Protocol I8R-MC-IGBI(b)

Comparison of Glucagon Administered by Either the Nasal(LY900018) or Intra-muscular (GlucaGen®) Routes in Adult Patients with Type 1 Diabetes Mellitus During Controlled Insulin-Induced Hypoglycemia

NCT03339453

Approval Date: 12-Oct-2017

Protocol I8R-MC-IGBI(b)
Comparison of Glucagon Administered by Either the Nasal (LY900018) or Intra-muscular (GlucaGen®) Routes in Adult Patients with Type 1 Diabetes Mellitus During Controlled Insulin-Induced Hypoglycemia

EudraCT Number 2017-000249-33

Confidential Information

Glucagon nasal powder (LY900018)

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Clinical Pharmacology Protocol Electronically Signed and Approved by Lilly:
08 May 2017
Amendment (a) Electronically Signed and Approved by Lilly:
16 Aug 2017
Amendment (b) Electronically Signed and Approved by Lilly on approval date provided below.

Approval Date: 12-Oct-2017 GMT

Table of Contents

Comparison of Glucagon Administered by Either the Nasal (LY900018) or Intra-muscular (GlucaGen®) Routes in Adult Patients with Type 1 Diabetes Mellitus During Controlled Insulin-Induced Hypoglycemia

Section **Page**

Protocol I8R-MC-IGBI(b) Comparison of Glucagon Administered by Either the Nasal (LY900018) or Intra-muscular (GlucaGen®) Routes in Adult Patients with Type 1 Diabetes Mellitus During Controlled Insulin-Induced Hypoglycemia 1
Table of Contents 2
1. Protocol Synopsis 8
2. Schedule of Activities 11
3. Introduction 16
3.1. Study Rationale 16
3.2. Background 16
3.3. Benefit–Risk Assessment 17
4. Objectives and Endpoints 19
5. Study Design 20
5.1. Overall Design 20
5.2. Number of Participants 21
5.3. End of Study Definition 21
5.4. Scientific Rationale for Study Design 22
5.5. Justification for Dose 22
6. Study Population 23
6.1. Inclusion Criteria 23
6.2. Exclusion Criteria 24
6.3. Lifestyle and/or Dietary Requirements 26
6.3.1. Meals and Dietary Restrictions 26
6.3.2. Alcohol 26
6.3.3. Activity 26
6.4. Screen Failures 26
7. Treatment 27
7.1. Treatment Administered 27
7.1.1. Packaging and Labeling 27
7.1.2. Medical Devices 28

7.2. Method of Treatment Assignment 28
7.2.1. Selection and Timing of Doses 28
7.3. Blinding 28
7.4. Dose Modification 28
7.5. Preparation/Handling/Storage/Accountability 28
7.6. Treatment Compliance 29
7.7. Concomitant Therapy 29
7.8. Treatment after the End of the Study 29
8. Discontinuation Criteria 30
8.1. Discontinuation from Study Treatment 30
8.1.1. Discontinuation of Inadvertently Enrolled Patients 30
8.2. Discontinuation from the Study 30
8.3. Patients Lost to Follow-up 30
9. Study Assessments and Procedures 31
9.1. Efficacy Assessments 31
9.2. Procedures 31
9.2.1. Inducing Hypoglycemia 31
9.2.2. Glucagon Administration 31
9.2.2.1. Nasal Administration 32
9.2.2.2. Intra-muscular Administration 32
9.2.3. Procedures for Insufficient Response to Glucagon Administration 32
9.2.4. End of Admission 32
9.3. Adverse Events 32
9.3.1. Serious Adverse Events 33
9.3.1.1. Suspected Unexpected Serious Adverse Reactions 34
9.3.1.2. Adverse Event Monitoring with a Systematic Questionnaire 34
9.3.2. Complaint Handling 34
9.4. Treatment of Overdose 35
9.5. Safety 35
9.5.1. Laboratory Tests 35
9.5.2. Vital Signs 35
9.5.3. Electrocardiograms 35
9.5.4. Other Tests 36
9.5.5. Safety Monitoring 36
9.5.5.1. Hepatic Safety 37
9.6. Pharmacokinetics 37

9.6.1. Bioanalysis....37
9.7. Pharmacodynamics....38
9.7.1. Exploratory Sample Assessments and Storage....38
9.8. Genetics....38
9.9. Biomarkers....39
9.10. Health Economics....39
10. Statistical Considerations and Data Analysis....40
10.1. Sample Size Determination....40
10.2. Populations for Analyses....40
10.2.1. Study Participant Disposition....40
10.2.2. Study Participant Characteristics....40
10.2.3. Treatment Compliance....40
10.3. Statistical Analyses....40
10.3.1. Efficacy Analyses....41
10.3.1.1. Primary Efficacy....41
10.3.1.2. Secondary Efficacy Analyses....42
10.3.1.2.1. Plasma Glucose Values....42
10.3.1.2.2. Symptoms of Hypoglycemia....42
10.3.2. Safety Analyses....42
10.3.2.1. Clinical Evaluation of Safety....42
10.3.2.2. Nasal and Non-nasal Score Questionnaire....43
10.3.2.3. Statistical Evaluation of Safety....43
10.3.3. Pharmacokinetic Analyses....43
10.3.3.1. Pharmacokinetic Parameter Estimation....43
10.3.3.2. Pharmacokinetic Statistical Inference....43
10.3.4. Pharmacodynamic Analyses....44
10.3.4.1. Pharmacodynamic Parameter Estimation....44
10.3.4.2. Pharmacodynamic Statistical Inference....44
10.3.5. Pharmacokinetic/Pharmacodynamic Analyses....45
10.3.6. Data Review during the Study....45
10.3.7. Interim Analyses....45
11. References....46

List of Tables

Table **Page**

Table IGBI.1. Objectives and Endpoints 19
Table IGBI.2. Treatments Administered 27

List of Figures

Figure **Page**

Figure IGBI.1. Illustration of study design for Protocol I8R-MC-IGBI. 21

List of Appendices

Appendix		Page
Appendix 1.	Abbreviations and Definitions	47
Appendix 2.	Clinical Laboratory Tests	51
Appendix 3.	Study Governance, Regulatory, and Ethical Considerations	52
Appendix 4.	Hepatic Monitoring Tests for Treatment-Emergent Abnormality	55
Appendix 5.	Blood Sampling Summary	56
Appendix 6.	Nasal and Non-nasal Score Questionnaire	57
Appendix 7.	Edinburgh Hypoglycemia Scale	59
Appendix 8.	Clarke Hypoglycemia Awareness Survey	62
Appendix 9.	Protocol Amendment I8R-MC-IGBI(b) Summary: Comparison of Glucagon Administered by Either the Nasal (LY900018) or Intramuscular (GlucaGen®) Routes in Adult Patients with Type 1 Diabetes Mellitus During Controlled Insulin-Induced Hypoglycemia	65

1. Protocol Synopsis

Title of Study:
Comparison of Glucagon Administered by Either the Nasal (LY900018) or Intra-Muscular (GlucaGen®) Routes in Adult Patients with Type 1 Diabetes Mellitus During Controlled Insulin-Induced Hypoglycemia

Rationale:
LY900018 is an investigational drug–device combination product consisting of a single-use nasal dosing device that delivers a fixed 3-mg dose of glucagon powder absorbed through the nasal mucosa. The glucagon component of LY900018 is a synthetic single-chain, 29-amino-acid polypeptide identical to human glucagon. LY900018 is being developed for the treatment of severe hypoglycemia.

Currently, glucagon in a liquid form lacks physical and chemical stability; thus marketed products require reconstitution of glucagon before the product can be administered through subcutaneous or intra-muscular (IM) injection. LY900018 combines stable, synthetic glucagon and a nasal dosing device that for effective use obviates reconstitution, injection, and moreover, patient inhalation. Because of these advantages, LY900018 may offer a significant improvement in the treatment of severe hypoglycemia occurring outside of the hospital setting.

The aim of this study is to compare GlucaGen®, a currently approved product that requires reconstitution prior to administration through IM injection, and LY900018 in those patients who achieve treatment success during controlled insulin-induced hypoglycemia in patients with type 1 diabetes mellitus (T1DM). Treatment success is defined as an increase in plasma glucose (PG) to ≥70 mg/dL (3.9 mmol/L) or an increase of ≥20 mg/dL from the plasma glucose nadir within 30 minutes after receiving glucagon, without the patient receiving additional actions to increase PG. The nadir is defined as the minimum plasma glucose measurement at the time of or within 10 minutes following glucagon administration.

Objectives/Endpoints

Objectives	Endpoints
Primary To compare LY900018 versus GlucaGen® in the percentage of adult patients with T1DM who achieve treatment success during controlled insulin-induced hypoglycemia	The percentage of patients who achieve treatment success will be defined as an increase in plasma glucose to ≥70 mg/dL or an increase of ≥20 mg/dL from plasma glucose nadir within 30 minutes after receiving glucagon, without receiving additional actions to increase the plasma glucose concentration. The nadir will be defined as the minimum plasma glucose concentration at the time of or within 10 minutes following glucagon administration.
Secondary 1. To assess the safety and tolerability of LY900018 versus GlucaGen® 2. To characterize the PD profiles of LY900018 versus GlucaGen® 3. To characterize the PK profiles of LY900018 versus GlucaGen®	1. Summary of AEs, including nasal and non-nasal AEs; vital signs 2. The PD parameters include BGmax, Tmax 3. The PK parameters include AUC, Cmax, Tmax

Abbreviations: AE = adverse event; AUC = area under the concentration versus time curve; BGmax = maximal blood glucose; Cmax = maximal concentration; PD = pharmacodynamics; PK = pharmacokinetics; T1DM = type 1 diabetes mellitus; Tmax = time to maximal concentration.

Summary of Study Design:
Study I8R-MC-IGBI is a multicenter, randomized, open-label, 2-treatment, 2-period, crossover study conducted in adult patients with T1DM.

Treatment Arms and Planned Duration for an Individual Patient:
LY900018: Single 3-mg dose; nasal administration by study site personnel
GlucaGen® (Novo Nordisk A/S): Single 1-mg dose; IM injection

Number of Patients:
Approximately 70 patients with T1DM will be enrolled in order to have 66 patients complete both treatment visits with evaluable primary outcome.

Statistical Analysis: A total of 66 patients are required in the study in order to achieve the primary objective with at least 90% power using the following assumptions:

- A treatment success rate of 98% for both treatments
- A noninferiority margin of 10%
- One-sided alpha level of 0.025
- A within-patient correlation of zero between 2 treatment visits

The primary analysis will be a treatment comparison of the percentage of patients who achieve treatment success. The percentage of patients who achieve treatment success within each treatment arm and the difference in the percentages between 2 treatment arms will be computed. A 2-sided 95% confidence interval (CI) will be obtained from the 1-sample mean of the paired differences in outcome (1=outcome observed; 0=outcome not observed) across 2 study visits. Noninferiority of nasal glucagon (NG) will be declared if the upper limit of the 2-sided 95% CI constructed on the difference in percentage (IM glucagon – NG) is less than the noninferiority margin of 10%.

2. Schedule of Activities

Study Schedule Protocol I8R-MC-IGBI

Procedure	Screening Visit	Period 1 and Period 2 CRU Visits	Follow-up (or ED) Visit	Comments
	Up to 28 days before Period 1	Day 1	28(±2) days after last dose of study drug	
Sign informed consent form	X			Written informed consent has to be provided before any trial-related activity and may be obtained during a separate informed consent visit to the site
Medical history	X			
Clarke Hypoglycemia Awareness Survey	X			See Appendix 8.
Height	X			
Weight	X	X	X	During Periods 1 and 2, body weight will be collected before the start of the procedure to induce hypoglycemia
Vital signs (supine blood pressure, pulse rate, and body temperature)	X	X	X	See Section 9.5.2; the patient should be at rest for at least 5 minutes before vital signs are measured. During Periods 1 and 2, vital signs should be measured before the start of the procedure to induce hypoglycemia and at 45 minutes after glucagon administration. Time points may be added for Period 1 and Period 2 if warranted and agreed upon between Lilly and the investigator.
Clinical laboratory tests	X	X	X	See Appendix 2, Clinical Laboratory Tests, for details. Patients do not need to fast for laboratory samples collected at screening or follow-up. At Period 1 and Period 2 site visits, laboratory tests should be collected from patients who have fasted at least 8 hours before any study procedures. All screening, hepatic monitoring and study day laboratory tests to be processed at a local laboratory. Hepatitis E laboratory tests to be processed at a central laboratory.
Sample collection for HbA1c	X	X (Period 1 only)		Screening samples and samples collected before the start of the procedure to induce hypoglycemia to be processed at local laboratory.

Pregnancy test	X	X	X	Serum pregnancy test will be performed at screening and analyzed at a local laboratory. Urine pregnancy test will be performed at admission for study Periods 1 and 2 as well as at the follow-up visit and processed on site
Physical examination	X	X	X	Physical examinations will be performed before the start of the procedure to induce hypoglycemia in Periods 1 and 2 and at the follow-up visit. Patients will review recent insulin demand with site personnel prior to inducing hypoglycemia (see Section 7.7).
12-Lead ECG	X	X	X	See Section 9.5.3; single 12-lead ECGs will be collected for local safety assessment. During Periods 1 and 2, ECGs will be collected before the start of the procedure to induce hypoglycemia. Electrocardiograms may be obtained at additional times, when deemed clinically necessary
Adverse event assessment	X	X	X	See Section 9.3
Admission to CRU		X		The patient should arrive at the CRU at approximately 0700 hours, having fasted for at least 8 hours
Discharge from CRU		X		The patient may be discharged 6 hours following the procedure. A patient may remain inpatient at the CRU at the discretion of the investigator
Dinner		X		Following completion of all study procedures, the patient will be provided a carbohydrate-rich meal, and the investigator will ensure the patient's plasma glucose is stable
Nasal inspection		X		Nasal inspection should be conducted before the procedure to induce hypoglycemia and at 90 minutes postglucagon administration
Injection-site inspection (for IM glucagon only)		X		The injection site will be inspected before the procedure to induce hypoglycemia to confirm injection site is normal and at 90 minutes postglucagon administration
Nasal and Non-nasal Score Questionnaire		X		See Appendix 6, Nasal and Non-nasal Score Questionnaire. Questionnaire to be completed approximately 30 minutes prior to hypoglycemia induction and 15, 30, 60, and 90 minutes postglucagon administration

Edinburgh Hypoglycemia Scale		X		See Appendix 7, Edinburgh Hypoglycemia Scale.This questionnaire should be completed when PG ≤75 mg/dL and again at PG ≤60 mg/dL after the start of the insulin infusion and at 15, 30, 45, and 60 minutes postglucagon administration
Insulin infusion to induce hypoglycemia		X		Refer to Sections 9.2 and 7.7 for details regarding this procedure, including steps to take before the procedure begins and steps to take if there is an insufficient response to glucagon administration. Procedures taking place on Period 2 will occur at approximately the same time as those for Period 1.
Study drug administration		X		Once PG reaches below 60 mg/dL, the insulin infusion is stopped and approximately 5 minutes later study drug is administered
Sample collection for measurement of glucagon		X	X	Samples will be collected pre-dose (i.e., immediately prior to glucagon administration) and at 5, 10, 15, 20, 25, 30, 40, 50, 60, 90, 120, and 240 minutes post-glucagon administration at Periods 1 and 2 and once at follow-up. All samples will be processed at a central laboratory.
Sample collection for measurement of DPC		X		Samples will be collected from NG-treated patients pre-dose (i.e., immediately prior to glucagon administration) and at 10, 20, 30, 40, 60, 120, and 240 minutes post-glucagon administration. Three additional samples may be collected. Samples to be processed at a central laboratory.
Bedside glucose safety measurements (SuperGL laboratory analyzer)		X		Samples will be collected throughout the study procedure. During the hypoglycemia induction procedure, plasma glucose concentration will be measured no more than 10 minutes apart while the plasma glucose concentration is ≥100 mg/dL and no more than 5 minutes apart when the plasma glucose concentration is <100 mg/dL. Post-glucagon administration, plasma glucose concentration will be measured every 5 minutes for the first 30 minutes and every 10 minutes up to 90 minutes.
Sample collection for measurement of plasma glucose		X		Samples will be collected pre-dose (i.e., immediately prior to glucagon administration) and at 5, 10, 15, 20, 25, 30, 40, 50, 60, and 90 minutes post-glucagon administration. Samples to be processed at a central laboratory.
Exploratory sample		X (Period 1 only)	X	Serum samples will be collected prior to the procedure to induce hypoglycemia.

Genetic sample		X (Period 1 only)		

Abbreviations: CRU = clinical research unit; DPC = dodecylphosphocholine; ECG = electrocardiogram; ED = early discontinuation; HbA1c = hemoglobin A1c; IM = intra-muscular; NG = nasal glucagon; PG = plasma glucose.

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

3. Introduction

3.1. Study Rationale

Nasal glucagon (NG; LY900018) is an investigational drug–device combination product consisting of a single-use nasal dosing device that delivers glucagon powder for absorption through the nasal mucosa. Nasal glucagon represents a significant improvement in the evolution of the treatment of severe hypoglycemia with glucagon; it provides the same single-chain, 29-amino-acid polypeptide as human glucagon and the recombinant DNA-produced glucagon used in currently marketed glucagon emergency kits (Glucagon Emergency Kit [Lilly] and GlucaGen® HypoKit [Novo Nordisk A/S]).

The aim of this study (Study I8R-MC-IGBI [IGBI]) is to compare the planned commercial drug product of NG to GlucaGen, a currently approved product that requires reconstitution prior to administration through intra-muscular (IM) injection, in those patients who achieve treatment success during controlled insulin-induced hypoglycemia in patients with type 1 diabetes mellitus (T1DM). Treatment success is defined as an increase in plasma glucose (PG) concentration to ≥70 mg/dL or an increase of ≥20 mg/dL from the PG nadir within 30 minutes after receiving glucagon, without the patient receiving additional actions to increase PG. The nadir is defined as the minimum PG concentration at the time of or within 10 minutes following glucagon administration. The design and conduct of Study IGBI are similar to the completed Phase 3 Study I8R-MC-IGBC (IGBC) (Rickels et al. 2016).

3.2. Background

Glucagon is a widely available product currently indicated for the treatment of severe hypoglycemia. The principal action of glucagon is to increase PG concentration through its action in the liver. Nasal glucagon development has produced robust clinical data in adult healthy subjects, adult patients with T1DM and type 2 diabetes mellitus (T2DM), as well as pediatric patients with T1DM.

Nasal glucagon powder contains 3-mg of glucagon in a ready-to-use, single-use intranasal powder delivery device. Glucagon comprises 10% by weight of the powder in the device. The formulation also contains beta-cyclodextrin as a filler/bulking agent/absorption enhancer and dodecylphosphocholine (DPC) as an absorption enhancer/surfactant. Beta-cyclodextrin is a compendial excipient and DPC is a novel excipient. The device delivers a single dose to the nostril upon actuation.

Three clinical trials using NG have been completed in adults with T1DM and T2DM: Study IGBC, Study I8R-MC-IGBA (IGBA), and an actual use study (Study I8R-MC-B002 [B002]). Studies IGBC and IGBA demonstrated comparable safety and efficacy between NG and injectable glucagon in reversing insulin-induced hypoglycemia in adult patients with T1DM only (Study IGBA) or patients with T2DM and T1DM (IGBC). Study B002 was an actual use study that evaluated the effectiveness of NG administered by a trained caregiver to patients with T1DM experiencing moderate to severe hypoglycemia in a real-world environment of work and home. Study B002 demonstrated that 96% of moderate to severe hypoglycemic events were

resolved within 30 minutes. Finally, 2 trials were conducted in pediatric patients with T1DM: Study I8R-MC-IGBB (IGBB) and Study I8R-MC-B001 (B001). Studies IGBB and B001demonstrated effectiveness in rescuing pediatric patients from hypoglycemia.

All adult diabetic patients in the 2 inpatient clinical trials (Studies IGBA and IGBC) underwent hypoglycemia induction through intravenous (IV) insulin under close clinical supervision and were administered either NG or injectable glucagon.

Patients fully recovered from hypoglycemia without additional actions to increase glucose level. Specifically, in Study IGBC, at 30 minutes after glucagon dosing, 98.7% (74 out of 75 patients) of NG and 100% (75 out of 75) of intra-muscular glucagon (IMG)-treated patients achieved treatment success (defined as an increase in PG to $\geq$70 mg/dL or an increase of $\geq$20 mg/dL from nadir). The nadir is defined as the minimum glucose measurement at the time of or within 10 minutes following glucagon administration. The NG-treated patients who did not meet the above criteria did achieve both PG $\geq$70 mg/dL and an increase of $\geq$20 mg/dL from nadir at 40 minutes after dosing. Furthermore, the mean time to treatment success was 16 minutes in the NG treatment arm and 13 minutes in the IMG treatment arm (Rickels et al. 2016).

3.3. Benefit–Risk Assessment

Glucagon is generally well tolerated, with mild side effects noted. These included occasional nausea and vomiting; however, these side effects may also occur with hypoglycemia (for example, dizziness, fainting, light headedness, blurred vision, headaches, fatigue). Nasal glucagon is a needle-free, ready-to-use nasal dosing device for administration into nostrils requiring no inhalation. In contrast to other products on the market, this requires no reconstitution. Patients being treated with the investigational product will derive no direct benefit from it as treatment will follow an insulin-induced hypoglycemia.

To date, there have been 10 completed clinical studies (8 in adults, 2 in pediatric population) in which the safety, efficacy, or effectiveness of NG has been evaluated. No deaths or serious adverse events (SAEs) associated with NG occurred during these studies. The most frequently reported treatment-emergent adverse events (TEAEs) in NG-treated patients represent events related to local tolerability including lacrimation increased, headache, rhinorrhea, nasal discomfort, nasal congestion, and nasal pruritus, and gastrointestinal disorders including nausea and vomiting. All TEAEs were transient in nature and most resolved within 24 hours of exposure. Severe adverse reactions to glucagon are very rare, although generalized allergic reactions, urticaria, respiratory distress, and hypotension have been reported in patients who have received glucagon.

This study will expose patients with T1DM to an insulin-induced hypoglycemia meant to simulate hypoglycemia in a controlled setting. The protocols used to induce the controlled hypoglycemia have been adopted from a previously completed trial, specifically Study IGBC, that demonstrated the safe use of this method. This is an inpatient procedure in which the patients will be under constant supervision of the clinical research unit (CRU) staff. Safety provisions have been considered in that IV glucose will be administered if the patient

experiences signs and symptoms of severe hypoglycemia and gauged to require intervention during the experimental procedure, at the discretion of the investigator.

No clinically significant safety or tolerability concerns have been identified in patients to date for NG up to the highest single dose (6-mg) given in an acute setting.

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

4. Objectives and Endpoints

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

Table IGBI.1. Objectives and Endpoints

Objectives	Endpoints
Primary To compare LY900018 versus GlucaGen® in the percentage of adult patients with T1DM who achieve treatment success during controlled insulin-induced hypoglycemia	The percentage of patients who achieve treatment success, which will be defined as an increase in plasma glucose to ≥70 mg/dL or an increase of ≥20 mg/dL from plasma glucose nadir within 30 minutes after receiving glucagon, without receiving additional actions to increase the plasma glucose concentration; nadir will be defined as the minimum plasma glucose concentration at the time of or within 10 minutes following glucagon administration.
Secondary 1. To assess the safety and tolerability of LY900018 versus GlucaGen® 2. To characterize the PD profiles of LY900018 versus GlucaGen® 3. To characterize the PK profiles of LY900018 versus GlucaGen®	1. Summary of AEs, including nasal and non-nasal AEs; vital signs 2. The PD parameters include BGmax, Tmax 3. The PK parameters include AUC, Cmax, Tmax
Exploratory 1. To characterize the PK profile of the DPC excipient of LY900018 2. To assess the occurrence and severity of hypoglycemia symptoms during controlled insulin-induced hypoglycemia 3. To assess the awareness of hypoglycemia prior to its induction	1. The PK parameters include AUC, Cmax, Tmax 2. The Edinburgh Hypoglycemic Scale will be used to assess the occurrence and severity of hypoglycemia symptoms 3. The Clarke Hypoglycemia Awareness survey will be used to assess awareness of hypoglycemia symptoms

Abbreviations: AE = adverse event; AUC = area under the concentration versus time curve; BGmax = maximal blood glucose; Cmax = maximal concentration; DPC = dodecylphosphocholine; PD = pharmacodynamics; PK = pharmacokinetics; T1DM = type 1 diabetes mellitus; Tmax = time to maximal concentration.

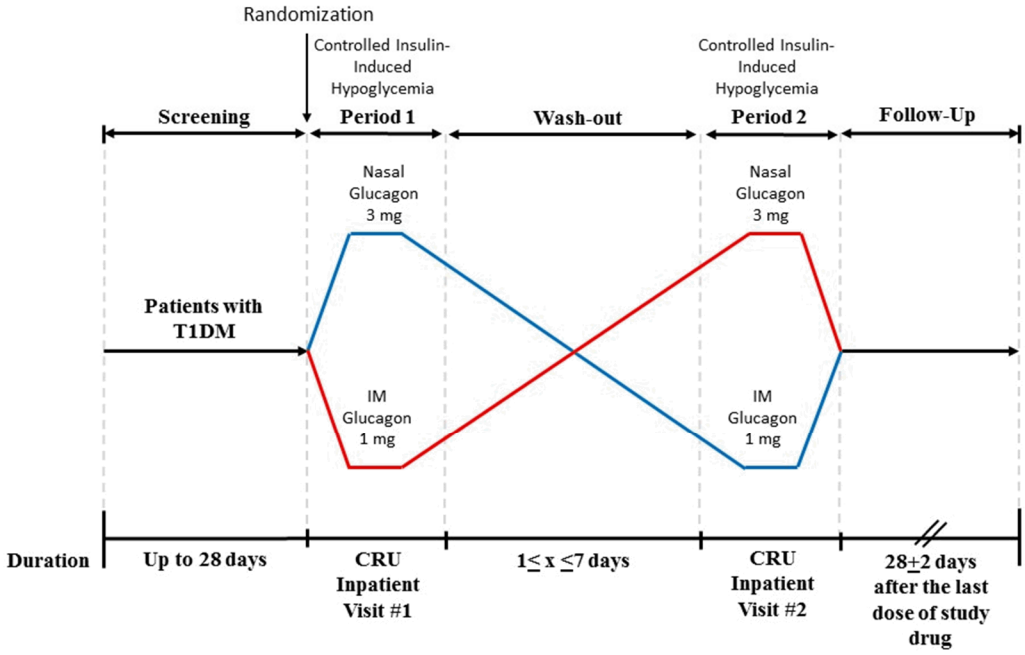
5. Study Design

5.1. Overall Design

This is a Phase 1, multicenter, randomized, open-label, 2-treatment, 2-period, crossover study. Figure IGBI.1 illustrates the study design. In each period, patients with T1DM will undergo a procedure to induce hypoglycemia using insulin infusion. The insulin infusion will be used to decrease PG and will be stopped once PG <60 mg/dL and it is expected that PG will continue to decrease for an additional 15 to 20 mg/dL to its lowest concentration. Approximately 5 minutes after the insulin infusion is stopped, patients will be administered either 3-mg NG (LY900018) or 1-mg IMG (GlucaGen) in the deltoid muscle of the nondominant arm by CRU staff members. Serial blood sampling will be performed for glucagon and PG concentration assessments immediately before and up to 6 hours following administration of glucagon. Following each test period, patients will remain in the CRU for at least 6 hours following the procedure. All patients will receive a carbohydrate-rich meal prior to discharge. Patients may stay longer as needed, at the discretion of the investigator.

After a wash-out period of at least 1 day (24 hours) and no more than 7 days, patients will return to the clinic and the procedure repeated with each patient crossed over to the alternate glucagon treatment.

A CRU visit for follow-up or early discontinuation should occur approximately 28±2 days after the last dose of study drug.



Abbreviations: CRU = clinical research unit; IM = intra-muscular; T1DM = type 1 diabetes mellitus.

Figure IGBI.1. Illustration of study design for Protocol I8R-MC-IGBI.

5.2. Number of Participants

Approximately 70 patients with T1DM may be enrolled to ensure that at least 66 patients complete both treatment visits with evaluable primary outcome (see Section 10.3.1.1).

If patients drop out of the study before completion of both periods or completed the study without evaluable primary outcome in at least 1 period, replacement patients will be enrolled to ensure at least 66 patients are available for the evaluation of primary objective. The replacement patients will assume the same treatment sequence as the patients to be replaced and will complete that treatment sequence in its entirety.

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 patient.

5.4. Scientific Rationale for Study Design

This study will be used to supplement the comprehensive chemistry, manufacturing control analytical plan for bridging the planned commercial drug product with the clinical trial drug product. Since the existing stores of clinical trial drug product have been exhausted, an indirect comparator/bridging study must be performed to demonstrate efficacy comparability.

This study design involves an open-label assessment of the planned commercial drug product compared to the marketed product (GlucaGen) within the T1DM population. The 2 study periods will be separated by a washout period of no less than 1 day (24 hours) and no more than 7 days due to the short half-life of NG (approximately $t_{1/2}$ = 25 minutes) The second of the 2 study periods will expose the same patients to the alternate study arm (for example, those randomly assigned to receive NG LY900018 will receive IM GlucaGen for Period 2). This crossover design will allow each individual patient to act as an internal control.

5.5. Justification for Dose

Results from studies in both pediatric and adult populations confirm that, while the physiological response to glucagon does appear to saturate between 2- and 3-mg NG dose, the lower 2-mg dose may not always elicit the maximum response needed in an emergency situation of severe hypoglycemia. The 3-mg dose provides more consistent clinical efficacy compared to the 2-mg dose and is similarly well tolerated in both pediatric and adult patients.

Based on LY900018 exposure, efficacy, and safety, the 3-mg dose was selected for the Phase 3 studies. Therefore, in the current study, the 3-mg NG dose will be used to compare against 1 mg of IM GlucaGen.

6. Study Population

Eligibility of patients for the study will be based on the results of screening medical history, physical examination, vital signs, clinical laboratory tests, and electrocardiogram (ECG). Refer Section 6.1 and Section 6.2 for full inclusion/exclusion criteria.

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. Patients who are not enrolled within 28 days of screening may be subjected to an additional medical assessment and/or clinical measurements to confirm their eligibility.

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

6.1. Inclusion Criteria

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

[1] are male or female with a diagnosis of T1DM for at least 2 years and receiving daily insulin since the time of diagnosis

[1a] for sexually active male patients, who have not been surgically sterilized, with a female partner of childbearing potential, the female partner must use a highly effective method of contraception (for example, surgical sterilization, hormonal intrauterine devices [coil], or oral hormone contraceptives, each in combination with spermicide-coated condoms); when female partners do not use these methods, the male patient must be willing to refrain from sexual intercourse from the first dosing until 1 month after the last dosing in the trial

[1b] female patients of child-bearing potential must agree to use a highly effective method of birth control (highly effective contraception methods are considered those with a failure rate <1% undesired pregnancies per year and include surgical sterilization, hormonal intrauterine devices [coil], oral hormone contraceptives, sexual abstinence, or a surgically sterilized partner) throughout the entire duration of this study (from the screening visit until study completion)

females of nonchildbearing potential may participate without using highly effective contraceptive methods which include those who are postmenopausal, defined as women aged <52 years and being amenorrheic for more than 1 year with a serum follicle-stimulating hormone (FSH) level compatible with postmenopausal status or aged ≥52 years and being amenorrheic for less than 1 year and with serum FSH level according to local laboratory reference range and not using highly effective contraceptive methods or aged ≥52 years being amenorrheic for more than 1 year.

[2] are between the ages of 18 to 64 years, inclusive

[3] have a body weight of at least 50 kg (110 lb)

[4] have a body mass index of 18.5 to 35 kg/m^2, inclusive

[5] have a hemoglobin A1c (HbA1c) value ≤10%

[6] have clinical laboratory test results within normal reference range for the population or investigational site, or results with acceptable deviations that are judged to be not clinically significant by the investigator

[7] have venous access sufficient to allow for blood sampling and required infusions as per the protocol

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

[9] has provided signed informed consent

6.2. Exclusion Criteria

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

[10] 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

[11] are Lilly employees

[12] 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

[13] have participated, within the past 30 days, in a clinical study involving an investigational product

[14] have previously completed or withdrawn from this study or any other study investigating LY900018, and have previously received the investigational product

[15] have known allergies to LY900018, related compounds or any components of the formulation, or history of significant atopy

[16] have a history of hypersensitivity to glucagon or any related products or severe hypersensitivity reactions (such as angioedema) to any drugs

[17] have an abnormality in the 12-lead ECG that, in the opinion of the investigator, increases the risks associated with participating in the study

[18] have a supine blood pressure at screening (after at least 5 minutes at rest) outside the range of 95 to 140 mmHg systolic blood pressure and/or greater than 90 mmHg for diastolic blood pressure (this excludes white-coat hypertension, and if repeated measurements are within this range, the subject may be included in the study); have symptoms of arterial hypotension and/or a heart rate at rest outside the range of 50 to 90 beats per minute

[19] have a history of pheochromocytoma (that is, adrenal gland tumor) or insulinoma

[20] occurrence of an episode of severe hypoglycemia (defined as requiring the assistance of another person in the 1 month prior to enrolling in the study)

[21] have a history of epilepsy or seizure disorder

[22] have a significant history of or current cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine (apart from T1DM), hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk when taking the study drug; or of interfering with the interpretation of data

[23] have a significant history of or current psychiatric disorders.

[24] regularly use known drugs of abuse and/or show positive findings on drug screening

[25] show evidence of human immunodeficiency virus (HIV) infection and/or positive human HIV antibodies

[26] show evidence of hepatitis C and/or positive hepatitis C antibody

[27] show evidence of hepatitis B and/or positive hepatitis B surface antigen

[28] are women who are pregnant according to a positive serum pregnancy test, actively trying to get pregnant, or are lactating

[29] have, except for the current regimen of insulin therapy and concomitant medication (for example, antihypertensive agents, lipid-lowering agents, contraceptives, and stable treatment with hormone replacement and thyroid hormone replacement therapy), regular use of or intended use of any over-the-counter or prescription medications or nutritional supplements that treat hyperglycemia or insulin resistance or that promote weight loss within 14 days before dosing

[30] daily use of systemic beta-blocker, indomethacin, warfarin or anticholinergic drugs.

[31] have had blood donation or blood loss of more than 500 mL within the past 3 months

[32] have a significant history of alcoholism or drug abuse as judged by the investigator, or regularly consume more than 24 g alcohol/day (males) or 12 g alcohol/day (females)

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

[34] any significant changes in insulin regimen and/or unstable blood glucose control within the past 3 months prior to screening as assessed by the investigator

[35] require daily insulin treatment >1.5 U/kg/body weight.

6.3. Lifestyle and/or Dietary Requirements

Throughout the study, patients may undergo medical assessments and review of compliance with requirements before continuing in the study. Patients should continue to meet the restrictions related to alcohol, caffeine, and medication use.

6.3.1. Meals and Dietary Restrictions

In both treatment periods, patients will fast for at least 8 hours prior to beginning the hypoglycemia induction procedure. Once this procedure is completed, the patients will receive a carbohydrate-rich meal. Patients will be given access to calorie-free water during the hypoglycemic procedure.

While resident in the CRU, patients may not consume any food or caloric drinks other than that provided by the CRU. When not resident in the CRU, patients will be encouraged to follow their normal diets. However, patients are encouraged to consume at least 100 g of carbohydrates during the washout period.

6.3.2. Alcohol

Please refer to Section 6.2 regarding excessive alcohol use. Alcohol use will be prohibited during the fasting procedure. However, alcohol may be consumed during the washout period as long as it conforms with the exclusion criteria and does not deviate from habitual patterns of consumption.

6.3.3. Activity

Patients are encouraged to maintain their regular exercise habits for the duration of the study. However, patients should avoid strenuous exercise 48 hours prior to study days.

During the procedure to induce hypoglycemia, patients should remain recumbent or sitting in the CRU until the end of the procedure.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may not be re-screened.

7. Treatment

7.1. Treatment Administered

This study involves a comparison of 3-mg glucagon administered once nasally to 1-mg IMG (GlucaGen; comparator). Table IGBI.2 shows the treatment regimens.

Table IGBI.2. Treatments Administered

Treatment Name	LY900018	GlucaGen
Dosage Formulation	Fine powder	Clear liquid
Unit Dose Strength(s)/Dosage Level(s)	3-mg glucagon	1-mg glucagon
Route of Administration	Nasal	Intra-muscular
Dosing instructions	Administer a single nasal dose upon hypoglycemia onset	Administer a single intra-muscular injection upon hypoglycemia onset

The procedure for insulin-induced hypoglycemia will require an IV infusion of 15-U human insulin [100 U/mL] in 49-mL saline.

The investigator or designee is responsible for:

- verifying that instructions are followed properly
- maintaining accurate records of investigational product dispensation and collection including documentation of lot or control numbers, as appropriate.
- returning all unused medications to Lilly or its designee at the end of the study

7.1.1. Packaging and Labeling

Clinical trial materials will be labeled according to the country's regulatory requirements. Lilly will supply to the clinical site LY900018 and GlucaGen Hypo Kits as well as insulin lispro U100 to induce hypoglycemia. Study materials will be provided as open-label material.

All insulin products must be stored at the investigational site, according to the instructions provided on the product label, in a locked and secure place.

Unused study materials will remain locked and securely stored, according to the instructions provided on the product label at the investigational site, until returned to the sponsor or destroyed, according to written instruction from the sponsor.

7.1.2. Medical Devices

The manufactured medical devices provided for use in the study include a nasal delivery device as part of the investigational drug–device combination product. The device component of the investigational drug–device product is inserted into the nasal cavity to deliver the contained drug constituent.

7.2. Method of Treatment Assignment

The treatment sequence to be administered for each enrolled patient will be determined according to a randomization schedule.

7.2.1. Selection and Timing of Doses

The hypoglycemia induction procedure should be initiated at approximately the same time at each treatment visit. An IV infusion of insulin will be given until PG level of <60 mg/dL is reached. At this point, insulin infusion will be stopped and approximately 5 minutes later, a single-dose glucagon (NG or IMG) will be administered to the patients by CRU staff. The actual date and time of glucagon administration will be recorded in the patient's case report form (CRF).

7.3. Blinding

This is an open-label study. However, the treatment assignment list for all randomized patients will not be shared with those responsible for doing either the treatment response assessments or making the decision to take additional action to raise the patients' PG concentration post-glucagon administration. The intent is to minimize any potential bias in administering additional rescue treatment for hypoglycemia.

7.4. Dose Modification

Not applicable.

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 investigational products received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive investigational product or study materials, and only authorized site staff may supply or administer investigational product. All investigational products 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 investigational product will be administered at the clinical site, and documentation of treatment administration will occur at the site.

7.7. Concomitant Therapy

Patients on stable concomitant medications at the time of study entry should continue their regular, unchanged dose throughout the study. These medications may include a stable regimen of insulin therapy (for example, basal and fast-acting insulin) as well as antihypertensive and antilipidemic agents. In addition to the physical examination, investigators should review the insulin regimen for all patients enrolled into the study to confirm acceptability to undergo the procedure to induce hypoglycemia (see Schedule of Activities; Section 2).

Patients taking multiple daily injections, or a basal/bolus regimen, of insulins should not change their basal dose prior to study drug administration. The last dose of short-acting insulin should be administered (by either pump or injection) approximately 6 hours prior to study drug administration. Patients on an insulin pump that is providing a continuous subcutaneous insulin infusion will suspend the use of the pump prior to procedure to induce hypoglycemia.

In general, new concomitant medications should be avoided; however, acetaminophen (1 g, maximum 2 g/24 hours) may be administered at the discretion of the investigator for treatment of headache, etc. If the need for concomitant medication (other than acetaminophen) arises, inclusion or continuation of the patient may be at the discretion of the investigator in consultation with a Lilly clinical pharmacologist. Any medication used during the course of the study must be documented. All changes in concomitant medications made during the study should be recorded.

7.8. Treatment after the End of the Study

Patients will continue their previous insulin regimen after the study procedure has been completed.

8. Discontinuation Criteria

Patients discontinuing from the study prematurely for any reason should complete AE and follow-up procedures per Section 2 of this protocol.

8.1. Discontinuation from Study Treatment

8.1.1. Discontinuation of Inadvertently Enrolled Patients

If the sponsor or investigator identifies a patient who did not meet enrollment criteria and was inadvertently enrolled, the patient must be discontinued from the study.

8.2. Discontinuation from the Study

Patients will be discontinued under the following circumstances:

- Enrollment in any other clinical study involving an investigational product 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 patient should be discontinued from the study
    - if the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent
    - if the patient experiences a severe hypoglycemic event following screening and prior to study Day 1 or during the washout period between Period 1 and Period 2
- Subject Decision
    - the patient requests to be withdrawn from the study.

8.3. Patients Lost to Follow-up

A patient 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. Study site personnel are expected to make diligent attempts to contact patients who fail to return for a scheduled visit or are otherwise unable to be followed up by the site.

9. Study Assessments and Procedures

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

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

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

Unless otherwise stated in subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

9.1. Efficacy Assessments

Plasma glucose levels will be measured prior to the administration of the glucagon product as well as at various time points following its administration (see Schedule of Activities; Section 2), and will be used to assess efficacy outcome.

Subjective hypoglycemia symptoms will be assessed using a self-reported assessment tool (Edinburgh Hypoglycemia Scale; Appendix 7) during the initiation of the hypoglycemia induction, as well as at various time points following the administration of either NG or IMG (see Schedule of Activities; Section 2).

The ability of the patient to identify hypoglycemic symptoms and describe their frequency will be captured at screening visit (see Schedule of Activities; Section 2). This self-report assessment will be done using the Clarke Hypoglycemia Awareness Survey (Appendix 8).

9.2. Procedures

9.2.1. Inducing Hypoglycemia

The patient will have this procedure after admission to the CRU. A study investigator, or qualified designee, must be present at the bedside for clinical assessments of the patient during the insulin infusion and for the 90 minutes following the glucagon administration.

The PG level must be >90 mg/dL to start the procedure. Hypoglycemia will be induced by an IV infusion of regular insulin diluted in saline and may be adjusted as necessary to decrease PG levels <60 mg/dL. Once the PG level is <60 mg/dL, the insulin infusion is stopped and approximately 5 minutes later NG or IMG is given. Blood samples are taken for PG (pharmacodynamics [PD]) and glucagon (pharmacokinetics [PK]) (see Schedule of Activities; Section 2).

9.2.2. Glucagon Administration

Either NG or IMG will be given according to the random assignment. The glucagon treatment will be administered approximately 5 minutes after the insulin infusion has been stopped.

9.2.2.1. Nasal Administration

Nasal glucagon will be administered by CRU staff with the patient lying in a fully reclined lateral position on the opposite side of the nostril being administered (that is, dose is given in the left nostril of a patient lying in right lateral recumbency).

The tip of the device is gently entered in the nostril to the point where the index and middle finger of the administrator are just touching the external nare of the patient. At that point, the bottom of the device is pushed with the thumb until the device is engaged, the green band disappears, and powder is discharged into the nostril. The drug is absorbed from the nasal cavity; thus the patient does not need to inhale after dosing and continues breathing normally throughout the process. If a subject sneezes immediately after administration, document using the Nasal and Non-nasal Score Questionnaire (Appendix 6).

9.2.2.2. Intra-muscular Administration

The GlucaGen HypoKit contains the necessary supplies to prepare the dose and administer the IMG. A dose of 1-mg of glucagon in a concentration of 1 mg/mL will be injected IM in the deltoid muscle of the participant's nondominant arm with the participant lying in a fully reclined lateral position on the opposite side of the arm being administered (that is, dose is given in the left arm of a patient lying in right lateral recumbency).

9.2.3. Procedures for Insufficient Response to Glucagon Administration

If the PG is declining too fast or symptoms become consistent for the progression to severe hypoglycemia to occur, the investigator may decide to start a glucose infusion to prevent a deterioration of the situation. Continuous venous access will be used while the patient resides in the CRU to enable immediate delivery of IV glucose if needed. If, following the administration of glucagon, a patient's PG concentration remains <55 mg/dL at 30 minutes or <60 mg/dL at 45 minutes, IV glucose may be given as appropriate to the clinical situation. If IV glucose is given or additional glucagon is given, any remaining blood samples for the admission will still be collected.

9.2.4. End of Admission

Before departure from the clinical site, the glucose and insulin dosing and stability of the participant will be evaluated by the study physician to ensure the safety of the participant. Patients will remain at the CRU for 6 hours following procedure, during which time a carbohydrate-rich meal will be provided. The patient may stay at the CRU longer, at the discretion of the investigator.

9.3. Adverse Events

Investigators are responsible for monitoring the safety of patients 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 patient.

The investigator is responsible for the appropriate medical care of patients 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 patient to discontinue the investigational product before completing the study. All AEs will be followed until restoration or until a stable condition has been achieved. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator. The follow-up should not be interrupted, even if there is a reasonable explanation for the event.

After the informed consent form (ICF) is signed, study site personnel will record, via designated data collection methods, the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. Additionally, study 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, study device, or a study procedure, taking into account the disease, concomitant treatment, or pathologies.

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

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

9.3.1. Serious Adverse Events

An SAE is any AE from this study that results in 1 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 1 of the other outcomes listed in the definition above.
- when a condition related to the drug delivery system necessitates medical or surgical intervention to preclude either permanent impairment of a body function or permanent damage to a body structure, the serious outcome of "required intervention" will be assigned.

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

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

Although all AEs are recorded in the designated date collection methods after signing informed consent, SAE reporting to the sponsor begins after the patient has signed informed consent and has received investigational product. However, if an SAE occurs after signing informed consent, but prior to receiving investigational product, 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 patients once they have discontinued from and/or completed the study (the patient 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 investigational product) 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.

9.3.1.1. 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.

9.3.1.2. Adverse Event Monitoring with a Systematic Questionnaire

Before administering the Nasal and Non-nasal Score Questionnaire (see Appendix 6 for a copy of the questionnaire) and Edinburgh Hypoglycemia Scale (see Appendix 7), study site personnel will question the patient about any change in the preexisting condition(s) and the occurrence and nature of any AEs. Study site personnel will explain the possibility to the patient of AEs associated with the study and that these AEs will be captured during the study through the use of the Nasal and Non-nasal Score Questionnaire and Edinburgh Hypoglycemia Scale.

Nonserious AEs obtained through the questionnaire are recorded and analyzed separately.

Only SAEs elicited through the Nasal and Non-nasal Score Questionnaire and Edinburgh Hypoglycemia Scale are to be recorded as AEs via electronic data entry and reported to Lilly or its designee within 24 hours as SAEs.

9.3.2. 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.

Patients should be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product (or drug delivery system) so that the situation can be assessed.

9.4. Treatment of Overdose

Not applicable.

9.5. Safety

9.5.1. Laboratory Tests

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

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.

9.5.2. Vital Signs

For each patient, vital sign measurements should be conducted according to the Schedule of Activities (Section 2), and following the study-specific recommendations included in the Manual of Operations for the study.

Blood pressure and pulse rate should be measured after at least 5 minutes supine.

If orthostatic measurements are required, patients should be supine for at least 5 minutes and stand for at least 2 minutes.

If the patient feels unable to stand, supine vital signs only will be recorded.

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

9.5.3. Electrocardiograms

For each patient, ECGs should be collected according to the Schedule of Activities (Section 2) and the study-specific recommendations included in Manual of Operations for the study.

Any clinically significant findings from ECGs that result in a diagnosis and that occur after the patient receives the first dose of the investigational product should be reported to Lilly, or its designee, as an AE via electronic data entry.

For each patient, a single 12-lead digital ECG will be collected according to the Schedule of Activities (Section 2). Electrocardiograms must be recorded before collecting any blood samples. Patients 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 patient is still present, to determine whether the patient meets entry criteria at the relevant visit(s) and for immediate patient 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 patient can continue in the study. The investigator, or qualified designee, is responsible for determining if any change in patient 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.

9.5.4. Other Tests

Blood samples will be collected as specified in the Schedule of Activities (Section 2) and stored for future exploratory analyses, which may include an assessment of anti-glucagon antibodies. Should immunogenicity be assessed, it will be done using a validated assay designed to detect antidrug antibodies in the presence of LY900018. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the LY900018.

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 LY900018. Any samples remaining after 15 years will be destroyed.

A nasal and injection-site inspection will be conducted in advance of the hypoglycemic induction procedure. This inspection will ascertain whether either sites are normal in appearance prior to drug administration. The nasal and inspection-site inspection will also be done 90 minutes following glucagon administration.

9.5.5. Safety Monitoring

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

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

- trends in safety data
- laboratory analytes including HbA1c and electrolytes (see Appendix 2)
- adverse events including monitoring of nasal cavity and injection site.

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

9.5.5.1. Hepatic Safety

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

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

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

9.6. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (see Section 2), venous blood samples of approximately 4 mL each will be collected to determine the plasma concentrations of glucagon and DPC. Three samples may be collected per subject at additional time points during the study if warranted and agreed upon between both the investigator and sponsor. DPC samples are collected from patients treated with NG only. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock) of each sampling will be recorded.

9.6.1. Bioanalysis

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

Concentrations of glucagon will be assayed using a validated liquid chromatography with tandem mass spectrometry (LC/MS) method.

Concentrations of DPC will be assayed using a validated liquid chromatography with tandem mass spectrometry (LC/MS) method. Analyses of samples collected from patients who received IMG 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.

9.7. Pharmacodynamics

At times specified in the Schedule of Activities (see Section 2), venous blood samples will be collected and used to determine the PG concentration. The samples will be stored for up to a maximum of 1 year after the last patient visit for the study at a facility selected by the sponsor.

Samples used to assess the secondary objective endpoints will be processed within 1 year following last patient visit. Any samples remaining after 1 year will be destroyed.

9.7.1. Exploratory Sample Assessments and Storage

Collection of samples for exploratory research is also part of this study. Blood samples will be collected as specified in the Schedule of Activities (see Section 2). Samples collected and stored for exploratory analysis may be used for immunogenicity assessments.

Samples will be retained for a maximum of 15 years after the last patient visit, or for a shorter period if local regulations and ERBs allow, at a facility selected by the sponsor. The duration allows the sponsor to respond to future regulatory requests related to the NG (LY900018). 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 (see Section 2), where local regulations allow.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable exposure or response to glucagon nasal powder (LY900018) and to investigate genetic variants thought to play a role in diabetes mellitus and related complications. Assessment of variable response may include evaluation of AEs or differences in efficacy.

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

Samples will be retained for a maximum of 15 years after the last patient visit, or for a shorter period if local regulations and/or ERBs/IRBs impose shorter time limits, for the study at a facility selected by Lilly or its designee. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of glucagon nasal powder (LY900018) or after glucagon nasal powder (LY900018) 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

Not applicable.

9.10. Health Economics

Not applicable.

10. Statistical Considerations and Data Analysis

10.1. Sample Size Determination

Assuming a 5% dropout rate, the study will enroll approximately 70 patients to have 66 patients completing both treatment visits with evaluable primary outcome.

A total of 66 patients are required in the study in order to achieve the primary objective with at least 90% power under the following assumptions:

- A treatment success rate of 98% for both treatments
- A noninferiority margin of 10%
- One-sided alpha level of 0.025
- A within-patient correlation of zero between 2 treatment visits

10.2. Populations for Analyses

10.2.1. Study Participant Disposition

Proportion of patients discontinued from the study and the reasons for discontinuation will be summarized by treatment group for all randomized patients.

10.2.2. Study Participant Characteristics

The patients' baseline characteristics and demographics will be obtained at entry and will be summarized for all randomized patients.

10.2.3. Treatment Compliance

No specific study data will be collected for analysis of treatment compliance.

10.3. Statistical Analyses

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

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the statistical analysis plan (SAP) and/or in the clinical study report.

All data will be entered, verified, and archived at a contract research organization (CRO) external to Lilly and/or at Lilly. Data listings, summaries, and analyses will be performed by a CRO and/or by Lilly under the guidance and approval of statisticians at Lilly.

Unless otherwise specified, efficacy analyses will be conducted on all randomized patients who received at least 1 dose of the study drug and have evaluable efficacy outcome.

Pharmacokinetic/pharmacodynamic analyses will be conducted on data from all randomized patients who receive at least 1 dose of the study drug and have evaluable PK/PD.

Safety analyses will be conducted for all randomized patients who receive at least 1 dose of the study drug, whether or not they completed all protocol requirements (see Section 10.3.2.1).

All analyses will be based on the treatment patients actually received (if different from assigned treatment). Unless otherwise specified, all tests of statistical significance for treatment comparisons will be evaluated at a nominal level of 0.05 using 2-tailed test procedures, and confidence intervals (CIs) will be computed as 2-tailed using a 95% significance level. All tests of interactions between treatment group and other covariates will be conducted as 2-sided with an alpha level of 0.10. SAS version 9.2 or higher will be used to perform the analyses.

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 analyses purposes to avoid issues with post hoc analyses and incomplete disclosures of analyses.

10.3.1. Efficacy Analyses

10.3.1.1. Primary Efficacy

The primary outcome is the treatment success, which is defined as an increase in PG to ≥70 mg/dL or an increase of ≥20 mg/dL from PG nadir within 30 minutes after receiving glucagon, without receiving additional actions to increase the PG concentration. The nadir is defined as the minimum PG concentration at the time of or within 10 minutes following glucagon administration.

The primary analysis will be a treatment group comparison of the primary outcome. The percentage of treatment successes in each treatment and the difference in percentages will be computed. A 2-sided 95% CI will be obtained from the 1-sample mean of the paired differences in primary outcome (1=outcome observed; 0=outcome not observed) across 2 treatment visits. Noninferiority of NG will be declared if the upper limit of a 2-sided 95% CI constructed on the difference in percentages (IMG – NG) is less than the noninferiority margin of 10%.

The proposed noninferiority margin of 10% has been chosen based on the previously completed Phase 3 study (Rickels et al. 2016).

Primary efficacy analysis will only include patients who complete both treatment visits with evaluable primary outcome. The following will be considered as nonevaluable primary efficacy outcome and excluded from the analysis related to primary efficacy outcome:

- Patients with at least 1 treatment visit in which the lowest PG concentration at the time of or within 10 minutes following glucagon administration is ≥70 mg/dL;
- Patients receive an external measure to raise PG concentration either before glucagon administration or within the first 10 minutes of glucagon administration.

Plasma glucose concentrations assessed through a central laboratory will be used to assess treatment success. If a central laboratory measurement is missing, the SuperGL (or equivalent)

measurement from that time point will be used in general with the following additional provisions:

- Out-of-window blood draws (blood draws taken before/after the midpoint between consecutive planned measurements) that occur prior to the 30-minute time point will be included.
- Central laboratory PG concentrations and SuperGL (or equivalent) concentrations at the 30-minute time point that are measured more than 35 minutes after administration of glucagon will be considered missing.
- If a PG concentration is missing for both central laboratory and SuperGL (or equivalent) measurements, the missing value will be imputed using linear interpolation of central laboratory values.

Additional analysis will be performed if deemed necessary. The details will be provided in the SAP.

10.3.1.2. Secondary Efficacy Analyses

10.3.1.2.1. Plasma Glucose Values

Descriptive statistics will be used to summarize the baseline, various postdose time points, and absolute change from baseline in PG values by treatment group. Additional analysis will be performed if deemed necessary. The details will be provided in the SAP.

If a patient receives additional intervention to raise PG concentrations, measurements taken after the time of intervention will be excluded from the analysis.

10.3.1.2.2. Symptoms of Hypoglycemia

Descriptive statistics will be used to summarize the baseline, various postdose time points, and absolute change from baseline in total score and each subscale score of Edinburgh Hypoglycemia Scale by treatment group. Additional analysis will be performed if deemed necessary. The details will be provided in the SAP.

10.3.2. Safety Analyses

10.3.2.1. Clinical Evaluation of Safety

All investigational products 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 investigational product as perceived by the investigator. Symptoms reported to occur prior to enrollment will be distinguished from those reported as new or increased in severity during the study.

The number of investigational product-related SAEs will be reported.

Nasal/respiratory and anosmia AEs will be identified using preferred terms and summarized by treatment group, the details will be provided in the SAP.

This section is applicable to spontaneously reported AE. Events solicited through Nasal and Non-nasal Score Questionnaire will be analyzed separately and the details are provided in Section 10.3.2.2.

10.3.2.2. Nasal and Non-nasal Score Questionnaire

The scoring for each response to Nasal and Non-nasal Score Questionnaire will follow the scale displayed on the questionnaire ('None'=0, 'Mild'=1, 'Moderate'=2, 'Severe'=3). The total score of the questionnaire will be calculated as the sum of the scores for each question. Descriptive statistics will be used to summarize the baseline, various postdose time points, and absolute change from baseline in total score of Nasal and Non-nasal Score Questionnaire by treatment group. See Appendix 6 for a copy of the questionnaire. Additional analysis will be performed if deemed necessary. The details will be provided in the SAP.

10.3.2.3. Statistical Evaluation of Safety

Safety parameters will be assessed including safety laboratory parameters, vital signs, and ECG parameters. The parameters will be listed and summarized using standard descriptive statistics. Additional analysis will be performed if deemed necessary. The details will be provided in the SAP.

10.3.3. Pharmacokinetic Analyses

10.3.3.1. Pharmacokinetic Parameter Estimation

Pharmacokinetic parameter estimates for glucagon and DPC will be calculated using standard noncompartmental methods of analysis (NCA).

The primary parameters for PK analysis will be maximum drug concentration (C_{max}), area under the concentration versus time curve (AUC), time to maximal concentration (T_{max}) of glucagon and DPC. Other noncompartmental parameters, such as half-life, apparent clearance, and apparent volume of distribution may be reported.

Parameters will be individually calculated for each subject based on actual time of collection.

10.3.3.2. Pharmacokinetic Statistical Inference

Log-transformed PK parameters (such as C_{max} and AUC parameters) will be evaluated in a linear mixed-effects model with fixed effects for treatment, period, and sequence, and a random effect for patient. The treatment differences will be back-transformed to present the ratios of geometric means and the corresponding 90% CI.

The T_{max} will be analyzed using the Wilcoxon signed rank test. Estimates of the median difference based on the observed medians, 90% CIs, and p-values from the Wilcoxon test will be calculated.

Exploratory analyses may be performed for other PK parameters as deemed appropriate.

10.3.4. Pharmacodynamic Analyses

10.3.4.1. Pharmacodynamic Parameter Estimation

Pharmacodynamic parameters will be calculated using NCA. Key PD parameters will be derived to assess the exposure to glucose and duration of exposure above, below, and within the normal glucose range. The normal range for PG will be considered to be 70 to 108 mg/dL. Actual sampling times will be used for all calculations.

The following PD parameters will be calculated using concentrations of glucose:

$AUEC_{above}$	area under the effect concentration-time curve above the normal range
$AUEC_{below}$	area under the effect concentration-time curve below the normal range
$AUEC_{within}$	area under the effect concentration-time curve within the normal range
$AUEC_{0-1.5}$	area under the effect concentration-time curve from time zero (predose) up to 1.5 hours
BG_{max}	maximal blood glucose
$Duration_{above}$	duration above normal range
$Duration_{below}$	duration below normal range
$Duration_{within}$	duration within normal range
t_{above}	time to concentrations above normal range
t_{below}	time to concentrations below normal range (after t_{above})
t_{within}	time to concentrations within normal range
T_{max}	time to maximum concentration

The following PD parameters will be calculated using baseline-adjusted concentrations of PG:

$AUEC_{0-1.5}$	area under the effect concentration-time curve from time zero (predose) up to 1.5 hours
BG_{max}	maximal blood glucose
T_{max}	time to maximum concentration

Baseline PG concentrations will be calculated from samples obtained immediately prior to glucagon dosing (e.g., pre-dose).

Other PD parameters of PG may be calculated if required. Individual concentrations and PD parameters of PG will be summarized with descriptive statistics by treatment.

10.3.4.2. Pharmacodynamic Statistical Inference

The PD parameters (such as BG_{max} and AUEC parameters) will be log-transformed prior to analysis and a linear mixed-effects model fitted to the data, with treatment, period, and sequence as fixed effects and patient as a random effect. For each parameter, the treatment difference will be back-transformed to present the ratios of geometric means and the corresponding 90% CI.

The values of T_{max} will be analyzed nonparametrically using the Wilcoxon signed-rank test. Median differences and approximate 90% CIs for the difference will be calculated for the comparisons of treatments.

Exploratory analyses may be performed for other PD parameters as deemed appropriate.

10.3.5. Pharmacokinetic/Pharmacodynamic Analyses

Exploratory analyses may be performed to evaluate exposure–response relationship if needed.

10.3.6. Data Review during the Study

Trial-level safety review will be conducted during the study by the study team.

10.3.7. Interim Analyses

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

A primary data lock will be conducted after last patient discharge from CRU. The aim of the primary data lock is to enable data analysis to assess the primary/secondary objectives, and may include assessment of exploratory objectives. The primary data lock will include all study data up to last patient discharge from CRU. There will be a final study data lock after all patients completed the safety follow-up visit.

11. References

Rickels MR, Ruedy KJ, Foster NC, Piché CA, Dulude H, Sherr JL, Tamborlane WV, Bethin KE, DiMeglio LA, Wadwa RP, Ahmann AJ, Haller MJ, Nathan BM, Marcovina SM, Rampakakis E, Meng L, Beck RW; T1D Exchange Intranasal Glucagon Investigators. Intranasal glucagon for treatment of insulin-induced hypoglycemia in adults with type 1 diabetes: a randomized crossover noninferiority study. *Diabetes Care*. 2016;39(2):264-270.

Appendix 1. Abbreviations and Definitions

Term	Definition
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AUC	area under the concentration versus time curve
AUEC	area under the effect concentration-time curve
BGmax	maximal blood glucose
CI	confidence interval
C_{max}	maximum drug concentration
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the study-related requirements, 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 points, depending on the steps required to obtain confirmed results.
CRF	case report form
CRO	contract research organization
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
DPC	dodecylphosphocholine
ECG	electrocardiogram

enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the study are those who have been assigned to a treatment.
enter	Patients entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
FSH	follicle-stimulating hormone
GCP	good clinical practice
HbA1c	hemoglobin A1c
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonization
LC-MS/MS	liquid chromatography with tandem mass spectrometry
IM	intra-muscular
IMG	intra-muscular glucagon
informed consent	A process by which a patient 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 patient's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
investigational product	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
legal representative	An individual or judicial or other body authorized under applicable law to consent, on behalf of a prospective patient, to the patient's participation in the clinical study.
NCA	noncompartmental methods of analysis

NG	nasal glucagon
non-investigational product	A product that is not being tested or used as a reference in the clinical study, but is provided to patients and used in accordance with the protocol, such as concomitant or rescue/escape medication for preventative, diagnostic, or therapeutic reasons, medication to ensure adequate medical care and/or products used to induce a physiological response.
open-label	A study in which there are no restrictions on knowledge of treatment allocation, therefore the investigator and the study participant are aware of the drug therapy received during the study.
PG	plasma glucose
PK/PD	pharmacokinetics/pharmacodynamics
randomize	The process of assigning patients to an experimental group on a random basis.
SAE	serious adverse event
SAP	statistical analysis plan
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.
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	drug half-life
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TBL	total bilirubin
TEAE	treatment-emergent adverse event: Any untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
T_{max}	time to maximum concentration
ULN	upper limit of normal

Appendix 2. Clinical Laboratory Tests

Laboratory Tests

Hematology	**Clinical Chemistry**
Hematocrit	Sodium
Hemoglobin	Potassium
	Magnesium[a]
Erythrocyte count (RBC)	Chloride
Mean cell volume	Bicarbonate
Mean cell hemoglobin	Glucose[d]
Mean cell hemoglobin concentration	Blood urea nitrogen (BUN)
Leukocytes (WBC) Platelets	Total bilirubin
Differential WBC % of:	Albumin
Neutrophils	Alkaline phosphatase (ALP)
Lymphocytes	Aspartate aminotransferase (AST)
Monocytes	Alanine aminotransferase (ALT)
Eosinophils	Creatinine
Basophils	Phosphorus
HbA1c	
Urinalysis[b]	**Other**
Specific gravity	Ethanol breath testing[c]
pH	Urine drug screen[c]
Leukocyte esterase	Hepatitis B surface antigen[a]
Protein	Hepatitis C antibody[a]
Glucose	HIV[a]
Ketones	Pregnancy test (a serum pregnancy test will be done at screening, and urine pregnancy tests will be done prior to inducing hypoglycemia at the CRU visits in Periods 1 and 2)
Bilirubin	FSH[a] for confirmation of postmenopausal status
Urobilinogen	Pharmacogenetics
Blood	
Nitrite	
Color	

Abbreviations: CRU = clinical research unit; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; RBC = red blood cell; WBC = white blood cell.

a Performed at screening only

b Microscopic examination will be performed only if dipstick test is positive for leukocyte esterase, blood, nitrite, or protein.

c Urine drug screen and ethanol level may be repeated prior to admission to the CRU and at other times indicated in the Schedule of Activities (Section 2).

d Random at screening and follow-up visits and fasting procedure visits.

Appendix 3. Study Governance, Regulatory, and Ethical Considerations

Informed Consent

The investigator is responsible for

- ensuring that the patient 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 patient or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of investigational product.
- answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the study.
- providing a copy of the ICF to the participant or the participant's legal representative(s) and retaining a copy on file.

Recruitment

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

Ethical Review

The investigator or appropriate local representative must give assurance that the ERB was properly constituted and convened as required by International Council for Harmonization (ICH) guidelines and other applicable laws and regulations.

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

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

- the current IB and updates during the course of the study
- ICF
- relevant curricula vitae

Regulatory Considerations

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

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

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

Protocol Signatures

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

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

Final Report Signature

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

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

Data Quality Assurance

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

- provide instructional material to the study sites, as appropriate.
- provide training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the CRFs, and study procedures.
- make periodic visits to the study site.
- be available for consultation and stay in contact with the study site personnel through 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 patient 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 patient personal information collected will be provided in a written document to the patient by the sponsor.

Study and Site Closure

Discontinuation of Study Sites

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

Discontinuation of the Study

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

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with patients in consultation with Lilly or its designee CRP. Hepatic monitoring tests will be conducted at local laboratory or central laboratory in the case of hepatitis E.

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**
CPK	**Antibody)[a]**

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

a Assayed by Lilly-designated or local laboratory.

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

Appendix 5. Blood Sampling Summary

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

Protocol I8R-MC-IGBI Sampling Summary

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
HbA1c	2	2	4
Clinical laboratory tests[a]	15	4	60
Pharmacokinetics – glucagon	4	27	108
Pharmacokinetics – DPC	4	≤11	44
Pharmacodynamics – plasma glucose	2	22	44
Exploratory sample	10	2	20
Pharmacogenetics	10	1	10
Bedside plasma glucose (SuperGL)	0.5	144 (max)	72
Total			362
Total for clinical purposes			370

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

Appendix 6. Nasal and Non-nasal Score Questionnaire

Nasal and Non-nasal Score Questionnaire

Please select the number that corresponds best to the effects/symptoms you are experiencing at this time, or have experienced since last questioning.

0=Not experiencing this (no symptoms at all).

1=Only experiencing a mild case of this and it is easily tolerated.

2=Experiencing a moderate level of this symptom. It is bothersome but tolerable.

3=Experiencing a severe level of this symptom. It is hard to tolerate and interferes with your activities.

Symptoms	Scale			
	0 None	1 Mild	2 Moderate	3 Severe
1. Runny nose	0 None	1 Mild	2 Moderate	3 Severe
2. Nasal congestion (nostrils plugged)	0 None	1 Mild	2 Moderate	3 Severe
3. Nasal itching	0 None	1 Mild	2 Moderate	3 Severe
4. Sneezing	0 None	1 Mild	2 Moderate	3 Severe
5. Watery eyes	0 None	1 Mild	2 Moderate	3 Severe
6. Itchy eyes	0 None	1 Mild	2 Moderate	3 Severe
7. Redness of eyes	0 None	1 Mild	2 Moderate	3 Severe
8. Itching of ears	0 None	1 Mild	2 Moderate	3 Severe
9. Itching of throat	0 None	1 Mild	2 Moderate	3 Severe

Appendix 7. Edinburgh Hypoglycemia Scale

Edinburgh Hypoglycemia Scale

Each of the 13 symptoms will have a score of 1 to 7:

1 = not experiencing this (no symptoms at all).
2 = only experiencing a very mild case of this and it is easily tolerated.
3 = only experiencing a mild case of this and it is tolerated.
4 = experiencing a mild to moderate case of this and it is tolerated.
5 = experiencing a moderate case of this and it is tolerated.
6 = experiencing a moderate to severe level of this symptom. It is bothersome but tolerable.
7 = experiencing a severe level of this symptom. It is hard to tolerate.

Neuroglycopenic symptoms

Cognitive dysfunction

Inability to concentrate:

1	2	3	4	5	6	7
○	○	○	○	○	○	○
No symptom			mild to moderate symptom			severe symptom

Blurred vision:

1	2	3	4	5	6	7
○	○	○	○	○	○	○
No symptom			mild to moderate symptom			severe symptom

Anxiety:

1	2	3	4	5	6	7
○	○	○	○	○	○	○
No symptom			mild to moderate symptom			severe symptom

Confusion:

1	2	3	4	5	6	7
○	○	○	○	○	○	○
No symptom			mild to moderate symptom			severe symptom

Difficulty speaking:

1	2	3	4	5	6	7
○	○	○	○	○	○	○
No symptom			mild to moderate symptom			severe symptom

Double vision:

1	2	3	4	5	6	7
○	○	○	○	○	○	○
No symptom			mild to moderate symptom			severe symptom

Neuroglycopenia

Drowsiness:

1	2	3	4	5	6	7
○	○	○	○	○	○	○
No symptom			mild to moderate symptom			severe symptom

Tiredness:

1	2	3	4	5	6	7
○	○	○	○	○	○	○
No symptom			mild to moderate symptom			severe symptom

Hunger:

1	2	3	4	5	6	7
○	○	○	○	○	○	○
No symptom			mild to moderate symptom			severe symptom

Weakness:

1	2	3	4	5	6	7
○	○	○	○	○	○	○
No symptom			mild to moderate symptom			severe symptom

Autonomic symptoms

Sweating:

1	2	3	4	5	6	7
○	○	○	○	○	○	○
No symptom			mild to moderate symptom			severe symptom

Trembling:

1	2	3	4	5	6	7
○	○	○	○	○	○	○
No symptom			mild to moderate symptom			severe symptom

Warmness:

1	2	3	4	5	6	7
○	○	○	○	○	○	○
No symptom			mild to moderate symptom			severe symptom

Appendix 8. Clarke Hypoglycemia Awareness Survey

Clarke Hypoglycemia Awareness Survey

Check the category that best describes you: (check one only)

	I always have symptoms when my blood sugar is low	A
	I sometime have symptoms when my blood sugar is low	R
	I no longer have symptoms when my blood sugar is low	R

2. Have you lost some of the symptoms that used to occur when your blood sugar was low:

	Yes	R
	No	A

3. In the past six months, how often have you had moderate hypoglycemia episodes? *(Episodes where you might feel confused, disoriented or lethargic and were unable to treat yourself)*

	Never	A
	Once or twice	R
	Every other month	R
	Every month	R
	More than once a month	R

4. In the past year, how often have you had severe hypoglycemic episodes? *(Episodes where you were unconscious or had a seizure and needed glucagon or intravenous glucose)*

	Never	A		5 times	R		10 times	R
	1 time	R		6 times	R		11 times	R
	2 times	R		7 times	R		12 times or more	R
	3 times	R		8 times	R			
	4 times	R		9 times	R			

5. How often in the last month have you had readings <70 mg/dL (3.9 mmol/L) with symptoms?

	Never		1 time/week		4 to 5 times/week
	1 to 3 times		2 to 3 times/week		Almost daily

6. How often in the last month have you had readings <70 mg/dL (3.9 mmol/L) without symptoms?

	Never		1 time/week		4 to 5 times/week
	1 to 3 times		2 to 3 times/week		Almost daily

If answer to question 5 < answer to question 6	R
If answer to question 6 < answer to question 5	A

7. How low does your blood sugar need to go before you feel symptoms?

	60-69 mg/dL;	3.3-3.8 mmol/L	A
	50-59 mg/dL;	2.8-3.3 mmol/L	R
	40-49 mg/dL;	2.2-2.7 mmol/L	R
	Less than 40 mg/dL;	less than 2.2 mmol/L	R

8. To what extent can you tell by your symptoms that your blood sugar is low?

	Never	R
	Rarely	R
	Sometimes	R
	Often	A
	Always	A

Abbreviations: A = aware; R = reduced awareness.

Final Score: Total Number of "R" responses. Reduced awareness = 4 or more reduced responses; Intermediate = 3 reduced responses; Aware = 2 or fewer reduced responses.

Appendix 9. Protocol Amendment I8R-MC-IGBI(b) Summary: Comparison of Glucagon Administered by Either the Nasal (LY900018) or Intra-muscular (GlucaGen®) Routes in Adult Patients with Type 1 Diabetes Mellitus During Controlled Insulin-Induced Hypoglycemia

Overview

Protocol I8R-MC-IGBI, Comparison of Glucagon Administered by Either the Nasal (LY900018) or Intra-muscular (GlucaGen®) Routes in Adult Patients with Type 1 Diabetes Mellitus During Controlled Insulin-Induced Hypoglycemia, has been amended. The new protocol is indicated by Amendment (b) and will be used to conduct the study in place of any preceding version of the protocol.

The amendment is in response to regulatory feedback. The overall changes made to this protocol are as follows:

- In Section 6.2 (Exclusion Criteria), criterion [23] was revised to exclude patients with current stable psychiatric disorders.
- In Section 9.2.3 (Procedures for Insufficient Response to Glucagon Administration), text was added to clarify that continuous venous access will be used to enable immediate delivery of glucose to patients if needed.
- In Section 9.3 (Adverse Events), text was added to clarify that all AEs will be documented, not just those deemed to have a causal relationship with the investigational product or those that are severe or medically important. In addition, text was added to clarify that the follow-up for all AEs should not be interrupted, even if there is a reasonable explanation for the event.

Additional clarifications were made to the bedside glucose safety measurement thresholds.

Revised Protocol Sections

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

Schedule of Activities

Procedure	Screening Visit	Period 1 and Period 2 CRU Visits	Follow-up (or ED) Visit	Comments
	Up to 28 days before Period 1	Day 1	28(±2) days after last dose of study drug	
Bedside glucose safety measurements (SuperGL laboratory analyzer)		X		Samples will be collected throughout the study procedure. During the hypoglycemia induction procedure, plasma glucose concentration will be measured no more than 10 minutes apart while the plasma glucose concentration is ≥100 mg/dL and no more than 5 minutes apart when the plasma glucose concentration is <100 mg/dL. Post-glucagon administration, plasma glucose concentration will be measured every 5 minutes for the first 30 minutes and every 10 minutes up to 90 minutes.

6.2. Exclusion Criteria

[23] have a significant history of or current psychiatric disorders. ~~However, patients may be included if the disease is stable and patient is receiving treatment~~

9.2.3. Procedures for Insufficient Response to Glucagon Administration

If the PG is declining too fast or symptoms become consistent for the progression to severe hypoglycemia to occur, the investigator may decide to start a glucose infusion to prevent a deterioration of the situation. Continuous venous access will be used while the patient resides in the CRU to enable immediate delivery of IV glucose if needed. If, following the administration of glucagon, a patient's PG concentration remains <55 mg/dL at 30 minutes or <60 mg/dL at 45 minutes, IV glucose may be given as appropriate to the clinical situation. If IV glucose is given or additional glucagon is given, any remaining blood samples for the admission will still be collected.

9.3. Adverse Events

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 patient to discontinue the investigational product before completing the study. All AEs will be followed until restoration or until a stable condition has been achieved. ~~The patient 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 follow-up should not be interrupted, even if there is a reasonable explanation for the event.

Leo Document ID = 1cc55e42-4968-40f4-9359-311adbfd69eb

Approver: [redacted]
Approval Date & Time: 12-Oct-2017 11:52:26 GMT
Signature meaning: Approved

Approver: [redacted]
Approval Date & Time: 12-Oct-2017 15:46:34 GMT
Signature meaning: Approved