Protocol Addendum I8F-MC-GPGE(1)

Pharmacokinetics, Safety, and Tolerability of a Solution Formulation of LY3298176 in Healthy Subjects

NCT03375463

Approval Date: 31-Aug-2018

1. Protocol Addendum I8F-MC-GPGE(1) Pharmacokinetics, Safety, and Tolerability of a Solution Formulation of LY3298176 in Healthy Subjects

LY3298176

This addendum is to be performed in addition to all procedures required by protocol I8F-MC-GPGE or any subsequent amendments to that protocol.

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Protocol Addendum (1) Electronically Signed and Approved by Lilly on date provided below.

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3. Rationale for Addendum

Dosing has been completed in all 3 existing parts (A, B, and C) of Study I8F-MC-GPGE (GPGE). This protocol addendum adds a fourth part, D.

Part D will evaluate the pharmacokinetics (PK) of LY3298176 following bolus intravenous (IV) administration. This information will enable the study team to calculate the absolute bioavailability of LY3298176 following subcutaneous (SC) administration (using prior SC PK data from Phase 1 Study I8F-MC-GPGA [GPGA]). Subcutaneous administration is the intended route for this drug as a therapeutic.

Part D will mimic the design and study population of Part B. Part B was an IV arm, with 0.5 mg LY3298176 administered as infusion via pump over 10 minutes. Evaluation of IV PK in Part B led to inconclusive results: LY3298176 exposure following 0.5-mg IV infusion was lower than expected in all 8 subjects. Expectation was based on prior understanding of LY3298176 PK, [redacted] The reason for the lower-than-expected exposure is currently unclear despite a completed investigation.

The aim of Part D is to provide IV PK data to estimate the absolute bioavailability of LY3298176. Part D will use 0.5 mg LY3298176 lyophilized drug product (GPGE protocol Section 7.1.1). This contrasts with Part B, which used LY3298176 solution drug product (GPGE protocol Section 7.1.2).

4. Protocol Additions

4.1. Study Schedule

Study Schedule Protocol I8F-MC-GPGE, Part D

Procedure (Part D)	Screening	Treatment												ET	Comments
Days	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**15**	**35 - 37**	**≥70 days**		
Informed Consent	X														
Subject Admission to CRU		X													
Subject Discharge from CRU						X									Subjects may stay longer according to investigator's discretion
Outpatient Visit	X						X	X	X	X	X	X	X	X	
Investigational Product Administration			X												Study drug will be administered after an overnight fast of at least 8 hours. Study drug will be administered through bolus IV infusion
Medical History	X														
Height	X														
Weight	X	X										X		X	
Vital Signs (BP/PR/T) (supine) (hours)	X	X	**P**	24h	48h	X				X		X		X	Time points may be added if warranted and agreed upon between Lilly and the investigator
Clinical Laboratory Tests	X	X				X				X		X		X	Requires an 8-hour fast. See GPGE protocol Appendix 2 for details.
Adverse Event		X	X	X	X	X	X	X	X	X	X	X	X	X	

Procedure (Part D)	Screening	Treatment												ET	Comments
Days	-28 to -2	-1	1	2	3	4	5	6	7	8	15	35 - 37	≥70 days		
PK Samples			**P**, 5 min, 10 min, 30 min 1h, 2h, 4h, 8h, 12h	24 h, 36 h	48 h	72h	96h	120h	144h	168h	336h	X	X	X	All sampling times are from start of dose administration. Predose sample must be collected before dose administration. If a subject withdraws from the study prior to completion of scheduled PK sampling, every effort will be taken to draw an unscheduled blood sample for PK assessment. This will not be required if a sample has already been taken within the previous 24 hours. For ET, a PK sample can be taken at any time during the visit timed close to the immunogenicity sample.
Pregnancy Test	X	X										X		X	All females only. Serum pregnancy test will be performed at screening. Urine pregnancy test will be performed at Day -1 and at ET/Follow-up.
Physical Examination	X	X				X						X		X	After screening, medical assessment is performed only to include medical review and targeted examination, as appropriate.

Procedure (Part D)	**Screening**	**Treatment**												**ET**	**Comments**
Days	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**15**	**35 - 37**	**≥70 days**		
12-lead ECG	X	X				X						X		X	Single 12-lead ECG will be collected. ECGs must be recorded before collecting any blood samples. Subjects must be supine for at least 5 minutes before ECG collection and remain supine but awake during ECG collection.
Genetic Sample			**P**												Single sample for pharmacogenetic analysis taken prior to dosing on Day 1.
Immunogenicity Samples			**P**								X	X	X	X	All samples for immunogenicity should be taken predose and follow up. Time-matched PK sample should be collected at each time point.

Abbreviations: BP = blood pressure; CRU = clinical research unit; ECG = electrocardiogram; ET = early termination; hr = hour(s); IV = intravenous(ly); min = minute(s); **P** = Predose; PK = pharmacokinetic(s); PR = pulse rate; T= Temperature

Note: If multiple procedures take place at the same time point, the following order of the procedures should be used: ECG, vital signs, and venipuncture.

4.2. Objectives and Endpoints

Table GPGE(1).4.1 shows the objectives and endpoints of Part D of the study.

Table GPGE(1).4.1. Objectives and Endpoints

Objectives	Endpoints
Part D: • **Primary:** To evaluate the PK of a single bolus IV dose of LY3298176, lyophilized formulation, in healthy subjects. • **Secondary:** To investigate the safety and tolerability of LY3298176, administered to healthy subjects via bolus IV.	• PK parameters, including AUC • AEs

Abbreviations: AE = adverse event; AUC = area under the concentration versus time curve; IV = intravenous(ly); PK = pharmacokinetic(s).

4.3. Overall Design

Study GPGE is a single-center, Phase 1 study in 4 parts. Parts A, B, and C are detailed in Protocol I8F-MC-GPGE.

Part D is a single, 0.5-mg bolus IV dose of LY3298176 lyophilized formulation administered to healthy subjects.

In Part D, each subject will provide informed consent for study participation, and will undergo a screening examination within 28 days prior to enrollment.

Subjects will be admitted to the clinical research unit (CRU) on Day -1. On the morning of Day 1, following an overnight fast of at least 8 hours, 2 subjects will receive a single bolus IV dose of 0.5 mg LY3298176. This dose is expected to be safe while also providing plasma concentrations that can be adequately measured over the course of the sampling time period to enable adequate characterization of the PK profile.

- If the dose of 0.5 mg is found to be safe and well tolerated, then 6 more subjects will be dosed.
- If the dose is not tolerated due to extensive gastrointestinal events, a lower dose of 0.25 mg may be administered to an additional 8 subjects.

Plasma samples will be collected multiple times, including predose and up to 336 hours postdose, to measure LY3298176 concentrations.

At a minimum, subjects will remain in the CRU for 4 days. The investigator (or qualified designee) will review all available inpatient safety data before discharging subjects from the CRU on the morning of Day 4, provided that the subjects are deemed medically fit. Subjects may be required to remain in the CRU longer than Day 4, at the investigator's discretion.

Each subject will be required to return to the CRU for a follow-up visit at least 35 days after the LY3298176 dose. In addition, subjects will need to attend a study visit on Day ≥70 for an antidrug antibody follow-up sample.

4.4. Number of Participants

Part D: Approximately 10 healthy subjects will be enrolled so that at least 6 complete this part of the study.

4.5. Scientific Rationale for Study Design

Similarly to other parts of Study GPGE, a population of healthy subjects will be enrolled for Part D because it is likely there will be less physiologic variability than in a patient population. This is due to the absence of disease states that may affect multiple organ systems, and the absence of other confounding factors such as concomitant medications.

Part D will investigate the PK of LY3298176 following administration via a single IV dose administered as a bolus.

Safety and tolerability of LY3298176 were established by data from Study GPGA.

A safety review will be performed after dosing the first 2 subjects to review safety and tolerability following discharge from the CRU on Day 4 of the study, and to check if there is a need for dose adjustment prior to dosing the remaining subjects.

4.6. Justification of Dose and Route of Administration

A dose of 0.5 mg LY3298176 (administered via bolus IV) is chosen because this dose is expected to lead to measureable PK profile, since PK was quantifiable following a 0.5-mg IV 10-minute infusion dose in Part B of the study. Preliminary data from Part B indicate that administration of LY3298176 via infusion pump was well tolerated by the 8 subjects, with no adverse events being reported.

The IV bolus route in Part D is expected to provide data to estimate the absolute bioavailability of LY3298176. Pharmacokinetic exposure following IV infusion of a 0.5-mg dose in Part B was lower than anticipated, in all 8 subjects dosed [redacted]

4.7. Inclusion and Exclusion Criteria

There are no additional inclusion or exclusion criteria, or other study population requirements, for Part D of the study.

4.8. Treatment Administered

LY3298176 lyophilized formulation will be used in Part D. See GPGE protocol Section 7.1.1 for details.

No randomization is required for Part D. A single, 0.5-mg bolus IV dose of LY3298176 will be administered in the morning following an 8-hour, overnight fast. The actual time of dose administration will be recorded in the subject's electronic case report form.

4.9. Blinding

Part D is open-label.

4.10. Dose Modification

A 0.5-mg LY3298176 dose is planned to be administered to the first 2 subjects of Part D. If vomiting is noted in the first 2 subjects, to the extent that treatment with antiemetics and IV fluids is required, a reduced dose (0.25 mg) may be administered to the next 8 subjects planned in this part. If there are no safety concerns, then the same planned dose of 0.5 mg will be administered to the next 6 subjects enrolled in this part.

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