC injection. Table OHAA.3 shows the treatment regimens.

In Cohorts 1 through 6, the investigational product 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 4 hours after subjects have completed their infusion. In Cohort 7, the investigational product will be administered SC in the abdominal wall, approximately 5 cm from the umbilicus and skin biopsy site. If more than 1 SC injection is required, then each injection will be at least 5 cm apart. The site(s) of injection will be recorded.

Table OHAA.3. Treatments Administered

Treatment Name	LY3478006	Placebo
Dosage Formulation	Solution for Injection, 200 mg/4-mL	Sterile saline (0.9% sodium chloride)
Unit dose strength(s)/Dosage Level(s)	50 mg/mL Single dose; 10 mg, 30 mg, 100 mg, 300 mg, 600 mg, 1000 mg	N/A Single dose; equivalent volume to each dose level of LY3478006
Route of Administration	Cohorts 1 through 6: IV Cohort 7: SC	
Dosing instructions	Cohorts 1 through 6: slow IV infusion over at least 30 minutes Cohort 7: SC injection via syringe into the abdomen	

Abbreviations: IV = intravenous; N/A = not applicable; SC = subcutaneous.

The investigator or designee is responsible for:

- explaining the correct use of the investigational product(s) to the site personnel
- verifying that instructions are followed properly
- maintaining accurate records of investigational product dispensing and collection (this responsibility can only be performed by unblinded pharmacy staff)
- and returning all unused medication to Lilly or its designee at the end of the study

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

7.1.1. Packaging and Labeling

Clinical trial materials will be labelled as investigational product (IP) as appropriate, and according to the country's regulatory requirements. Clinical trial materials are manufactured in accordance with current good manufacturing practices and will be supplied by Lilly or its representative.

The LY3478006 Injection, 200-mg/vial is supplied as sterile, preservative-free solution in a single-use vial for SC and IV administration. Each milliliter of drug product solution delivers 50 mg of LY3478006.

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

7.2. Method of Treatment Assignment

Treatment assignment will be determined according to a randomization schedule.

7.2.1. Selection and Timing of Doses

It is planned that all subjects will receive a fixed dose of LY3478006 or placebo, according to the randomization schedule. The planned dose levels are 10-, 30-, 100-, 300-, 600-, and 1000-mg LY3478006, administered IV to subjects in Cohorts 1 through 6, respectively. Subjects in Cohort 7 will receive a planned SC dose of 100-mg LY3478006. However, based on emerging data a higher dose may be administered but will not exceed 300 mg. The actual dose for each cohort will be determined as described in Section 7.4.1.

The actual time of all dose administrations will be recorded in the subject's electronic case report form (eCRF). The actual duration time of infusion will be recorded in the eCRF. If the infusion is terminated, this should be recorded in the eCRF.

7.3. Blinding

This is a subject- and investigator-blind study. The study site pharmacist will be unblinded.

To preserve the blinding of the study, a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is complete.

Randomization tables for allocation of LY3478006 and placebo will be prepared by the Lilly statistician or designee and provided to the study site pharmacists or pharmacy staff involved in dose preparation. Blinding will be maintained throughout the conduct of the study until all data are cleaned to an acceptable level of quality and locked. The details are included in a separate Blinding Plan.

Emergency codes will be available to the investigator. A code, which reveals the treatment group for a specific study subject, may be opened during the study only if the subject's well-being requires knowledge of the subject's treatment assignment.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted for medical management of the event. The subject's safety must always be the first consideration in making such a determination. If the

investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify Lilly as soon as possible.

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

7.4. Dose Modification

7.4.1. Dose Decision/Escalation

By nature of being a dose-escalation study, data will be evaluated on an ongoing basis until the maximum planned dose (1000 mg) is reached or a lower dose in the event that the dose escalation stopping criteria are met as described below.

Safety data will be the primary criteria for the dose escalation. In addition, LY3478006 concentrations will be reviewed to guide dose escalation, as described in Section 5.1. ADA results will be reviewed by the sponsor periodically to guide dose escalation, but is not necessary for making dose escalation decisions. No dose decision can occur without prior discussion and agreement between the investigator (or designee) and the Lilly clinical pharmacologist (CP)/ clinical research physician (CRP)/study team. In case of disagreement, the decision of the investigator will be followed, except in a situation where Lilly's proposal is the more conservative action (for example, where the investigator wishes to escalate and the Lilly CP/CRP dose not) in which case, the Lilly proposal will be followed.

Safety data collected through at least Day 15 will be evaluated from at least 6 of 8 subjects prior to each dose escalation. The safety data reviewed will include at least: AEs, clinical laboratory tests, vital signs, ECGs, and neurological/pupillometry examinations.

Safety data, in particular AEs, SAEs, and adverse laboratory abnormalities, will be independently assessed by the investigator, and will be considered related to the investigational product unless there is clear evidence that the event is not related.

After review of these data, an agreement on the appropriate dose escalation will be made by the investigator and sponsor for the next cohort. The magnitude of dose escalations may be reduced following data review, but subsequent escalations cannot be increased by more than approximately 3-fold (a half-log increment).

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

1) 2 or more subjects experience an SAE or clinically significant event that is related to LY3478006 administration
2) 2 or more subjects develop acute AEs of moderate severity that are considered to be related to LY3478006 infusion, during or within 2 hours of completing the infusion, that do not resolve with a reduced infusion rate and/or supportive care (described in Section 7.4.2.2).
3) 3 or more subjects at 1 dose level experience moderate treatment-related AEs that impair normal activities

4) 2 or more subjects develop AEs within 14 days of dosing that are considered to be related to study treatment and graded as at least moderate, clinically significant and not responsive to supportive care

Dosing may continue in a new dose cohort if the risk-benefit is deemed appropriate by the sponsor and investigator, at a dose reduced by ≥50% of the dose resulting in termination of the dose escalation. Also, it is important to note that when the above criteria are met, any ongoing dosing at a dose level that is below the dose that triggered the stopping rule may continue when considered appropriate by the sponsor.

7.4.2. Special Treatment Considerations

7.4.2.1. Premedication for Infusions

Premedication for the infusions is not planned. However, if an infusion reaction occurs, appropriate medication may be used as determined by the study investigator. The sponsor should be informed when premedication for infusion reaction is recommended by the investigator.

If minor infusion reactions are observed, but review of the data suggests that dose escalation may continue, administration of acetaminophen, 500 to 1000 mg, or other appropriately indicated non-sedating medications may be administered orally approximately 30 to 60 minutes prior to the start of infusion for subsequent subjects.

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

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

7.4.2.2. Management of Infusion Reactions

There is a risk of infusion reaction with any biological agent; therefore, all subjects should be monitored closely as described in Section 9.4.5.1.

In the event that a significant infusion reaction occurs, the following guidance should be followed:

- The investigational product infusion should be slowed (for example, reduce infusion rate by 50% [for example, an infusion rate of 12 mL/hr becomes 6 mL/hr or slower]) or stopped, 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; the subject should complete AE and other follow-up procedures per Section 2
- Management of the infusion site reaction should proceed according to the severity of the reaction as described in Section 9.4.5.1.

- If a subject's infusion reaction is sufficiently severe to discontinue the infusion, then subsequent infusions may be administered to subjects with premedication at the discretion of the investigator following agreement with the Lilly CRP or CP (Section 7.4.2.1).
- If a subject's infusion rate is reduced due to an infusion reaction, then subsequent infusions may be administered to subjects at the discretion of the investigator following agreement with the Lilly CRP or CP. If further infusions are administered, the infusion rate must not exceed the slowest rate used to complete the infusion on the occasion the infusion reaction occurred. Premedication may be administered at the discretion of the investigator (Section 7.4.2.1).

7.5. Preparation/Handling/Storage/Accountability

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

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

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

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

Subjects on stable concomitant medication at the time of study entry should continue their regular, unchanged dose throughout the study. These medications include vitamins and mineral supplements (not providing >100% of the recommended daily allowance), hormone replacement, and/or occasional paracetamol/acetaminophen (Exclusion Criterion 26).

In general, concomitant medication should be avoided; however, acetaminophen (1 gram, maximum 3 grams/24 hours) may be administered at the discretion of the investigator for treatment of headaches, etc. Additional drugs are to be avoided during the study unless required to treat an AE or for the treatment of an ongoing medical problem.

If the need for concomitant medication (other than acetaminophen) arises, inclusion or continuation of the subject may be at the discretion of the investigator after consultation with a Lilly CP or CRP. Any medication used during the course of the study must be documented.

7.8. Treatment after the End of the Study

This section is not applicable for this study.

8. Discontinuation Criteria

Subjects who discontinue treatment or the study early will have early termination procedures performed as shown in the Schedule of Activities (Section 2).

8.1. Discontinuation from Study Treatment

Dose escalation discontinuation criteria are presented in Section 7.4.1. Subjects whose infusion is stopped before its completion (such as due to an infusion reaction), may continue in the study for safety monitoring if deemed appropriate by the sponsor and investigator.

8.1.1. Discontinuation of Inadvertently Enrolled Subjects

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

8.1.2. Systemic Allergic/Hypersensitivity Reactions

All biologic agents carry the risk of systemic allergic/hypersensitivity reactions. Clinical manifestations of these reactions are described in Section 9.4.5.2. Systemic allergic/hypersensitivity reactions may possibly lead to a subject's permanent discontinuation. The investigator, after consultation with the sponsor, determines that a clinically significant hypersensitivity reaction has occurred.

8.2. Discontinuation from the Study

Subjects will be discontinued from the study in the following circumstances:

- Enrollment in any other clinical study involving an IP or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- Participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- Investigator decision: the investigator decides that the subject should be discontinued from the study
- Subject decision: the subject requests to be withdrawn from the study.

8.3. Subjects Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the 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 4 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 investigational product or the study, or that caused the subject to discontinue the investigational product 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.

The investigator will record all relevant AE and SAE information in the electronic case report form (eCRF). After the informed consent form (ICF) is signed, study site personnel will record, via 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 concomitant treatment or pathologies.

A "reasonable possibility" means that there is a potential cause and effect relationship between the IP 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.

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

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/CP, 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.

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

Investigators are not obligated to actively seek AEs or SAEs in subjects once they have discontinued from and/or completed the study (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 investigational product 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 investigational products 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 or she has a complaint or problem with the investigational product so that the situation can be assessed.

9.3. Treatment of Overdose

For the purposes of this study, an overdose of LY3478006 is considered any dose higher than the dose assigned through randomization. There is no specific antidote for LY3478006. In the event of an overdose, the subject should receive supportive care and any AEs should be documented. Refer to the IB.

9.4. Safety

Laboratory tests, vital signs, ECGs, neurological examinations, and pupillometry assessments will be conducted according to the Schedule of Activities (Section 2).

9.4.1. Laboratory Tests

The safety laboratory tests detailed in Appendix 2 will be conducted for each subject.

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

Supine and orthostatic (standing) blood pressure and pulse rate will be measured; subjects should be supine for at least 5 minutes and stand for at least 2 minutes. If the measurements do not meet the criteria for orthostatic (postural) hypotension, no further measurements are needed. If the standing blood pressure measurements show systolic blood pressure and diastolic blood pressure decreases of ≥20 mmHg or ≥10 mmHg, the sequence of supine and standing measurements should be repeated up to 2 more times.

If the subject feels unable to stand, supine vital signs only will be recorded. In addition, 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 and agreed upon between the sponsor and investigator.

9.4.3. Electrocardiograms

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

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 investigational 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/QTc 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/her review of the ECG printed at the time of collection. Any new clinically relevant finding should be reported as an AE.

9.4.4. Other Tests

9.4.4.1. Neurological Examinations

Neurological examinations will be performed to evaluate the following:

- Strength of muscle groups (including those of the head and neck, upper limbs, and lower limbs),
- Deep tendon reflexes, and
- Sensation (tactile, vibration, joint position sense, and pin prick) of index fingers and great toes.

New or worsened abnormality on the neurologic exam should be reported as an AE. Subjects will be referred to a consulting neurologist for neurologic evaluation in the following circumstances:

- A subject experiences a significant change from baseline neurological examination
- A subject experiences an AE suggestive of peripheral neuropathy or abnormal peripheral sensation that is serious, or results in subject's discontinuation from the study, or is ongoing at the end of the subject's participation in the study, or is severe; including but not limited to
    - allodynia,

- burning sensation,
- carpal tunnel syndrome,
- dysesthesia,
- hyperesthesia,
- hyperpathia,
- hypoesthesia,
- neuralgia,
- neuritis,
- neuropathy peripheral,
- pallanesthesia,
- paresthesia,
- peripheral sensory neuropathy,
- sciatica,
- sensory disturbance,
- sensory loss,
- tarsal tunnel syndrome

9.4.4.2. Pupillometry Assessments

Dynamic pupillometry assessments will be performed to evaluate sympathetic autonomic nervous system function using a commercially available pupillometer (NeurOptics, Inc. 2017). Assessments will be made, where possible, by the same trained individual, at the same time of day (for example, between 10 AM and 12 PM), in the same light-controlled environment, and same eye. Subjects will sit in a darkened room and adapt for 5 minutes before each assessment. Objective measurements will include the following:

- Maximum diameter (maximum pupil size before constriction)
- Minimum diameter (pupil diameter at peak constriction)
- Delta % change (% of change [size-min]/size) as a %
- Latency of constriction (time of onset of constriction following initiation of the light stimulus)
- Constriction velocity (average velocity of how the pupil diameter is constricting measured in millimeters per second)
- Maximum constriction velocity (maximum velocity of how the pupil diameter is constricting measured in millimeters per second)

- Dilation velocity (the average pupillary velocity when, after having reached the peak of constriction, the pupil tends to recover and to dilate back to the initial resting size, measured in millimeters per second
- Time to reach 75% recovery (the time to reach 75% of the original baseline pupil diameter after the peak of the constriction).

9.4.5. Safety Monitoring

The Lilly CP 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 CP or CRP will periodically review the following data:

- trends in safety data
- laboratory analytes
- AEs

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

In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, additional analyses of the safety data will be conducted by the personnel included in the Blinding Plan.

9.4.5.1. Injection/Infusion Site Reactions

Symptoms of a local injection/infusion site reaction may include erythema, induration, pain, pruritus, and edema. If an injection/infusion site event is reported, the AE will be recorded, and additional data will be provided to the sponsor in the eCRF.

Injection/infusion sites may be inspected and photographically documented.

9.4.5.2. Allergic/Hypersensitivity Events

All biologic agents carry the risk of systemic allergic/hypersensitivity reactions. Clinical manifestations of these reactions may include but are not limited to skin rash, pruritus (itching), dyspnea, urticaria (hives), angioedema (for example, swelling of the lips and/or tongue), hypotension, and anaphylactic reaction. If such a reaction occurs, additional data describing each symptom should be provided to the sponsor in the eCRF.

All subjects will be monitored closely for symptoms and signs that may occur as part of a systemic infusion reaction (Section 7.4.2.2).

Sites will have appropriate advanced cardiac life support (ACLS) trained medical staff and appropriate medical equipment including a crash cart on site when study participants are receiving study drug. It is recommended that participants who experience a systemic hypersensitivity reaction be treated per the local standard of care.

In the presence of generalized urticaria, or if anaphylaxis is suspected, blood samples should be collected for hypersensitivity tests after the subject is stabilized and as directed in Appendix 5. The laboratory results will be provided to the sponsor via the central laboratory.

9.4.5.3. Hepatic Safety

Close monitoring

If a study participant who had normal or near normal baseline ALT, AST, ALP, TBL (i.e., <1.5x ULN) experiences elevated ALT≥3x ULN, AST≥3x ULN, ALP ≥2x ULN, or TBL≥2x, laboratory tests (Appendix 6) should be repeated within 48 to 72 hours, including ALT, AST, ALP, TBL, gamma-glutamyl transferase (GGT) and creatine kinase (CK) to confirm the abnormality and to determine if it is increasing or decreasing.

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

Initially, monitoring of symptoms and hepatic biochemical tests should be done at a frequency of 2 to 3 times weekly, based on the participant's clinical condition and hepatic biochemical tests. Subsequently, the frequency of monitoring may be lowered to once every 1 to 2 weeks, if the participant's clinical condition and lab results stabilize.

Comprehensive hepatic evaluation

If a study participant experiences elevated ALT≥5x ULN, AST≥5x ULN, ALP ≥3x ULN, TBL≥2x ULN, or elevated ALT, AST≥3x ULN with hepatic signs/symptoms (severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%), a comprehensive evaluation should be performed to search for possible causes of liver injury.

At a minimum, this evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for viral hepatitis A, B, C, E, tests for autoimmune hepatitis, and an abdominal imaging study (for example, ultrasound or computed tomography [CT] scan).

Based on the patient's history and initial results, further testing should be considered, in consultation with the Lilly designated medical monitor, including tests for HDV, CMV, EBV, acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethylglucuronide, and serum phosphatidylethanol. Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist/gastroenterologist consultation, MRCP, ERCP, cardiac echocardiogram, or a liver biopsy.

Additional hepatic data collection (hepatic safety CRF) in study participants who have abnormal liver tests during the study

Additional hepatic safety data collection (hepatic safety CRF) should be performed in study participants who meet 1 or more of the following 5 conditions:

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

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

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities, venous blood samples of approximately 3 mL each will be collected to determine the serum concentrations of LY3478006. A maximum of 5 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 investigative sites or blinded personnel until the study has been unblinded. Any PK data shared during dose escalation discussions will be in a blinded summary format.

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 LY3478006 will be assayed using a validated enzyme-linked immunosorbent assay method. Analyses of samples collected from placebo-treated subjects are not planned.

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

9.6. Pharmacodynamics

Not applicable.

9.7. Immunogenicity Assessments

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples will be collected and stored for potential future analysis to determine antibody production against LY3478006. Antibodies may be further characterized for their ability to neutralize the activity of LY3478006. To interpret the results of immunogenicity, a venous blood sample will be collected at the same time points to determine the serum concentrations of LY3478006. All samples for immunogenicity should be taken predose when applicable and possible.

Treatment-emergent antidrug antibodies (TE-ADAs) are defined in Section 10.3.3. If the immunogenicity sample at the last scheduled assessment or discontinuation visit is TE-ADA positive, additional samples may be taken until the signal returns to baseline (i.e. no longer TE-ADA positive) or for up to 1 year after last dose.

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

9.8. 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 variable exposure or response to LY3478006 and to investigate genetic variants thought to play a role in chronic pain. 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 ERBs impose shorter time limits, for the study at a facility selected by Lilly. 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 LY3478006 or after LY3478006 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.

9.9. Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, PD, mechanism of action, variability of patient response (including safety), and

clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules including deoxyribonucleic acid (DNA), ribonucleic acid (RNA), proteins, lipids, and other cellular elements.

Serum, plasma, whole blood RNA, whole blood for epigenetics, and skin biopsy samples for protein biomarkers samples for non-pharmacogenetic biomarker research will be collected at the times specified in the Schedule of Activities (Section 2) where local regulations allow.

Serum NGF levels will be evaluated over time to assess changes in NGF levels following single IV and SC administration of LY3478006. Abdomen skin biopsy samples will be collected and used to study protein biomarkers, including tTrkA and pTrkA, related to pain and/or related to the mechanism of action of LY3478006.

Techniques used may include but are not limited to immunoassays. Samples may be used for exploratory micro array expression profiling or transcriptome sequencing. Detailed instructions for sample collection and handling will be provided by the sponsor. Samples will be sent to a sponsor-designated laboratory for immunoassays.

Samples will be used for research on the drug target, disease process, variable response to LY3478006, pathways associated with chronic pain, mechanism of action of LY3478006, and/or research method, or for validating diagnostic tools or assay(s) related to chronic pain.

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 ERBs impose shorter time limits, at a facility selected by Lilly. 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 LY3478006 or after LY3478006 is commercially available.

9.10. Health Economics

This section is not applicable for this study.

10. Statistical Considerations and Data Analysis

10.1. Sample Size Determination

Up to 70 healthy subjects may be enrolled such that approximately 56 subjects complete the study. It is planned that 16 of these 56 subjects will be of Japanese origin (first-generation). Subjects who are randomized but not administered treatment may be replaced to ensure that enough subjects complete the study. The ethnicity of the replacement subject (Japanese or non-Japanese) should match the ethnicity of the discontinued subject, where possible.

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

10.2. Populations for Analyses

Summary statistics data tabulations and data graphs by ethnicity (Japanese and non-Japanese) will be provided as appropriate.

10.2.1. Study Participant Disposition

A detailed description of subject disposition will be provided at the end of the study.

10.2.2. Study Participant Characteristics

The subject's age, sex, race, weight, height, and other demographic characteristics will be summarized and may be used in the PK and safety analyses as quantitative or classification variables.

10.3. Statistical Analyses

Statistical analysis of this study will be the responsibility of Lilly or its designee. Pharmacokinetic analyses will be conducted on data from all subjects who receive at least 1 dose of the IP and have evaluable PK. Safety analyses will be conducted for all enrolled subjects, whether or not they completed all protocol requirements.

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

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 study entry 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.

10.3.1.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include safety laboratory, vital signs, neurologic examination, and pupillometry. The parameters will be listed, and summarized using standard descriptive statistics. Electrocardiogram and physical examination will be performed for safety monitoring purposes and will not be listed or summarized. Additional analysis will be performed if warranted upon review of the data.

10.3.2. Pharmacokinetic Analyses

10.3.2.1. Pharmacokinetic Parameter Estimation

Pharmacokinetic analysis will be conducted on subjects who received LY3478006 and have sufficient samples collected post dose.

Pharmacokinetic parameters for LY3478006 will be calculated by standard noncompartmental methods of analysis (NCA) using WinNonlin. The primary parameters for analysis will be maximum observed drug concentration (C_{max}) and area under the concentration versus time curve (AUC) from zero to infinity ($AUC_{0-\infty}$). Other noncompartmental parameters, such as half-life ($t_{1/2}$), CL, volume of distribution (apparent clearance, and apparent volume of distribution for SC administration) may be calculated and reported as deemed appropriate.

In addition, LY3478006 concentration time data may be analyzed using non-linear mixed effect modeling as implemented in software such as NONMEM. Serum data from all subjects will be pooled to determine the compartmental PK parameters (for example, CL, Vss, $t_{1/2}$, F) and between- and within-subject variability. Covariate relationships, such as CL or volume of distribution versus body size (for example, body weight and body mass index) or gender, may be investigated through graphical exploration and may be quantified through modeling. The effect of factors such as race/ethnicity (Japanese versus non-Japanese subjects) could be tested in the model and may be included in the final model.

The version of any software used for the analysis will be documented, and the program will meet the Lilly requirements of software validation. It is possible that other validated, equivalent PK software programs may be utilized if appropriate, warranted, and approved by Global PK/PD management.

10.3.2.2. Pharmacokinetic Statistical Inference

Pharmacokinetic parameter estimates from the NCA will be evaluated to delineate effects of dose proportionality. Log-transformed C_{max} and AUC estimates will be evaluated in a linear model with log-transformed IV dose for healthy subjects as explanatory variable. The treatment differences will be back-transformed to present the ratios of geometric means and the corresponding 90% confidence intervals (Smith et al. 2000).

For the SC dose, the bioavailability relative to IV infusion at the same dose will be evaluated via a log-transformed model. The log-transformed C_{max} and AUC will be the response variable, and route of administration (IV/SC) is the explanatory variable.

10.3.3. Evaluation of Immunogenicity

Upon full assay validation, TE-ADAs will be assessed. The frequency and percentage of subjects with preexisting ADA and with TE-ADA to LY3478006 may be tabulated.

Treatment-emergent ADAs are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution if no ADAs were detected at baseline (treatment-induced ADA) or those with a 4-fold (2 dilutions) increase in titer compared to baseline if ADAs were detected at baseline (treatment-boosted ADA).

The frequency of neutralizing antibodies may also be tabulated in TE-ADA+ subjects, when available.

The relationship between the presence of antibodies and the PK parameters and PD response may be assessed.

10.3.4. Data Review During the Study

Data will be reviewed during the study to evaluate the safety and PK of LY3478006, inform dose selection/escalation decisions, and confirm inclusion of data from an adequate number of Japanese and non-Japanese subjects.

The investigator and the Lilly CP/CRP will make the determination regarding dose escalation based on their review of the safety and tolerability data as described in Section 7.4.1. In addition, the Lilly study team will review safety, tolerability, and PK data (interim access to data review [IAD]) to guide dose selection/cohort initiation, and/or to inform the design of subsequent studies. Based upon review of data, the Lilly team and investigator will make the determination regarding dose selection/cohort initiation. The investigator will remain blinded, and the Lilly team will be unblinded during these reviews. Interim access to data reviews are planned as follows:

- Prior to initiating the planned 100-mg SC dose level cohort (Cohort 7), the IAD will include:
    - PK and safety data from Cohorts 1, 2, and 3 (LY3478006 10- 30, and 100-mg IV dose levels)
- Prior to initiating the 1000-mg IV dose cohort (Cohort 6), or a 300-mg SC dose level cohort (Cohort 7), the IAD will include:
    - PK data from Cohorts 1, 2, 3, and 4 (LY3478006 10-, 30-, 100-, and 300-mg dose levels)
    - Available safety data from Cohorts 1, 2, 3, 4, and 5 (LY3478006 10-, 30-, 100-, 300-, and 600-mg dose levels). Safety data from Cohort 5 will not be required for the 300-mg SC dose level cohort (Cohort 7) decision.

10.3.5. Interim Analyses

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary, the Lilly CP, CRP/investigator, or designee will consult with the appropriate medical director or designee to determine if it is necessary to amend the protocol.

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12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
ADA	antidrug antibody
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
$AUC_{0-\infty}$	area under the concentration versus time curve from time zero to infinity
blinding	A procedure in which one or more parties to the study are kept unaware of the treatment assignment(s). Unless otherwise specified, blinding will remain in effect until final database lock. A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the subject is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the subject are not. A double-blind study is one in which neither the subject nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received
BED	biologically effective dose
CIOMS	Council for International Organizations of Medical Sciences
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.
CP	clinical pharmacologist
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

C_{trough}	trough concentration
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.
ERB	ethical review board
FHD	first human dose
GCP	good clinical practice
IAD	interim access to data
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonization
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.
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(ly)
NCA	noncompartmental methods of analysis
NGF	nerve growth factor
NOAEL	no-observed-adverse-effect-level
PAD	pharmacology active dose
PD	pharmacodynamic
PK	pharmacokinetic

randomize	the process of assigning subjects to an experimental group on a random basis
SAE	serious adverse event
SC	subcutaneous(ly)
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
TBL	total bilirubin
TE-ADA	treatment-emergent antidrug antibody
TEAE	treatment-emergent adverse event: Any untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment
ULN	upper limit of normal

Appendix 2. Clinical Laboratory Tests

Safety Laboratory Tests

Hematology	Clinical Chemistry
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count (RBC)	Bicarbonate
Mean cell volume	Chloride
Mean cell hemoglobin	Calcium
Mean cell hemoglobin concentration	Phosphorus
Leukocytes (WBC)	Blood urea nitrogen (BUN)
Platelets	Total protein
	Albumin
Differential WBC [Absolute counts and %] of:	Total bilirubin
Neutrophils	Alkaline phosphatase (ALP)
Lymphocytes	Aspartate aminotransferase (AST)
Monocytes	Alanine aminotransferase (ALT)
Eosinophils	Creatinine
Basophils	
Urinalysis	Ethanol testing[a,b]
Specific gravity	Urine drug screen[a,b]
pH	Hepatitis B surface antigen[a]
Protein	Hepatitis C antibody[a]
Glucose	HIV[a]
Ketones	Pregnancy test
Bilirubin	FSH[a]
Urobilinogen	Coagulation tests[a]
Blood	PT/INR
Nitrite	aPTT

Abbreviations: aPTT = activated partial thromboplastin time; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; INR = international normalized ratio; PT = prothrombin time; RBC = red blood cells; WBC = white blood cells.

[a] Required at screening only.

[b] Urine drug screen and ethanol level may be repeated prior to admission to the clinical research unit and at other times indicated in the Schedule of Activities.

Appendix 3. Study Governance, Regulatory and Ethical Considerations

Informed Consent

The investigator is responsible for:

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

Recruitment

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

Ethical Review

The investigator or appropriate local representative must give assurance that the ethical review board (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 good clinical practice (GCP).

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

- the current Investigator's Brochure (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 (CIOMS) International Ethical Guidelines
2) applicable ICH GCP Guidelines
3) applicable laws and regulations

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

Protocol Signatures

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

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 personal information collected will be provided in a written document to the subject by the Sponsor.

Study and Site Closure

Discontinuation of Study Sites

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

Discontinuation of the Study

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

Appendix 4. 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 J2F-MC-OHAA Sampling Summary

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	20.5	1	20.5
Clinical laboratory tests[a,b]	12.5	12	150
Pharmacokinetics[b,d]	3	17	51
Nerve growth factor [b,d]	0.5	17	8.5
Immunogenicity[b,c,d]	10	4	40
Pharmacogenetics	10	1	10
Non-pharmacogenetic storage samples	10	3	30
Total[b,c,d]			310
Total for clinical purposes (rounded up to nearest 10 mL)			310

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

[b] If 12 weeks is shorter than 5 half-lives of LY3478006 based on emerging pharmacokinetic data, up to 3 additional follow-up visits may be added, at each of which additional samples will be taken. An additional blood volume of 78 mL (37.5 mL for clinical laboratory tests, 9 mL for pharmacokinetics, 1.5 mL for nerve growth factor, and 30 mL for immunogenicity) would be collected if the subject attended the maximum allowed number of follow-up visits.

[c] In the event of drug hypersensitivity reactions (immediate or non-immediate), 3 additional samples will be collected for immunogenicity (a total additional blood volume of 30 mL [one 10-mL sample collected as close to the onset of the event as possible, one 10-mL sample collected at the resolution of the event, and one 10-mL sample collected 30 days following the event]).

[d] If the immunogenicity sample at the last scheduled assessment or discontinuation visit is TE-ADA positive, up to 4 additional outpatient visits may be required to monitor ADA until the signal returns to baseline (e.g., no longer TE-ADA positive) or for up to 1 year after the last dose. An additional blood volume of 54 mL (12 mL for pharmacokinetics, 2 mL for nerve growth factor, and 40 mL for immunogenicity) would be collected if the subject attended outpatient visits for 1 year after the last dose.

Appendix 5. Laboratory Testing for Hypersensitivity Events

Laboratory testing should be performed at the time of a systemic hypersensitivity event. The management of the adverse event may warrant laboratory testing beyond what is described herein and should be performed as clinically indicated.

Laboratory testing during a systemic hypersensitivity event is not performed for diagnostic purposes. Its intent is several fold:

- To help characterize and classify systemic hypersensitivity reactions
- To meet regulatory expectations
- To improve subsequent clinical management by helping to distinguish between the various mechanistic bases of anaphylaxis

Blood samples will be obtained for laboratory testing in the presence of generalized urticaria or if anaphylaxis is suspected as follows:

- After the subject has been stabilized, obtain a sample within 1 to 2 hours of the event, however, samples may be obtained as late as 12 hours after the event as analytes can remain altered for an extended period of time. Record the time at which the sample was collected.
- Obtain a follow-up sample at the next regularly scheduled visit or after 4 weeks, whichever is later.

The following laboratory tests should be obtained, and will be assayed by a Lilly-designated laboratory:

- Tryptase

  Note: if a tryptase sample is obtained more than 2 hours after the event (i.e., within 2 to 12 hours), or is not obtained because more than 12 hours have lapsed since the event, obtain urine for N-methylhistamine (NMH) testing. Note that for tryptase serum samples obtained within 2 to 12 hours of the event, urine NMH testing is performed in addition to tryptase testing. Collect the first void urine following the event. Obtain a follow up urine for NMH testing at the next regularly scheduled visit or after 4 weeks, whichever is later.

- Anti-LY3478006 antibodies (ADA) and LY3478006 concentration (PK)
  - ADA testing should include drug-specific immunoglobulin-E (IgE)
  - If a drug-specific IgE assay is not available, a commercially-available alternative test that can indicate the presence of drug-specific IgE in serum is the basophil activation test (BAT)

- Complement C3a and C5a
- Cytokines IL-6, IL-1β, and IL-10 (or any cytokine panel that includes these 3 cytokines)

Appendix 6. 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 patients 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[a]**
AST	**Alkaline Phosphatase Isoenzymes[a]**
GGT	**Anti-smooth muscle antibody (or anti-actin antibody)[a]**
CPK	

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

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

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

Appendix 7. Protocol Amendment J2F-MC-OHAA(a) Summary
A Single Ascending Dose Study to Evaluate Safety, Tolerability, and Pharmacokinetics of LY3478006 in Healthy Subjects

Overview

Protocol J2F-MC-OHAA, A Single Ascending Dose Study to Evaluate Safety, Tolerability, and Pharmacokinetics of LY3478006 in Healthy Subjects, has been amended. The new protocol is indicated by Amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

The updates to this protocol are those agreed to in Lilly's response to a clinical information request sent by the Food and Drug Administration. The overall changes and rationale for the changes made to this protocol are as follows:

- Footnote a in Section 2 has been amended to, "*Full physical examination on Day -1 and Day 85 or E/T (may include body temperature and respiratory rate). At all other time points, the examination will include at a minimum, an assessment of skin, injection site, and oral cavity*", to ensure that a basic physical examination is performed at each time point.
- Exclusion criterion [23] was added per an FDA request to Section 6.2 to exclude patients with abnormal liver function tests at screening. Exclusion criterion [29] was modified in accordance with changes made to Section 6.3.2.
- Section 6.3.2 has been amended per an FDA request to state that subjects will not be permitted to consume alcohol from 48 hours before each visit until leaving the CRU. Subjects will be advised to abstain from alcohol consumption for the remainder of the trial until their final visit.
- Section 9.4.5.2 has been amended to state that, "*Sites will have appropriate advanced cardiac life support (ACLS) trained medical staff and appropriate medical equipment including a crash cart available on site when study participants are receiving study drug. It is recommended that participants who experience a systemic hypersensitivity reaction be treated per the local standard of care*", as LY3478006 may be associated with infusion reactions and hypersensitivity reactions.

Revised Protocol Sections

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

2. Schedule of Activities

Study Schedule Protocol J2F-MC-OHAA

		Study Day													
Procedure	**Screening ≤28 days prior to Day 1**	**-1**	**1**	**2**	**3**	**5**	**8**	**10 (±1)**	**15 (±1)**	**22 (±1)**	**29 (±1)**	**43 (±2)**	**57 (±2)**	**71 (±4)**	**Day 85 (±4)[m] or E/T**
Informed Consent	X														
Outpatient Visit	X						X	X	X	X	X	X	X	X	X
CRU Admission		X													
CRU Discharge						X									
Medical History	X														
Height	X														
Weight	X	X													X
Physical Examination[a]	X	X	Predose	24 hr	X	X	X	X	X	X	X	X	X	X	X
Directed Neurological Examination	X	X		24 hr	X	X	X		X		X		X		X
Pupillometry		X				X		X			X				
ECG[b]	X		Predose (1, -0.5, 0 hr), end of infusion[c], 3, 6, 12 hr	24 hr	48 hr	X	X	X	X	X	X	X	X		X
AE[d] and Medication Review		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug Administration[e]			0 hr												
Vital Signs[f]	X		Predose, end of infusion[c], 3, 6, 12 hr	24 hr	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test[g]	X	X													X
Serology (Hepatitis B Surface Antigen, HIV, Hepatitis C Antibody)	X														

Abbreviations: ADA = antidrug antibody; AE = adverse event; CRU = clinical research unit; ECG = electrocardiogram; E/T = early termination; HIV = human immunodeficiency virus; hr = hour; IV = intravenous; NGF = nerve growth factor, PK = pharmacokinetics; SC = subcutaneous; TE-ADA = treatment-emergent antidrug antibody.

Note: Study procedures scheduled relative to IV dosing time are to occur from the time of the start of infusion; e.g., 3 hours postdose would be 3 hours after the start of the IV infusion.

[a] Full physical examination on Day -1 and Day 85 or E/T (may include body temperature and respiratory rate). At all other time points, the examination will include at a minimum, an assessment of skin, injection site, and oral cavity. ~~Symptom-driven physical examination at all other times as deemed necessary by the investigator.~~

6.2 Exclusion Criteria

[23] Have liver function test (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP], total bilirubin [TBL]) above the upper limit of normal (ULN) at screening.

[29] Have an average weekly alcohol intake that exceeds 21 units per week (males) and 14 units per week (females), or are unwilling to stop alcohol consumption from 48 hours prior to dosing ~~until discharge from the CRU~~ (1 unit = 12 oz or 360 mL of beer; 5 oz or 150 mL of wine; 1.5 oz or 45 mL of distilled spirits).

6.3.2. Caffeine, Alcohol, and Tobacco

Consumption of caffeine- and xanthine-containing products is allowed, provided that the subject's consumption has been consistent for the past 30 days.

Subjects will not be permitted to consume alcohol from 48 hours before each visit until leaving the CRU. Subjects will be advised to abstain from alcohol consumption for the remainder of the trial until their final visit~~Subjects will not exceed their habitual alcohol consumption during the study. When not resident in the CRU, male subjects should be advised to limit alcohol consumption to no more than 21 units per week and female subjects to no more than 14 units per week, and all subjects should be advised to limit alcohol consumption to no more than 3 units in a day~~.

Subjects will not be permitted to smoke from CRU admission until discharge from the CRU.

9.4.5.2. Allergic/Hypersensitivity Events

All biologic agents carry the risk of systemic allergic/hypersensitivity reactions. Clinical manifestations of these reactions may include but are not limited to skin rash, pruritus (itching), dyspnea, urticaria (hives), angioedema (for example, swelling of the lips and/or tongue), hypotension, and anaphylactic reaction. If such a reaction occurs, additional data describing each symptom should be provided to the sponsor in the eCRF.

All subjects will be monitored closely for symptoms and signs that may occur as part of a systemic infusion reaction (Section 7.4.2.2).

Sites ~~should~~ will have appropriate advanced cardiac life support (ACLS) trained medical staff ~~appropriately trained medical staff~~ and appropriate medical equipment including a crash cart on site ~~available~~ when study participants are receiving study drug. It is recommended that participants who experience a systemic hypersensitivity reaction be treated per the local standard of care.

In the presence of generalized urticaria, or if anaphylaxis is suspected, blood samples should be collected for hypersensitivity tests after the subject is stabilized and as directed in Appendix 5. The laboratory results will be provided to the sponsor via the central laboratory.

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