J1H-MC-LAJA Statistical Analysis Plan

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

NCT03692949

Approval Date: 19 March 2020

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Statistical Analysis Plan

Protocol: J1H-MC-LAJA

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

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1. ABBREVIATIONS

ADA	Anti-drug antibody
AE	Adverse Event
AUC	Area under the concentration-time curve
C_{max}	Maximum drug concentration
CSR	Clinical study Report
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
IRB	Institutional review board
IB	Investigator's brochure
ICF	Informed consent form
IMP	Investigational Medicinal Product
MedDRA	Medical dictionary for regulatory activities
PACAP	Pituitary adenylate cyclase-activating polypeptide
PK	Pharmacokinetics
PD	Pharmacodynamic
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
TEADA	Treatment-emergent anti-drug antibody
TEAE	Treatment-emergent adverse event
T_{max}	Time to C_{max}

2. INTRODUCTION

The statistical analysis plan (SAP) contains the analysis information in detail on the definition of the analysis populations, derivation of variables, convention of analysis scope, and statistical methodology for the analyses of safety and tolerability of LY3451838 based on the data collected per the protocol J1H-MC-LAJA, a Phase I study sponsored by Eli Lilly and Company. In case of disagreement between the SAP and the Clinical Study Protocol, the SAP prevails.

Any deviations from this SAP during the actual data analysis will be documented properly in a change request or a note-to-file document, as well as in the Clinical Study Report (CSR).

3. OBJECTIVES AND ENDPOINTS

3.1 Objectives

The primary objective of this trial is to evaluate the safety and tolerability of a single dose of LY3451838 in healthy subjects.

The secondary objective is to evaluate the pharmacokinetics of LY3451838 in healthy subjects following a single dose of LY3451838.

The exploratory objectives:

- Assess immunogenicity of LY3451838.
- Assess target engagement.

3.2 Endpoints

3.2.1 Safety Endpoint

- Adverse Events
- Serious Adverse Events

3.2.2 Pharmacokinetics Endpoints

- AUC
- C_{max}

3.2.3 Exploratory Endpoints

- TEADA incidence and titers
- PACAP Concentration

4. STUDY DESIGN

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

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

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

4.1 Sample Size and Statistical Power Consideration

Up to 80 healthy subjects may be enrolled so that approximately 6 subjects in each LY3451838 dosing group (including that of pooled placebo groups in Part A) complete the 20-week study. Subjects who discontinued from the study completion may be replaced at the discretion of the sponsor.

4.2 Study Diagram and Flow Chart

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

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

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

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

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

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

b Height will be collected at Screening only.

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

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

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

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

g Body temperature to be obtained as single measurement.

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

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

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

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

5. ANALYSIS POPULATIONS (ANALYSIS SETS)

5.1 Safety Population

Safety Population consists of all subjects who are enrolled and received any IMP in this study.

6. TREATMENT DESCRIPTIONS

Unless otherwise indicated, on the summary tables, the subjects are to be identified as LY3451838 by each cohort (cohort 1, cohort 2, cohort 3, cohort 4, cohort 5, cohort 6, cohort 7, cohort 8) and all placebo subjects combined, where applicable.

As of the date of data locked for this analysis, there is no patients enrolled in the cohort 8.

7. STATISTICAL ANALYSIS METHODS AND ISSUES

7.1 Statistical Methods

Descriptive statistics, namely sample size (n), mean, standard deviation, median, minimum and maximum for continuous variables, count and percentage for categorical variables, are to be provided.

7.2 Interim Analysis

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

7.3 Missing Data

No imputation will be made for missing values of safety endpoints except some missing data associated with adverse events (AE), which is specified in Section 9.1.

7.4 Laboratory Data Issues

If there are two or more evaluable results in a given visit, the latest test result will be used for analysis. If the evaluable result was indicated by < nn, half of the value (=nn/2) will be used in the analysis. If the evaluable result was > nn, the value (=nn) will be used in the analysis.

7.5 Baseline Definition

The baseline is the results measured at Visit 3 prior to dosing or Visit 2 if Visit 3 is not available.

8. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

8.1 Subject Disposition

The number and percentage of subjects who were screened, enrolled, and treated will be summarized. The number and percentage of subjects who discontinued will also be summarized for each reason of the discontinuation. The analysis will be done by overall patients as well.

8.2 Demographics and Baseline Characteristics

The demographics and Baseline characteristics: gender, race, age, age in three categories (<65, >=65 and <85, >=85), weight, height, and the body-mass index [BMI] will be summarized using descriptive statistics. The analysis will be done by overall patients as well.

8.3 Medical History

The medical history data will be summarized by System Organ Class and preferred term based on coded data by MedDRA. The count and percentage of medical condition per preferred term and SOC will be provided.

9. ANALYSIS OF SAFETY ENDPOINTS

9.1 Adverse Events

The adverse events will be coded by the Medical Dictionary for Drug Regulatory Activities (MedDRA) version 22.0. The treatment-emergent adverse event (TEAE) is defined as any AE emerging or worsening after start of investigational medicinal product (IMP) administration (including placebo). Summary tables will include number of subjects reporting TEAEs and as percentage of number of subjects for the overall subjects. The number of serious TEAEs will be summarized in the appropriate summary table. Summary tables will also be presented for the frequency of adverse events by the MedDRA system organ class and preferred term. Multiple events in the same system organ class for a subject are only counted once in the statistics of that system organ class.

The SOC will be presented alphabetically and preferred term within SOC will be presented in descending order of overall frequency. Summary tables will also be provided for the frequency of adverse events by MedDRA system organ class and preferred term and severity of adverse events, and relationship of adverse events to study drug. In these summaries, the most extreme outcome (highest severity and closest relationship to study drug) will be used for those subjects who experience the same adverse event (per preferred term) on more than one occasion.

The number and percentage of patients with Serious TEAE by SOC and preferred term will be summarized. An individual listing of serious TEAE will also be provided.

The summary tables will be performed by each cohort in LY3451838, overall LY3451838 and all placebo subjects combined.

9.2 Vital Signs

Vital signs (systolic and diastolic blood pressure, pulse rate and body temperature) are to be summarized at each visit. Change from baseline to each post-baseline visit will also be provided. When triplicate blood pressure or pulse rate measurement precede the orthostatic measurement, the last supine blood pressure or pulse rate measurement will be used.

9.3 Laboratory Tests

The test results of clinical chemistry, hematology and urinalysis are to be summarized by visit. Change from baseline to each post-baseline visit will also be provided. When applicable, all the test result in the following list will be presented.

Clinical Chemistry:	**Hematology:**
Alkaline phosphatase	Erythrocytes count (RBC)
Alanine Aminotransferase	Hematocrit
Aspartate Transaminase	Hemoglobin
Albumin	Mean cell volume
Blood urea	Mean cell hemoglobin
Bicarbonate	Mean cell hemoglobin concentration
Total Bilirubin	Leukocyte count (WBC)
Calcium	Platelets
C-reactive Protein	Basophils
Complement 3	White blood cell count + differential
Complement 4	Erythrocyte sedimentation rate (ESR)
Sodium	
Total cholesterol	**Urinalysis**:
Chloride	pH
Creatinine	Specific gravity
Glucose	Blood
Potassium	Nitrite
	Bilirubin
	Ketones
	Protein
	Glucose
	Urobilinogen
	Leukocytes
	Microscopy

Additional analysis will be performed to C3, C4, CRP and ESR.

The number and percentage of subjects with significant decrease in C3 and C4 will be summarized at each of the scheduled visits by treatment and by cohort.

The number and percentage of subjects with significant increase in CRP and ESR will be summarized at each of the scheduled visits by treatment and by cohort.

The significant decrease in C3/C4 will be met if the lab result is classified as NORMAL at baseline, and classified as LOW (<LLN) at post-baseline visits, OR the lab result is classified as LOW at baseline(<LLN), and result gets LOWER than baseline at post-

baseline visits. The significant increase in CRP/ESR will be met if the lab result is classified as NORMAL at baseline, and classified as HIGH (>ULN) at post-baseline visits, OR the lab result is classified as HIGH at baseline(>ULN), and result gets HIGHER than baseline at post-baseline visits.

9.4 Electrocardiogram

Descriptive statistics of ECG parameters(quantitative) and assessments (qualitative) will be summarized at each visit. The change from baseline will be summarized as well for quantitative parameters at each visit. Shift tables from baseline will be presented for ECG qualitative assessment.

9.5 Neurological Examinations

Descriptive statistics of Neurological Examinations will be summarized at each visit. The number and percentage of Neurological Examinations result will be presented as well.

9.6 Concomitant Medications

The summary table for all concomitant medications reported during the study will be made by standardized name in each medication class, using descriptive statistics (count and percentage).

10. ANALYSIS OF EXPLORATORY ENDPOINTS

10.1 Immunogenicity Assessment

The incidence of TEADA (including preexisting ADA) to LY3451838 will be summarized in three categories: Subject evaluable for TEADA, Subject with ADA detected at baseline, and Subject with TEADA+ at postbaseline (Treatment-induced / Treatment boosted).

The summary will be performed by each cohort in LY3451838, overall LY3451838 and all placebo subjects combined.

Treatment-emergent ADAs are defined as those with a titer 2-fold (1dilution) 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 minimum required dilution is 1:40.

10.2 Exploratory Assessment of PACAP Concentration

The results of PACAP concentration will be summarized using descriptive statistics at each of the scheduled visits, as well as the change from baseline. The summary will be performed by each cohort in LY3451838, overall LY3451838 and all placebo subjects combined.

11. ANALYSIS OF PK ENDPOINTS

The PK analysis are not in the scope of this SAP and are planned to be documented and performed by a third party.

12. LIST OF TABLES AND DATA LISTINGS

12.1 Statistical Tables

The statistical tables are to be generated using SAS version 9.4. In general, the sample size (n), minimum, and maximum are to be presented by whole number. The mean, standard deviation, and median are to be rounded and presented to one decimal place. For some values with meaningful decimal digits, their mean, standard deviation, and median will be rounded to more than one decimal place when necessary. The count will be the whole number. The percentage will be presented to one decimal place.

Disposition of Subjects and Baseline Characteristics:

Number	Title	Population
14.1.1	Disposition of Subjects	All
14.1.2	Demographics and Baseline Characteristics	Safety
14.1.3	Medical History	Safety

Safety – Adverse Events

Number	Title	Population
14.3.1.1	Number of Subjects with Treatment-Emergent Adverse Events	Safety
14.3.1.2	Number of Treatment-Emergent Adverse Events	Safety
14.3.1.3	Number of Subjects with TEAE by MedDRA System Organ Class / Preferred Term	Safety
14.3.1.4	Number of Subjects with Serious TEAE by MedDRA System Organ Class / Preferred Term	Safety
14.3.1.5	Number of Subjects with TEAE by MedDRA System Organ Class / Preferred Term and Severity	Safety
14.3.1.6	Number of Subjects with TEAE by MedDRA System Organ Class / Preferred Term and Relationship to Study Drug	Safety
14.3.2.1	Listing of Serious TEAE	Safety

Safety – Laboratory Test Results:

Number	Title	Population
14.3.4.1	Laboratory Test Results – Chemistry	Safety
14.3.4.2	Laboratory Test Results – Hematology	Safety
14.3.4.3	Laboratory Test Results – Urinalysis	Safety
14.3.4.4	Laboratory Test Results – C3, C4, CRP and ESR	Safety
14.3.4.5	Immunogenicity	Safety
14.3.4.6	PACAP Concentration	Safety

Safety – Other:

Number	Title	Population
14.3.5.1	Vital Signs	Safety
14.3.5.2	Electrocardiogram (ECG)	Safety
14.3.5.3	Electrocardiogram (ECG) – Overall interpretation Shift from Baseline	Safety
14.3.5.4	Neurological Examinations	Safety
14.3.5.5	Concomitant Medications	Safety

12.2 Data Listings

The following data listings would not be provided if the data listings of the raw data are already provided and suffice per sponsor's perspective. Data listings will be sorted by the subject ID and visits.

Number	Title
1	Subject Disposition
2	Demographics
3	Concomitant Medications
4	Medical History
5	Vital Signs
6	Physical Examination
7	Electrocardiogram (ECG)
8.1	Laboratory Test Results – Chemistry
8.2	Laboratory Test Results – Hematology
8.3	Laboratory Test Results – Urinalysis
8.4	Laboratory Test Results - C3, C4, CRP and ESR
9	Immunogenicity
10	PACAP Concentration
11	Adverse Events
12	Neurological Examinations

13. TABLE SHELLS

The following table shells are provided in order to provide a framework of the statistical analysis for the study. These shells may not be reflective of every aspect of the study, but are intended to show the general layout of the tables that will be included in the final report.

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Table 14.1.1 - Disposition of Subject

		LY3451838								
		Cohort1 25mgIV	Cohort2 75mgIV	Cohort3 250mgIV	Cohort4 500mgIV	Cohort5 1000mgIV	Cohort6 1500mgIV	Cohort7 250mgSC	Placebo	Overall
Screened	xx									
Enrolled		xx	xx	xx	xx	xx	xx	xx	xx	xx
Treated	N	xx	xx	xx	xx	xx	xx	xx	xx	xx
	YES	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)
	NO	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)
Completed	N	xx	xx	xx	xx	xx	xx	xx	xx	xx
	YES	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)
	NO	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)

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Table 14.1.1 - Disposition of Subject (Safety)

	LY3451838								
Primary Reason for Discontinuation	Cohort1 25mgIV	Cohort2 75mgIV	Cohort3 250mgIV	Cohort4 500mgIV	Cohort5 1000mgIV	Cohort6 1500mgIV	Cohort7 250mgSC	Placebo	Overall
N	xx	xx	xx	xx	xx	xx	xx	xx	xx
Adverse Event	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)
Death	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)
Entry Criteria Not Met	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)
Lost To Follow-Up	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)
Physician Decision	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)
Progressive Disease	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)
Protocol Violation	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)
Sponsor Decision	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)
Other	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)

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Table 14.1.2 ╦ Demographics and Baseline Characteristics (Safety)

		LY3451838								
		Cohort1 25mgIV N=XX	Cohort2 75mgIV N=XX	Cohort3 250mgIV N=XX	Cohort4 500mgIV N=XX	Cohort5 1000mgIV N=XX	Cohort6 1500mgIV N=XX	Cohort7 250mgSC N=XX	Placebo N=XX	Overall N=XX
Age (years)	N	xx	xx	xx	xx	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Minimum	xx	xx	xx	xx	xx	xx	xx	xx	xx
	Maximum	xx	xx	xx	xx	xx	xx	xx	xx	xx
Gender	N	xx	xx	xx	xx	xx	xx	xx	xx	xx
	Male	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)
	Female	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)
Race	N	xx	xx	xx	xx	xx	xx	xx	xx	xx
	AMERICAN INDIAN OR ALASKA NATIVE	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)
	ASIAN	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)
	BLACK OR AFRICAN AMERICAN	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)
	NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)
	WHITE	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)

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Table 14.1.2 ╦ Demographics and Baseline Characteristics (Safety)

		LY3451838								
		Cohort1 25mgIV N=XX	Cohort2 75mgIV N=XX	Cohort3 250mgIV N=XX	Cohort4 500mgIV N=XX	Cohort5 1000mgIV N=XX	Cohort6 1500mgIV N=XX	Cohort7 250mgSC N=XX	Placebo N=XX	Overall N=XX
Ethnicity	N	xx	xx	xx	xx	xx	xx	xx	xx	xx
	HISPANIC OR LATINO	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)
	NOT HISPANIC OR LATINO	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)
Height (cm)	N	xx	xx	xx	xx	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Minimum	xx	xx	xx	xx	xx	xx	xx	xx	xx
	Maximum	xx	xx	xx	xx	xx	xx	xx	xx	xx
Weight (kg)	N	xx	xx	xx	xx	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Minimum	xx	xx	xx	xx	xx	xx	xx	xx	xx
	Maximum	xx	xx	xx	xx	xx	xx	xx	xx	xx

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Table 14.1.2 ╥ Demographics and Baseline Characteristics (Safety)

		LY3451838								
		Cohort1 25mgIV N=XX	Cohort2 75mgIV N=XX	Cohort3 250mgIV N=XX	Cohort4 500mgIV N=XX	Cohort5 1000mgIV N=XX	Cohort6 1500mgIV N=XX	Cohort7 250mgSC N=XX	Placebo N=XX	Overall N=XX
BMI (kg/m2)	N	xx	xx	xx	xx	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Minimum	xx	xx	xx	xx	xx	xx	xx	xx	xx
	Maximum	xx	xx	xx	xx	xx	xx	xx	xx	xx

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Table 14.3.1.1 ╦ Number of Subjects with Treatment-Emergent Adverse Events (Safety)

		LY3451838								
		Cohort1 25mgIV N=XX	Cohort2 75mgIV N=XX	Cohort3 250mgIV N=XX	Cohort4 500mgIV N=XX	Cohort5 1000mgIV N=XX	Cohort6 1500mgIV N=XX	Cohort7 250mgSC N=XX	Total LY N=XX	Placebo N=XX
With At Least One Adverse Event	N	xx	xx	xx	xx	xx	xx	xx	xx	xx
	Yes	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)
	No	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)
With At Least One Mild or Moderate Adverse Event	N	xx	xx	xx	xx	xx	xx	xx	xx	xx
	Yes	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)
	No	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)
With At Least One Severe Adverse Event	N	xx	xx	xx	xx	xx	xx	xx	xx	xx
	Yes	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)
	No	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)
With At Least One Serious Adverse Event	N	xx	xx	xx	xx	xx	xx	xx	xx	xx
	Yes	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)
	No	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)
With At Least One Not Related Adverse Event	N	xx	xx	xx	xx	xx	xx	xx	xx	xx
	Yes	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)
	No	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)
With At Least One Related Adverse Event	N	xx	xx	xx	xx	xx	xx	xx	xx	xx
	Yes	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)
	No	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)

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Table 14.3.1.2 ╦ Number of Treatment-Emergent Adverse Events (Safety)

	LY3451838								
	Cohort1 25mgIV N=XX	Cohort2 75mgIV N=XX	Cohort3 250mgIV N=XX	Cohort4 500mgIV N=XX	Cohort5 1000mgIV N=XX	Cohort6 1500mgIV N=XX	Cohort7 250mgSC N=XX	Total LY N=XX	Placebo N=XX
Adverse Event	xx	xx	xx	xx	xx	xx	xx	xx	xx
Mild or Moderate Adverse Events	xx	xx	xx	xx	xx	xx	xx	xx	xx
Severe Adverse Events	xx	xx	xx	xx	xx	xx	xx	xx	xx
Serious Adverse Events	xx	xx	xx	xx	xx	xx	xx	xx	xx
Adverse Events Not Related To Study Drug	xx	xx	xx	xx	xx	xx	xx	xx	xx
Adverse Events Related To Study Drug	xx	xx	xx	xx	xx	xx	xx	xx	xx

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Table 14.3.1.3 ╦ Number of Subjects with TEAE by MedDRA System Organ Class /Preferred Term (Safety)

System Organ Class/ Preferred Term	LY3451838								
	Cohort1 25mgIV N=XX	Cohort2 75mgIV N=XX	Cohort3 250mgIV N=XX	Cohort4 500mgIV N=XX	Cohort5 1000mgIV N=XX	Cohort6 1500mgIV N=XX	Cohort7 250mgSC N=XX	Total LY N=XX	Placebo N=XX
System Organ Class #1									
Preferred Term #1.1	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
Preferred Term #1.2	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
Preferred Term #1.3	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
System Organ Class #2									
Preferred Term #2.1	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
Preferred Term #2.2	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
Preferred Term #2.3	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)

Multiple events with the same preferred term in a system organ class for a subject are only counted once in the statistics of that preferred term.
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Table 14.3.1.4 ╦ Number of Subjects with TEAE by MedDRA System Organ Class /Preferred Term and Severity (Safety)

Treatment: LY3451838 (cohort 1 - 25 mg IV)

Number of Subjects: xx

System Organ Class / Preferred Term	Severity N (%)			
	Mild	Moderate	Severe	Very Severe
System Organ Class #1				
Preferred Term #1.1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred Term #1.2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred Term #1.3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
etc.				
System Organ Class #2				
Preferred Term #2.1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred Term #2.2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred Term #2.3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
etc.				

For multiple events with the same preferred term in a system organ class for a subject, the most severe one is counted. The percentage represents the incidence of an event by the preferred term as a percentage of the total number of subjects in the treatment group.

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Table 14.3.1.5 ╦ Number of Subjects with TEAE by MedDRA System Organ Class /Preferred Term and Severity (Safety)

Treatment: LY3451838 (cohort 1- 25 mg IV)

Number Of Subjects: xx

System Organ Class / Preferred Term	Relationship to Study Drug N (%)	
	Unrelated	Related
System Organ Class #1		
Preferred Term #1.1	xx (xx.x%)	xx (xx.x%)
Preferred Term #1.2	xx (xx.x%)	xx (xx.x%)
Preferred Term #1.3	xx (xx.x%)	xx (xx.x%)
etc.		
System Organ Class #2		
Preferred Term #2.1	xx (xx.x%)	xx (xx.x%)
Preferred Term #2.2	xx (xx.x%)	xx (xx.x%)
Preferred Term #2.3	xx (xx.x%)	xx (xx.x%)
etc.		

For multiple events with the same preferred term in a system organ class for a subject, the one with the most closely related to the study drug is counted. The percentage represents the incidence of an event by the preferred term as a percentage of the total number of subjects in the study group.

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Table 14.3.4.4 ╤ Laboratory Test Results - C3, C4, CRP and ESR (Safety)

Number of Subjects with Significant Decrease in C3		LY3451838 Cohort1 25mgIV N=XX	Cohort2 75mgIV N=XX	Cohort3 250mgIV N=XX	Cohort4 500mgIV N=XX	Cohort5 1000mgIV N=XX	Cohort6 1500mgIV N=XX	Cohort7 250mgSC N=XX	Total LY N=XX	Placebo N=XX
Post-baseline Visit #1	N	xx	xx	xx	xx	xx	xx	xx	xx	xx
	YES	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)
	NO	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)
Post-baseline Visit #2	N	xx	xx	xx	xx	xx	xx	xx	xx	xx
	YES	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)
	NO	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)

...

The baseline is the measurement at Visit 3 prior to dosing, or Visit 2 whichever is the last available one.
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Table 14.3.4.5 ╤ Immunogenicity (Safety)

	LY3451838								
	Cohort1 25mgIV N=XX	Cohort2 75mgIV N=XX	Cohort3 250mgIV N=XX	Cohort4 500mgIV N=XX	Cohort5 1000mgIV N=XX	Cohort6 1500mgIV N=XX	Cohort7 250mgSC N=XX	Total LY N=XX	Placebo N=XX
Subject Evaluable for TEADA*	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)
Subject with ADA Detected at Baseline	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)
Subject with TEADA+ at Post-baseline**	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)
Treatment-Induced	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)
Treatment-Boosted	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)	x(xx.x%)

* Subjects evaluable for TEADA if there is at least one baseline assessment and at least post-baseline assessment of ADA.
** Treatment-emergent ADAs are defined as those with a titer 2-fold (1dilution) greater than the minimum required dilution if no ADAs were detected at baseline (treatment-included ADA) or those with a 4-fold (2 dilutions) increase in titer compared to baseline if ADAs were detected at baseline (treatment-boosted ADA).
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Table 14.3.4.6 ╤ PACAP Concentration (Safety)

		LY3451838								
3451838P		Cohort1 25mgIV N=XX	Cohort2 75mgIV N=XX	Cohort3 250mgIV N=XX	Cohort4 500mgIV N=XX	Cohort5 1000mgIV N=XX	Cohort6 1500mgIV N=XX	Cohort7 250mgSC N=XX	Total LY N=XX	Placebo N=XX
Baseline	N	xx	xx	xx	xx	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Minimum	xx	xx	xx	xx	xx	xx	xx	xx	xx
	Maximum	xx	xx	xx	xx	xx	xx	xx	xx	xx
Post-baseline #1	N	xx	xx	xx	xx	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Minimum	xx	xx	xx	xx	xx	xx	xx	xx	xx
	Maximum	xx	xx	xx	xx	xx	xx	xx	xx	xx
Change from Baseline to Post-baseline #1	N	xx	xx	xx	xx	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Minimum	xx	xx	xx	xx	xx	xx	xx	xx	xx
	Maximum	xx	xx	xx	xx	xx	xx	xx	xx	xx

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