Statistical Analysis Plan Version 1 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

NCT03339453

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# 1. Statistical Analysis Plan
# 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



Glucagon nasal powder (LY900018) for Severe Hypoglycemia

Study I8R-MC-IGBI is a multicenter, randomized, open-label, 2-treatment, 2-period, crossover study conducted in adult patients with type 1 diabetes mellitus.


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Protocol I8R-MC-IGBI
Phase 1

Statistical Analysis Plan electronically signed and approved by Lilly on date provided below.

Approval Date: 22-Sep-2017 GMT

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# 3. Revision History

This is the first version of the Statistical Analysis Plan (SAP) for Study I8R-MC-IGBI (IGBI).

# 4. Study Objectives

## 4.1. Primary Objective

To compare LY900018 (nasal glucagon [NG]) versus GlucaGen® (intramuscular glucagon [IMG]) in the percentage of adult patients with type 1 diabetes mellitus who achieve treatment success during controlled insulin-induced hypoglycemia.

## 4.2. Secondary Objectives

- To assess the safety and tolerability of LY900018 versus GlucaGen
- To characterize the pharmacodynamic (PD) profiles of LY900018 versus GlucaGen
- To characterize the pharmacokinetic (PK) profiles of LY900018 versus GlucaGen

## 4.3. Exploratory Objectives

- To characterize the PK profile of the dodecylphosphocholine (DPC) excipient of LY900018
- To assess the occurrence and severity of hypoglycemia symptoms during controlled insulin-induced hypoglycemia
- To assess the awareness of hypoglycemia prior to its induction

# 5. A Priori Statistical Methods

## 5.1. Sample Size Determination

Assuming a 5% dropout rate, the study will enroll approximately 70 patients to get 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 using the following assumptions:

- A treatment success rate of 98% for both treatments
- A noninferiority margin of 10%
- Two-sided alpha level of 0.05
- A within-patient correlation of zero between 2 treatment visits

## 5.2. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company (Lilly) 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 SAP and/or in the clinical study report (CSR). Additional exploratory analyses will be conducted, as deemed appropriate.

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.

Five patient populations are defined for the analysis of this study:

1). *All Entered Set Population (AES)*: All patients who sign inform consent and enter in this study
2). *All Randomized Set Population (ARS)*: All patients who are randomized to study treatments
3). *Full Analysis Set Population (FAS):* All randomized patients who receive at least 1 dose of study drug
4). *Efficacy Analysis Set Population (EAS):* Patients in the FAS and have evaluable primary efficacy outcome
5). *PK/PD Population***:** Patients in the FAS and have evaluable PK/PD.

Unless otherwise specified, efficacy analyses related to primary efficacy outcome will be conducted on data from EAS; other efficacy analyses and all safety analyses will be conducted on data from FAS; PK/PD analyses will be conducted on data from PK/PD population.

Unless otherwise specified, baseline is the last nonmissing value collected prior to study drug administration.

Summary statistics will include number of patients, mean, standard deviation (SD), minimum (and/or 1st quartile), maximum (and/or 3rd quartile), and median.

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 group comparisons (NG vs IMG) 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 groups and other covariates will be conducted at a 2-sided with alpha level of 0.10. SAS version 9.2 or higher will be used to perform the analysis.

## 5.3. Patient Disposition

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

The primary reasons for discontinuation will be listed for the AES.

## 5.4. Patient Characteristics

Patient baseline characteristics and demographics will be obtained at entry and will be summarized for the ARS.

The following baseline parameters will be included in (but are not limited to) the summary report:

- Age (years),
- Gender (Male, Female),
- Race (White, American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander),
- Ethnicity (Hispanic, Non-Hispanic),
- Body weight (kilograms),
- Height (centimeters),
- Body mass index (BMI) (kilograms per meters squared),
- Duration of diabetes (years),
- Baseline HbA1c value (%),
- Baseline Clarke Hypoglycemia Awareness status (%) (Aware, Intermediate, Reduced awareness, as defined in Study IGBI Protocol, Appendix 8)
- Baseline substance use (alcohol)

## 5.5. Concomitant Therapy

A listing and summary of concomitant medications will be provided for the ARS. Concomitant medication will be coded using the World Health Organization (WHO) drug dictionary Enhanced B2 format Version March 2017.

A listing of rescue therapy will be provided for the ARS. The listing will include, but not be limited to, patient ID, treatment group, rescue therapy date/time, and rescue therapy name/dose.

## 5.6. Treatment Compliance

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

## 5.7. Important Protocol Deviations

Important protocol deviations (IPDs) are defined as deviations from the study protocol that may significantly compromise the data integrity and patients' safety. The details of identification of IPDs is provided in a separate document (ie, the trial issue management plan). A listing and/or summary of IPDs will be provided by the study manager after primary outcome database lock.

## 5.8. Primary Outcome and Methodology

The primary outcome is the treatment success, which is defined as an increase in plasma glucose (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 in the EAS. The percentage of patients achieving treatment success in each treatment group 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 minus NG) is less than the noninferiority margin of 10%. Specifically, for each patient, the paired difference of treatment success between IMG and NG will be calculated and PROC TTEST will be used to create the 95% CI of the mean difference.

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 nadir PG is ≥70 mg/dL;
- Patients receiving an external measure to raise PG concentration either before glucagon administration or within the first 10 minutes after 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.

### *5.8.1. Additional Analyses Related to Primary Efficacy Outcome*

For each of the following populations, the proportion of patients achieving treatment success will be summarized for each treatment group and compared using the same method as for the primary efficacy analysis specified above.

- ARS
- Patients in EAS population with nadir glucose is <50 mg/dL on both treatment visits.

Among patients who achieve treatment success, the proportion of patients achieving (1) an increase in glucose to ≥70 mg/dL, or (2) an increase of ≥20 mg/dL from nadir, or (3) an increase in glucose to ≥70 mg/dL and an increase of ≥20 mg/dL from nadir will be summarized for each treatment group and compared using the same method as for the primary efficacy analysis specified above for all 3 populations (ie, EAS, ARS, and EAS with nadir <50mg/dL on both treatment visits).

As an additional sensitivity analysis, in the EAS population, the primary efficacy outcome will be assessed by comparing the upper limit of a 2-sided 95% CI on the difference in proportions obtained from a Poisson regression model using the binary primary outcome, accounting for the correlation due to the cross-over design using a generalized estimating equation. The model will include adjustments for nadir glucose level and treatment period.

Below is the example SAS code computing the treatment difference in proportion of patients achieving treatment success and 95% CI using the Poisson regression model:

```
proc genmod data=a;
  class visit treatment patient;
  model success = treatment visit nadir / dist=poisson link=identity;
  repeated subject=patient / type=un;
  estimate 'success' treatment 1 -1;
  lsmeans treatment / diff cl om;
run;
```

The time from study drug administration to achieve treatment success will be summarized. A Kaplan-Meier (KM) analysis will be used to analyze the time from study drug administration to achieve treatment success. If both components of the treatment success (ie, an increase in

glucose to ≥70 mg/dL and an increase of ≥20 mg/dL), are achieved for a patient, the earlier time point will be used. If a patient receives an external measure to raise glucose at any point, right censoring will be used. A treatment group comparison of the time to achieve treatment success will be performed using Cox proportional hazard models accounting for the correlation due to the crossover design, adjusted for baseline glucose value and treatment period. Due to the discrete time data (5-, 10-, or 30-minute intervals), the exact method will be used. This method averages the Cox proportional hazards likelihood over all possible orderings of tied event times. In addition, time to achieving either an increase in glucose to ≥70 mg/dL or an increase of ≥20 mg/dL from nadir will also be analyzed, separately, using the KM estimator of the survival function.

Below is the example SAS code creating KM life table and curve by treatment group:

```
proc lifetest data=b plots=(s) outsurv=kmtable;
  time minutes*censor(1);
  strata treatment;
run;
```

Below is the example SAS code using proportional hazard model:

```
proc phreg data=b covs(aggregate);
  id patient;
  class treatment visit;
  model minutes*censor(1)= treatment visit nadir / ties=exact;
run;
```

For the time to event analysis, if a patient receives additional intervention treatment to raise glucose prior to achieving a glucose value ≥70 mg/dL or an increase of ≥20 mg/dL from nadir, the remaining time points will be considered as non-events (ie, glucose is not ≥70 mg/dL and does not increase ≥20 mg/dL from nadir).

The time to treatment success analysis will also be repeated in EAS patients with nadir glucose value <50 mg/dL.

A complete by-patient listing of primary efficacy data will be created.

## 5.9. Secondary Efficacy Outcomes and Analyses

### *5.9.1. Plasma Glucose Values*

Descriptive statistics will be used to summarize the baseline, various postdose time points (15, 30, 45, 60, and 90 minutes post glucagon administration), and absolute change from baseline in PG values by treatment group for the FAS.

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

For this analysis, baseline is defined as the last nonmissing PG measured at the time of or immediately prior to glucagon administration at each treatment visit. A treatment comparison of glucose over the 90 minutes following administration of glucagon will be completed using a

linear mixed model with repeated measures (MMRM) that accounts for the correlation due to the crossover design and the correlation due to multiple measures. The baseline score, treatment period, and time points will be included as covariates in the model. Least-square means and 2-sided 95% confidence limits will be calculated for the difference in PG between treatment groups (IMG minus NG) at each time point.

In the MMRM model, the within-patient errors are modeled as an unstructured variance-covariance matrix. If the analysis fails to converge, the following variance-covariance matrix will be used (in the order listed) until one converges:

1. Heterogeneous Toeplitz (TOEPH)
2. Heterogeneous First-order Autoregressive (ARH[1])
3. Heterogeneous Compound Symmetry (CSH)
4. Toeplitz (TOEP)
5. First-order Autoregressive (AR[1])
6. Compound Symmetry (CS)

The Kenward-Roger approximation will be used to estimate denominator degrees of freedom for the MMRM models.

Below is the example SAS code performing the MMRM analysis:

```
proc mixed data=c;
  class  patient time visit treatment;
  model value = treatment time visit baseline /solution ddfm=kr;
  repeated time(visit)/subject=patient type=un;
  lsmeans treatment*time/cl diff om;
run;
```

### *5.9.2. Symptoms of Hypoglycemia*

Descriptive statistics will be used to summarize the baseline, various postdose time points (15, 30, 45, and 60 minutes post glucagon administration), and absolute change from baseline in total score and each subscale score of Edinburgh Hypoglycemia Scale by treatment group for the ARS.

If a patient receives rescue treatment to raise PG concentrations, measurements taken after the rescue will be excluded from the analysis.

For this analysis, baseline is defined as the last nonmissing score collected prior to glucagon administration at each treatment visit.

The total score and subscale scores will be compared between treatment groups through a linear MMRM accounting for the correlation due to the crossover design and the correlation due to multiple measures of the questionnaire. The MMRM analysis of hypoglycemia symptom score will be performed using the similar approach as specified in Section 5.9.1.

## 5.10. Safety Analyses

### *5.10.1. Adverse Event*

This section is applicable to spontaneously reported adverse events (AEs). Events solicited through Nasal and Non-Nasal Score Questionnaire will be analyzed separately, and details are provided in Section 5.10.2.

All investigational products and protocol procedure AEs will be listed.

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

The summary/figure/listing related to AEs will be created using Medical Dictionary for Regulatory Activities (MedDRA) version 18.1.

Where changes in severity are recorded in the case report form, each separate severity of the AE will be reported in the listings; only the most severe will be used in the summary tables. A preexisting condition is defined as an AE that starts before the patient has provided written informed consent and is ongoing at the time of giving consent. A non-treatment-emergent AE is defined as an AE that starts after informed consent but prior to dosing. A treatment-emergent AE (TEAE) is defined as an AE that occurs postdose or that is present prior to dosing and becomes more severe postdose. For AEs with missing severity, the severity will be imputed as either mild (if collected prior to study drug administration) or severe (if collected post study drug administration). If an AE occurs or worsens after the glucagon administration of the first treatment visit but prior to the glucagon administration of the second treatment visit, it will be counted as a TEAE of the first treatment.

Treatment-emergent AEs will be summarized by treatment, severity, and relationship to the study drug. The frequency (the number of AEs, the number of patients experiencing an AE, and the percentage of patients experiencing an AE) of TEAEs for each preferred term within each System Organ Class will be summarized by treatment. The summary and frequency AE tables will be presented for all causalities and those considered related to the study drug. In these analyses, patients experiencing the same AE multiple times will be counted once under each specific treatment for the corresponding preferred term and body system.

The following will also be presented by treatment group:

- The number and proportion of patients who experienced at least 1 TEAE, serious AE, TEAE related to study drug (or study device), died, or discontinued from the study due to an AE.

Nasal/respiratory/anosmia AEs will be identified using MedDRA preferred term (see Appendix 1 for the list of preferred terms) and summarized by treatment group. The frequency (the number of AEs, the number of patients experiencing an AE, and the percentage of patients experiencing an AE) of nasal/respiratory/anosmia TEAEs for each preferred term will be summarized by treatment.

The time needed for resolution of nasal/respiratory/anosmia AEs will be calculated based on the start and end date/time reported by the investigator and summarized using descriptive statistics. Events that did not resolve will be excluded from calculation of the time to resolution. This analysis will include all AEs (ie, patients experiencing AEs with the same preferred term at different time points will be counted multiple times).

Kaplan-Meier curve for each treatment will be produced for time to resolution of nasal/respiratory/anosmia AEs. If the event did not resolve during the study, then it will be treated as censored observation at the end of the study.

### *5.10.2. Nasal and Non-Nasal Score Questionnaire*

The scoring for each response to the 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 (15, 30, 60, and 90 minutes), and absolute change from baseline in total score of Nasal and Non-Nasal Score Questionnaire by treatment group.

For this analysis, baseline is defined as the score measured prior to glucagon administration at each treatment visit.

The total score will be compared between treatment groups through a linear MMRM that accounts for the correlation due to the crossover design and the correlation due to repeated measures of the questionnaire. The MMRM analysis of nasal symptom score will be performed using the similar approach as specified in Section 5.9.1.

The number and proportion of patients within each score categories of each question in the Nasal and Non-Nasal Score Questionnaire in increasing severity (none, mild, moderate, and severe) at each time point and shift of categories from baseline to maximal (and last) postdose severity category will be provided by treatment group.

### *5.10.3. Vital Signs*

The vital signs (diastolic blood pressure [DBP], systolic blood pressure [SBP], pulse, and body temperature) collected at both pre- and 45 minutes post-glucagon administration at the treatment visit will be summarized by treatment group using descriptive statistics.

The shift of abnormalities of DBP, SBP, and pulse from baseline to post treatment will also be summarized by treatment group. For this shift analysis, the high limit is 140 mm Hg for SBP, 90 mm Hg for DBP, and 100 bpm for pulse; the low limit is 90 mm Hg for SBP, 50 mm Hg for DBP, and 50 bpm for pulse.

All abnormal vital sign findings during the study (including screening, pre- and post- glucagon administration at each treatment, and poststudy follow-up) will be listed.

Additional analysis will be performed if warranted upon review of the data.

### 5.10.4. Other Safety Evaluations

Abnormal safety laboratory findings will be listed.

Clinically significant abnormal findings through electrocardiograms, nasal inspection, injection site inspection, and physical examination will be captured as AEs (Section 5.10.1).

## 5.11. Pharmacokinetic Analyses

### 5.11.1. Pharmacokinetic Parameter Estimation

Patients who receive glucagon treatment and have measurable glucagon concentrations will be included in the PK analysis. The PK parameter estimates will be calculated by standard noncompartmental methods of analysis using validated software program (Phoenix WinNonlin Version 6.4.1 or later).

Plasma concentrations of glucagon will be used to determine the following PK parameters, when possible:

| Parameter | Units | Definition |
|---|---|---|
| AUC(0-$t_{last}$) | pg.h/mL | Area under the concentration vs time curve from time zero to time t, where t is the last time point with a measurable concentration |
| AUC(0-∞) | pg.h/mL | Area under the concentration vs time curve from zero to infinity |
| %AUC($t_{last}$-∞) | % | Percentage of AUC(0-∞) extrapolated |
| $C_{max}$ | pg/mL | Maximum observed drug concentration |
| $t_{max}$ | h | Time of maximum observed drug concentration |
| $t_{1/2}$ | h | Half-life associated with the terminal rate constant (λz) in noncompartmental analysis |
| CL/F | L/h | Apparent total body clearance of drug calculated after extravascular administration |
| $V_Z$/F | L | Apparent volume of distribution during the terminal phase after extravascular administration |
| $V_{SS}$/F | L | Apparent volume of distribution at steady state after extravascular administration |

An alternative AUC measure, such as AUC to a common time point, may be calculated if AUC(0-∞) cannot be reliably calculated.

The following PK parameters will also be calculated using baseline-adjusted (ie, change from baseline) concentrations of glucagon: AUC, $C_{max}$, and $t_{max}$.

Baseline glucagon concentrations will be concentrations from samples obtained immediately prior to glucagon dosing (ie, predose). Any resulting negative concentrations will be considered below the lower limit of quantitation (BQL) for the purposes of treatment within PK analysis (see BQL handling in subsequent subsections).

Additional PK parameters may be calculated, as appropriate. The software and version used for the final analyses will be specified in the CSR. Any exceptions or special handling of data will be clearly documented within the final study report.

Formatting of tables, figures, and abbreviations will follow the Eli Lilly Global PK/PD/TS Tool: Non-Compartmental Pharmacokinetic Style Guide. The version of the tool effective at the time of PK analysis will be followed.

**General PK Parameter Rules**

- Actual sampling times will be used in the final analyses of individual PK parameters, except for nonbolus predose sampling times, which will be set to zero.
- $C_{max}$ and $t_{max}$ will be reported from observed values. If $C_{max}$ occurs at more than 1 time point, $t_{max}$ will be assigned to the first occurrence of $C_{max}$.
- AUC parameters will be calculated using a combination of the linear and logarithmic trapezoidal methods (linear-log trapezoidal rule). The linear trapezoidal method will be applied up to $t_{max}$ and then the logarithmic trapezoidal method will be used after $t_{max}$. The minimum requirement for the calculation of AUC will be the inclusion of at least 3 consecutive plasma concentrations above the lower limit of quantification, with at least one of these concentrations following $C_{max}$. AUC(0-∞) values where the percentage of the total area extrapolated is more than 20% will be flagged. Any AUC(0-∞) value excluded from summary statistics will be noted in the footnote of the summary table.
- Half-life ($t_{½}$) will be calculated, when appropriate, based on the apparent terminal log-linear portion of the concentration-time curve. The start of the terminal elimination phase for each subject will be defined by visual inspection and generally will be the first point at which there is no systematic deviation from the log-linear decline in plasma concentrations. The $t_{½}$ will only be calculated when a reliable estimate for this parameter can be obtained comprising of at least 3 data points. If $t_{½}$ is estimated over a time window of less than 2 half-lives, the values will be flagged in the data listings. Any $t_{½}$ value excluded from summary statistics will be documented in the footnote of the summary table.
- A uniform weighting scheme will be used in the regression analysis of the terminal log-linear portion of the concentration-time curve.
- The parameters based on observed last quantifiable drug concentration ($C_{last}$) will be reported.

**Individual PK Parameter Rules**

- Only quantifiable concentrations will be used to calculate PK parameters with the exception of special handling of certain concentrations reported BQL. Plasma concentrations reported as BQL will be set to a value of zero when all of the following conditions are met:
  - The samples are from the initial dose period for a subject or from a subsequent dose period following a suitable washout period.
  - The time points occur before the first quantifiable concentration.

- All other BQL concentrations that do not meet the above criteria will be set to missing.
- In addition, where 2 or more consecutive concentrations are BQL toward the end of a profile, the profile will be deemed to have terminated; therefore, any further quantifiable concentrations will be set to missing for the calculation of the PK parameters unless it is considered to be a true characteristic of the profile of the drug.

**Individual Concentration versus Time Profiles**

- Individual concentrations will be plotted utilizing actual sampling times.
- The terminal point selections will be indicated on a semilogarithmic plot.

**Average Concentration versus Time Profiles**

- The average concentration profiles will be graphed using scheduled (nominal) sampling times.
- The average concentration profiles will be graphed using arithmetic average concentrations.
- Quantifiable concentrations will be used to calculate average concentrations, including predose concentrations.
- Concentrations at a sampling time exceeding the sampling time window specified in the protocol, or ±10%, will be excluded from the average concentration profiles.
- Concentrations excluded from the mean calculation will be documented in the final study report.
- A concentration average will be plotted for a given sampling time only if 2/3 of the individual data at the time point have quantifiable measurements that are within the sampling time window specified in the protocol or ±10%. An average concentration estimated with less than 2/3 but more than 3 data points may be displayed on the mean concentration plot if determined to be appropriate and will be documented within the final study report.

**Treatment of Outliers during Pharmacokinetic Analysis**

Application of this procedure to all PK analyses is not a requirement. Rather, this procedure provides justification for exclusion of data when scientifically appropriate. This procedure describes the methodology for identifying an individual value as an outlier for potential exclusion, but does not require that the value be excluded from analysis. The following methodology will not be used to exclude complete profiles from analysis.

<u>Data within an Individual Profile</u>
A value within an individual profile may be excluded from analysis if any of the following criteria are met:

- For PK profiles during multiple dosing, the concentration of the predose sample exceeds all measured concentrations for that individual in the subsequent postdose samples.
- For PK profiles during single dosing of nonendogenous compounds, the concentration in a predose sample is quantifiable.

- For any questionable datum that does not satisfy the above criteria, the profile will be evaluated and results reported with and without the suspected datum.

Data between Individual Profiles

1. If n<6, then the dataset is too small to conduct a reliable range test. Data will be analyzed with and without the atypical value, and both sets of results will be reported.
2. If n≥6, then an objective outlier test will be used to compare the atypical value to other values included in that calculation:
   a. Transform all values in the calculation to the logarithmic domain.
   b. Find the most extreme value from the arithmetic mean of the log transformed values and exclude that value from the dataset.
   c. Calculate the lower and upper bounds of the range defined by the arithmetic mean ±3*SD of the remaining log-transformed values.
   d. If the extreme value is within the range of arithmetic mean ±3*SD, then it is not an outlier and will be retained in the dataset.
   e. If the extreme value is outside the range of arithmetic mean ±3*SD, then it is an outlier and will be excluded from analysis.

If the remaining dataset contains another atypical datum suspected to be an outlier and n≥6 following the exclusion, then repeat step 2 above. This evaluation may be repeated as many times as necessary, excluding only 1 suspected outlier in each iteration, until all data remaining in the dataset fall within the range of arithmetic mean ±3*SD of the log-transformed values.

Reporting of Excluded Values

Individual values excluded as outliers will be documented in the final study report. Approval of the final study report will connote approval of the exclusion.

### *5.11.2. Pharmacokinetic Statistical Inference*

Log-transformed PK parameters listed in Section 5.11.1 with the exception of $T_{max}$ 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.

## 5.12. Pharmacodynamic Analyses

### *5.12.1. Pharmacodynamic Parameter Estimation*

Pharmacodynamic parameters will be calculated using NCA Drug Effect Model in validated software program (Phoenix WinNonlin Version 6.4.1 or later) and/or SAS. 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:

| Parameter | Definition |
|---|---|
| $AUEC_{above}$ | 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 |
| $AUEC_{0\text{-}1.5}$ | 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 (ie, change from baseline) concentrations of PG: $AUEC_{0\text{-}1.5}$, $BG_{max}$, and $T_{max}$.

Baseline PG concentrations will be concentrations from samples obtained immediately prior to glucagon dosing (ie, time point of 0.00 hour).

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

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.

### *5.12.2. Pharmacodynamic Statistical Inference*

The PD parameters ($AUEC_{0\text{-}1.5}$, $BG_{max}$) 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.

## 5.13. Pharmacokinetic/Pharmacodynamic Analyses

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

## 5.14. Exploratory Objectives Analyses

### *5.14.1. PK Profile of DPC*

Patients who receive glucagon treatment and have measurable DPC concentrations will be included in the DPC PK analysis. The NCA methods and similar rules for calculating glucagon PK parameters (Section 5.11.1) will be used for DPC PK parameters calculation.

Plasma concentrations of DPC will be used to determine the following PK parameters, when possible:

| Parameter | Units | Definition |
|---|---|---|
| AUC(0-$t_{last}$) | pg.h/mL | Area under the concentration vs time curve from time zero to time t, where t is the last time point with a measurable concentration |
| AUC(0-∞) | pg.h/mL | Area under the concentration versus time curve from zero to infinity |
| %AUC($t_{last}$-∞) | % | Percentage of AUC(0-∞) extrapolated |
| $C_{max}$ | pg/mL | Maximum observed drug concentration |
| $t_{max}$ | H | Time of maximum observed drug concentration |
| $t_{1/2}$ | H | Half-life associated with the terminal rate constant (λz) in noncompartmental analysis |
| CL/F | L/h | Apparent total body clearance of drug calculated after extravascular administration |
| $V_Z$/F | L | Apparent volume of distribution during the terminal phase after extravascular administration |
| $V_{SS}$/F | L | Apparent volume of distribution at steady state after extravascular administration |

An alternative AUC measure, such as AUC to a common time point, may be calculated if AUC(0-∞) cannot be reliably calculated.

### *5.14.2. Symptoms of Hypoglycemia*

Specified in Section 5.9.2.

### *5.14.3. Clarke Hypoglycemia Awareness*

Specified in Section 5.4.

## 5.15. Interim Analyses

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary, the Lilly clinical pharmacologist/clinical research physician, investigator, or designee

will consult with the appropriate medical director or designee to determine if it is necessary to amend the protocol.

A primary outcome database lock will be conducted after last treatment discharge from Clinical Research Unit (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 following the end of study safety follow-up visit.

# 6. Unblinding Plan

Study IGBI is an open-label study. Treatment assignment will be unblinded to the study team.

# 7. 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.

# 8. Appendices

# Appendix 1. Definitions of Nasal/Respiratory/Anosmia AEs

| MedDRA Preferred Term Code | MedDRA Preferred Term | MedDRA System Organ Class |
|---|---|---|
| 10001315 | Administration site reaction | General disorders and administration site conditions |
| 10069773 | Administration related reaction | Injury, poisoning and procedural complications |
| 10049153 | Allergic sinusitis | Respiratory, thoracic and mediastinal disorders |
| 10002653 | Anosmia | Nervous system disorders |
| 10071399 | Chronic eosinophilic rhinosinusitis | Respiratory, thoracic and mediastinal disorders |
| 10071380 | Chronic hyperplastic eosinophilic sinusitis | Respiratory, thoracic and mediastinal disorders |
| 10010588 | Congenital perforated nasal septum | Congenital, familial and genetic disorders |
| 10011224 | Cough | Respiratory, thoracic and mediastinal disorders |
| 10013789 | Dry throat | Respiratory, thoracic and mediastinal disorders |
| 10076417 | Empty nose syndrome | Injury, poisoning and procedural complications |
| 10068957 | Eosinophilic rhinitis | Respiratory, thoracic and mediastinal disorders |
| 10015090 | Epistaxis | Respiratory, thoracic and mediastinal disorders |
| 10020039 | Hiccups | Respiratory, thoracic and mediastinal disorders |
| 10050515 | Hyposmia | Nervous system disorders |
| 10049419 | Increased upper airway secretion | Respiratory, thoracic and mediastinal disorders |
| 10067068 | Intranasal hypoaesthesia | Respiratory, thoracic and mediastinal disorders |
| 10051660 | Intranasal paraesthesia | Respiratory, thoracic and mediastinal disorders |
| 10072926 | Maxillary sinus pseudocyst | Respiratory, thoracic and mediastinal disorders |
| 10075834 | Nasal adhesions | Respiratory, thoracic and mediastinal disorders |
| 10062771 | Nasal cavity mass | Respiratory, thoracic and mediastinal disorders |
| 10074617 | Nasal cavity toxicity | Respiratory, thoracic and mediastinal disorders |
| 10028735 | Nasal congestion | Respiratory, thoracic and mediastinal disorders |
| 10076524 | Nasal crusting | Respiratory, thoracic and mediastinal disorders |
| 10051712 | Nasal cyst | Respiratory, thoracic and mediastinal disorders |
| 10052437 | Nasal discomfort | Respiratory, thoracic and mediastinal disorders |
| 10062209 | Nasal disorder | Respiratory, thoracic and mediastinal disorders |
| 10028740 | Nasal dryness | Respiratory, thoracic and mediastinal disorders |

| MedDRA Preferred Term Code | MedDRA Preferred Term | MedDRA System Organ Class |
|---|---|---|
| 10028741 | Nasal inflammation | Respiratory, thoracic and mediastinal disorders |
| 10051208 | Nasal mucosa atrophy | Respiratory, thoracic and mediastinal disorders |
| 10057537 | Nasal mucosal discolouration | Respiratory, thoracic and mediastinal disorders |
| 10061305 | Nasal mucosal disorder | Respiratory, thoracic and mediastinal disorders |
| 10076585 | Nasal mucosal erosion | Respiratory, thoracic and mediastinal disorders |
| 10057358 | Nasal mucosal hypertrophy | Respiratory, thoracic and mediastinal disorders |
| 10065546 | Nasal mucosal ulcer | Respiratory, thoracic and mediastinal disorders |
| 10028747 | Nasal necrosis | Respiratory, thoracic and mediastinal disorders |
| 10051181 | Nasal odour | Respiratory, thoracic and mediastinal disorders |
| 10028750 | Nasal oedema | Respiratory, thoracic and mediastinal disorders |
| 10028756 | Nasal polyps | Respiratory, thoracic and mediastinal disorders |
| 10076406 | Nasal pruritus | Respiratory, thoracic and mediastinal disorders |
| 10028762 | Nasal septum deviation | Respiratory, thoracic and mediastinal disorders |
| 10028763 | Nasal septum disorder | Respiratory, thoracic and mediastinal disorders |
| 10075027 | Nasal septum haematoma | Respiratory, thoracic and mediastinal disorders |
| 10028765 | Nasal septum perforation | Respiratory, thoracic and mediastinal disorders |
| 10028766 | Nasal septum ulceration | Respiratory, thoracic and mediastinal disorders |
| 10052354 | Nasal turbinate abnormality | Respiratory, thoracic and mediastinal disorders |
| 10028779 | Nasal turbinate hypertrophy | Respiratory, thoracic and mediastinal disorders |
| 10028780 | Nasal ulcer | Respiratory, thoracic and mediastinal disorders |
| 10076553 | Nasal varices | Respiratory, thoracic and mediastinal disorders |
| 10065120 | Oroantral fistula | Gastrointestinal disorders |
| 10068319 | Oropharyngeal pain | Respiratory, thoracic and mediastinal disorders |
| 10062321 | Paranasal cyst | Respiratory, thoracic and mediastinal disorders |
| 10074401 | Paranasal sinus aplasia | Congenital, familial and genetic disorders |
| | Paranasal sinus discomfort | Respiratory, thoracic and mediastinal disorders |
| 10069702 | Paranasal sinus haematoma | Respiratory, thoracic and mediastinal disorders |
| 10057392 | Paranasal sinus hypersecretion | Respiratory, thoracic and mediastinal disorders |
| 10067998 | Paranasal sinus mucosal hypertrophy | Respiratory, thoracic and mediastinal disorders |
| 10072591 | Paranasal sinus necrosis | Respiratory, thoracic and mediastinal disorders |
| 10034018 | Parosmia | Nervous system disorders |

| MedDRA Preferred Term Code | MedDRA Preferred Term | MedDRA System Organ Class |
|---|---|---|
| 10064037 | Rhinalgia | Respiratory, thoracic and mediastinal disorders |
| 10039085 | Rhinitis allergic | Respiratory, thoracic and mediastinal disorders |
| 10039088 | Rhinitis atrophic | Respiratory, thoracic and mediastinal disorders |
| 10059235 | Rhinitis hypertrophic | Respiratory, thoracic and mediastinal disorders |
| 10039094 | Rhinitis perennial | Respiratory, thoracic and mediastinal disorders |
| 10039096 | Rhinitis ulcerative | Respiratory, thoracic and mediastinal disorders |
| 10067770 | Rhinolithiasis | Respiratory, thoracic and mediastinal disorders |
| 10039101 | Rhinorrhoea | Respiratory, thoracic and mediastinal disorders |
| 10048908 | Seasonal allergy | Immune system disorders |
| 10075540 | Silent sinus syndrome | Respiratory, thoracic and mediastinal disorders |
| 10040740 | Sinus barotrauma | Injury, poisoning and procedural complications |
| 10040742 | Sinus congestion | Respiratory, thoracic and mediastinal disorders |
| 10062244 | Sinus disorder | Respiratory, thoracic and mediastinal disorders |
| 10040747 | Sinus headache | Nervous system disorders |
| 10040748 | Sinus perforation | Respiratory, thoracic and mediastinal disorders |
| 10040749 | Sinus polyp | Respiratory, thoracic and mediastinal disorders |
| 10040750 | Sinus polyp degeneration | Respiratory, thoracic and mediastinal disorders |
| 10064770 | Sinusitis noninfective | Respiratory, thoracic and mediastinal disorders |
| 10041232 | Sneezing | Respiratory, thoracic and mediastinal disorders |
| 10043521 | Throat irritation | Respiratory, thoracic and mediastinal disorders |
| 10070488 | Upper-airway cough syndrome | Respiratory, thoracic and mediastinal disorders |
| 10047145 | Vasomotor rhinitis | Respiratory, thoracic and mediastinal disorders |

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities.

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