I8R-JE-IGBJ Statistical Analysis Plan

A Phase 3 Study of Nasal Glucagon (LY900018) Compared to Intramuscular Glucagon for Treatment of Insulin-induced Hypoglycemia in Japanese Patients with Diabetes Mellitus

NCT03421379

Approval Date: 02-Feb-2018

# STATISTICAL ANALYSIS PLAN

**A Phase 3 Study of Nasal Glucagon (LY900018) Compared to Intramuscular Glucagon for Treatment of Insulin-induced Hypoglycemia in Japanese Patients with Diabetes Mellitus**

Statistical Analysis Plan Status: Final
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Clinical Phase I

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## 1. TABLE OF CONTENTS

## 2. ABBREVIATIONS

Abbreviations pertain to the Statistical Analysis Plan (SAP) only (not the tables, figures and listings [TFLs]).

| | |
|---|---|
| AE | Adverse event |
| AES | All Entered Set Population |
| ALP | Alkaline phosphatase |
| ALT | Alanine aminotransferase |
| ARS | All Randomized Set Population |
| AUC | Area under the concentration versus time curve |
| AUEC | Area under the effect concentration-time curve |
| AUC(0-4) | Area under the concentration versus time curve from time zero to 4 hours post-dose |
| AUC(0-$t_{last}$) | Area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration |
| AUC(0-∞) | Area under the concentration versus time curve from time zero to infinity |
| %AUC($t_{last}$-∞) | percentage of AUC(0-∞) extrapolated |
| $BG_{max}$ | Maximal plasma glucose concentration |
| BQL | Below the lower limit of quantitation |
| $C_{last}$ | Last measureable drug concentration |
| CL/F | Apparent total body clearance of drug calculated after extra-vascular administration |
| CI | Confidence interval |
| $C_{max}$ | Maximum observed drug concentration |
| CRF | Case Report Form |
| CRP | Clinical research physician |
| CRU | Clinical Research Unit |
| CSR | Clinical Study Report |
| CV | Coefficient of variation |
| EAS | Efficacy Analysis Set Population |
| EC | Early Clinical |
| ECG | Electrocardiogram |

| | |
|---|---|
| e.g. | For example (Latin: *exempli gratia*) |
| FAS | Full Analysis Set Population |
| ICH | International Council on Harmonisation |
| IM | Intramuscular |
| IN | Intranasal |
| IMG | Intramuscular glucagon |
| IV | Intravenous |
| KM | Kaplan-Meier |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MMRM | Mixed model with repeated measures |
| NG | Nasal glucagon |
| NIM | Non-inferiority margin |
| PD | Pharmacodynamic |
| PK | Pharmacokinetic |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| SD | Standard deviation |
| TBL | Total bilirubin |
| TFLs | Tables, Figures, and Listings |
| T1DM | Type 1 diabetes mellitus |
| T2DM | Type 2 diabetes mellitus |
| $t_{1/2}$ | Half-life associated with the terminal rate constant ($\lambda_z$) in non-compartmental analysis |
| $t_{max}$ | Time of maximum observed drug concentration |
| $T_{max}$ | Time to maximum concentration |
| ULN | Upper limit of normal |
| $V_z/F$ | Apparent volume of distribution during the terminal phase after extra-vascular administration |
| $V_{ss}/F$ | Apparent volume of distribution at steady state after extra-vascular administration |
| WHO | World Health Organization |

# 3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 26 October 2017 and protocol amendment (a) (final version dated 05 December 2017).

This SAP describes the planned analysis of the safety, tolerability and pharmacokinetic (PK) and pharmacodynamic (PD) data from this study. A detailed description of the planned TFLs to be presented in the clinical study report (CSR) is provided in the accompanying TFL shell document.

The intent of this document is to provide guidance for the statistical and PK analyses of data. In general, the analyses are based on information from the protocol, unless they have been modified by agreement between Eli Lilly and Company and Covance Early Clinical (EC) Biometrics. A limited amount of information concerning this study (e.g., objectives, study design) is given to help the reader's interpretation. This SAP must be signed off prior to first subject administration for this study. When the SAP and TFL shells are agreed upon and finalized, they will serve as the template for this study's CSR.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the CSR. Any substantial deviations from this SAP will be agreed upon between Eli Lilly and Company and Covance EC Biometrics and identified in the CSR. Any minor deviations from the TFLs may not be documented in the CSR.

This SAP is written with consideration of the recommendations outlined in the International Council on Harmonisation (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials[1] and the ICH E3 Guideline entitled Guidance for Industry: Structure and Content of Clinical Study Reports[2].

# 4. STUDY OBJECTIVES

## 4.1 Primary

The primary objective is:

- To demonstrate that 3 mg LY900018 is non-inferior to 1 mg intramuscular glucagon (IMG) for the proportion of patients achieving treatment success from insulin-induced hypoglycaemia using a non-inferiority margin of 10%.

## 4.2 Secondary

The secondary objectives are:

- To compare the safety and tolerability of 3 mg LY900018 with 1 mg IMG
- To characterize the PK profile of 3 mg LY900018 compared to 1 mg IMG
- To characterize the PD profile of 3 mg LY900018 compared to 1 mg IMG

### 4.3 Exploratory Objectives

The exploratory objectives are:

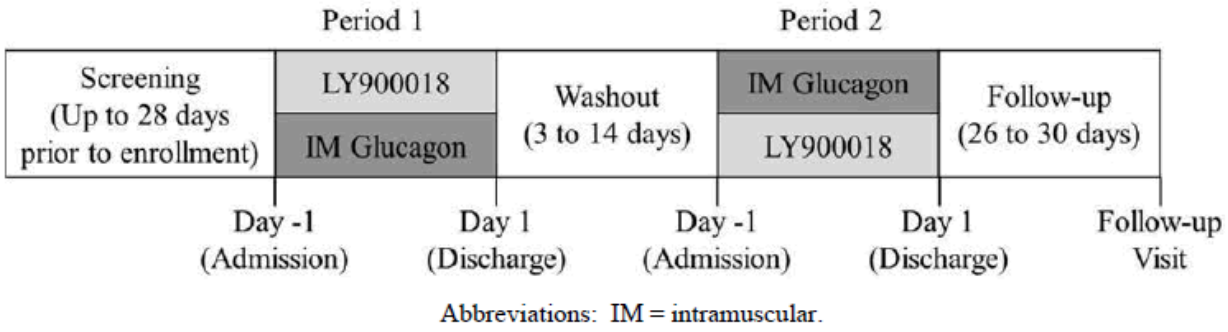
- To explore the formation of anti-glucagon antibodies to glucagon
- To evaluate the recovery from clinical symptoms of hypoglycemia

## 5. STUDY DESIGN

This is a Phase 3, multicenter, randomized, open-label, active comparator, single-dose, 2-period, 2-treatment, crossover study in Japanese patients with Type 1 diabetes mellitus (T1DM) and Type 2 diabetes mellitus (T2DM). The study consists of a screening period; treatment period 1 (Period 1); washout period; treatment period 2 (Period 2); follow-up period. Figure 1 illustrates the study design. Prior to the study drug administration on Period 1 Day 1, patients will be randomly assigned to a treatment sequence (either LY900018 in Period 1 and IMG in Period 2, or vice versa).

Safety data will be reviewed after the first 6 patients (regardless of type of diabetes) are administered LY900018 in Period 2, and the remaining patients will be dosed after confirmation of the safety. The investigator and Lilly clinical research physician (CRP) or scientist will review available safety data, including adverse events (AEs), serious adverse events (SAEs), vital signs, electrocardiograms (ECGs), and safety laboratory tests, from these patients after they complete Period 2 Day 1. If no clinically significant safety findings for treatment or study procedure are noted, the remaining patients will be dosed.

In each treatment period, patients will undergo a procedure to induce hypoglycemia using intravenous (IV) insulin infusion and serial blood sampling will be conducted to monitor bedside plasma glucose (PG) for safety. The insulin infusion will be stopped once the PG level reaches <60 mg/dL and approximately 5 minutes later patients will be administered either 3 mg LY900018 or 1 mg IMG (GlucaGen). Serial blood sampling will be performed for glucagon (for PK) and PG (for PD) concentration measurements immediately before and up to 4 hours following the administration of glucagon. In each period, patients will remain in the Clinical Research Unit (CRU) for at least 6 hours after glucagon administration. All patients will receive a carbohydrate-rich meal prior to discharge. Patients may stay longer as needed, at the discretion of the investigator. Study governance considerations are described in detail in Appendix 3 of the protocol.




Abbreviations: IM = intramuscular.

**Figure 1. Illustration of study design**

## 6. TREATMENTS

The following is a list of the study treatment abbreviations that will be used in the TFLs.

| Study Treatment Name | Treatment order in TFL |
|---|---|
| 3 mg LY900018 glucagon IN | 1 |
| 1 mg GlucaGen glucagon IM | 2 |

IM = intramuscular; IN = intranasal

## 7. SAMPLE SIZE JUSTIFICATION

Seventy five patients may be enrolled in order to have at least 66 patients (at least 30 patients with T1DM and T2DM, respectively) complete the study. For purposes of this study, a completer is defined as a patient who completes both periods with evaluable primary outcome. If patients discontinue from the study before completion of both periods with evaluable primary outcome for any reason, the patient may be replaced to ensure 66 patients complete the study. The replacement patients will be assigned the same treatment sequence as the patients to be replaced and will complete that treatment sequence in its entirety. Replacement should not occur beyond 75 patients enrolled, if it is expected to have at least 66 patients complete the study.

Assuming a non-inferiority margin (NIM) of 10%, a 98% treatment success rate for both treatment groups, and a within-patient correlation of zero, 66 completers will provide at least 90% power to show non-inferiority between LY900018 and IMG in treatment success from insulin-induced hypoglycemia with one-sided alpha level of 0.025 based on the Chi-square test.

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

# 8. DEFINITION OF ANALYSIS POPULATIONS

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.

All protocol deviations that occur during the study will be considered for their severity/impact and will be taken into consideration when subjects are assigned to analysis populations.

# 9. STATISTICAL METHODOLOGY

## 9.1 General

Data listings will be provided for all data that is databased. Summary statistics and statistical analysis will only be presented for data where detailed in this SAP. For continuous data, summary statistics will include the arithmetic mean, arithmetic standard deviation (SD), median, minimum (and/or 1st quartile), maximum (and/or 3rd quartile) and N; for log-normal data (e.g. the PK parameters: area under the concentration versus time curve [AUCs] and the maximum observed drug concentration [$C_{max}$]) the geometric mean and geometric coefficient of variation (CV%) will also be presented. For categorical data, frequency count and percentages will be presented. Data listings will be provided for all subjects up to the point of withdrawal, with any subjects excluded from the relevant population highlighted. Summary statistics and statistical analyses will generally only be performed for subjects included in the relevant analysis population. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

Mean change from baseline is the mean of all individual subjects' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual subject's baseline value from the value at the timepoint. The individual subject's change from baseline values will be used to calculate the mean change from baseline using a SAS procedure such as Proc Univariate.

As the study includes T1DM and T2DM patients, the following parameters will be reported by diabetes type and the results will be included in (but not limited to) the summary report:

- Subject Disposition
- Demographics
- Proportion of Treatment Success
- PK parameters
- PD parameters
- Plasma Glucose values over time
- Adverse events
- Hypoglycemia

Data analysis will be performed using SAS® Version 9.4 or greater.

## 9.2 Demographics and Subject Disposition

Subject disposition will be listed. The demographic variables age, sex, race, ethnicity, country of enrolment, site ID, body weight, height, body mass index, duration of diabetes (years), baseline HbA1c value (%), baseline Clarke Hypoglycemia Awareness status (%) and baseline substance use (alcohol) will be summarized and listed. A frequency of previous diabetic therapy will also be produced and listed.

Summary outputs and statistical analyses will be produced by diabetes type.

## 9.3 Efficacy Assessment

### 9.3.1 Primary Efficacy Analysis

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 nasal glucagon (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.

Primary efficacy analysis will only include patients who complete both treatment visits with evaluable primary outcome. The analysis will be performed separately for each diabetes type. 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.

### 9.3.2 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 diabetic type, and compared using the same method as for the primary efficacy analysis specified above.

- ARS
- Patients in EAS population with nadir glucose <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.

## 9.4 Pharmacokinetic Assessment

### 9.4.1 Pharmacokinetic Analysis

Pharmacokinetic parameter estimates will be determined using non-compartmental procedures in validated software program (Phoenix WinNonlin Version 6.4 or later).

Plasma concentrations of glucagon will be used to determine the following PK parameters following LY900018 and GlucaGen administration, when possible:

| Parameter | Units | Definition |
|---|---|---|
| AUC(0-4) | pmol.h/L | area under the concentration versus time curve from time zero to 4 hours post-dose |
| AUC(0-$t_{last}$) | pmol.h/L | area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration |
| AUC(0-∞) | pmol.h/L | area under the concentration versus time curve from time zero to infinity |
| %AUC($t_{last}$-∞) | % | percentage of AUC(0-∞) extrapolated |
| $C_{max}$ | pmol/L | 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 non-compartmental analysis |
| CL/F | L/h | apparent total body clearance of drug calculated after extra-vascular administration |
| $V_z$/F | L | apparent volume of distribution during the terminal phase after extra-vascular administration |
| $V_{ss}$/F | L | apparent volume of distribution at steady state after extra-vascular administration |

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).

Additional PK parameters may be calculated, as appropriate. The software and version used for the final analyses will be specified in the clinical study report. 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 non-bolus pre-dose 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 one 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 three consecutive plasma concentrations above the lower limit of quantification (LLOQ), 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. Half-life 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 $C_{last}$ 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 below the lower limit of quantitation (BQL). Plasma concentrations reported as BQL will be set to a value of zero when all of the following conditions are met:
    - The compound is non-endogenous.
    - The samples are from the initial dose period for a subject or from a subsequent dose period following a suitable wash-out 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.
- Also, where two or more consecutive concentrations are BQL towards the end of a profile, the profile will be deemed to have terminated and 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 vs. Time Profiles**

- Individual concentrations will be plotted utilizing actual sampling times.
- The terminal point selections will be indicated on a semi-logarithmic plot.
- Baseline corrected concentration plots will also be presented

**Average Concentration vs. 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.

- 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 pharmacokinetic 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.

Data within an Individual Profile

A value within an individual profile may be excluded from analysis if any of the following criteria are met:

- 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 $n\geq6$, 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 $n \geq 6$ following the exclusion, then repeat step 2 above. This evaluation may be repeated as many times as necessary, excluding only one 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 report. Approval of the final report will connote approval of the exclusion.

### 9.4.2 Pharmacokinetic Statistical Methodology

The PK parameters will be statistically analysed, listed and summarized by diabetic type and overall.

Log-transformed PK parameters (such as $C_{max}$ and AUC) 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% confidence intervals (CIs).

Example SAS code:

```
proc mixed data=test covtest alpha=0.1;
   by parameter;
   class treatment patient period sequence;
   model log_pk = treatment period sequence / ddfm=kr alpha=0.1;
   random patient;
   lsmeans treatment / pdiff cl alpha=0.1;
   ods output lsmeans=lsmeans;
   ods output diffs=diffs;
  ods output covparms=cov;
run;
```

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.

## 9.5 Pharmacodynamic Assessment

### 9.5.1 Pharmacodynamic Analysis

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 |
| $AUEC_{0-1.5}$ | 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: $AUEC_{0-1.5}$, $BG_{max}$, 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.

### 9.5.2 Pharmacodynamic Statistical Methodology

The PD parameters will be statistically analysed, listed and summarized by diabetic type and overall.

The PD parameters (such as $BG_{max}$ and area under the effect concentration-time curve [AUEC]) 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. Similar SAS code will be used as in the PK analysis.

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.

### 9.5.3 Plasma Glucose Values Statistical Methodology

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, time points and their interaction 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 modelled 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 treatment*time /solution
ddfm=kr;
repeated time(visit)/subject=patient type=un;
lsmeans treatment*time/cl diff om;
run;
```

As an exploratory analysis and if there is sufficient data, a subgroup analysis of plasma glucose over time by concomitant oral diabetes drug will be performed (with particular focus on Sulfonylureas). The purpose of the analysis is to assess whether the concomitant oral diabetes

drug triggers rebound hypoglycaemia or not. For each concomitant oral diabetes drug, the data will be summarized by treatment and diabetes type.

## 9.6 Safety and Tolerability Assessments

### 9.6.1 Adverse events

Where changes in severity are recorded in the Case Report Form (CRF), each separate severity of the AE will be reported in the listings, only the most severe will be used in the summary tables. A pre-existing condition is defined as an AE that starts before the subject has provided written informed consent and is ongoing at consent. A non-treatment emergent AE is defined as an AE which starts after informed consent but prior to dosing. A treatment-emergent AE is defined as an AE which occurs postdose or which is present prior to dosing and becomes more severe postdose.

All AEs will be listed. Treatment-emergent AEs will be summarized by diabetic type, treatment, severity and relationship to the study drug. The frequency (the number of AEs, the number of subjects experiencing an AE and the percentage of subjects experiencing an AE) of treatment-emergent AEs will be summarized by treatment, Medical Dictionary for Regulatory Activities (MedDRA) version 20.1 system organ class and preferred term. The summary and frequency AE tables will be presented for all causalities and those considered related to the study drug. Any serious AEs will be tabulated.

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.

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

### 9.6.2 Concomitant medication

Concomitant medication will be coded using the World Health Organization (WHO) drug dictionary (Version March 2017). Concomitant medication will be listed. A listing of rescue therapy will also be provided for the ARS.

### 9.6.3 Clinical laboratory parameters

All clinical chemistry and hematology data will be summarized by parameter and treatment, and listed. Urinalysis data will be listed. Additionally clinical chemistry, hematology and urinalysis data outside the reference ranges will be listed.

Values for any clinical chemistry, hematology and urinalysis values outside the reference ranges will be flagged on the individual subject data listings.

### 9.6.4 Vital signs

Vital signs data will be summarized by treatment together with changes from baseline, where baseline is defined as Day 1 predose of each period. Figures of mean vital signs and mean changes from baseline profiles by treatment will be presented by treatment.

Furthermore, values for individual subjects will be listed.

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

All timepoints will be presented on summary tables and figures.

### 9.6.5 Electrocardiogram (ECG)

Triplicate ECG data will be obtained directly from the 12-lead ECG traces. These data include the PR, QT, QTcB intervals, QRS duration and heart rate, where QTcB is the QT interval corrected using Bazett's formula. In addition, the QT interval corrected using Fridericia's formula (QTcF) will be calculated as follows:

$$QTcF = \frac{QT}{\sqrt[3]{\left(60/HR\right)}}$$

The mean of the triplicate data will be used for subsequent calculations. The ECG data will be summarized by treatment together with changes from baseline, where baseline is defined as Day 1 predose of each period. Figures of mean ECG data and mean changes from baseline will be presented by treatment. The frequency of subjects with a maximum increase from baseline in QTcF interval will be summarized for each treatment according to the following categories: >30 ms and >60 ms. In addition, the frequency of subjects with QTcF postdose values, according to the following categories: >450 ms, >480 ms and >500 ms, will be summarized by treatment.

All timepoints will be presented on summary tables and figures.

A plasma LY900018 concentration-QT analysis will be performed to assess the changes from baseline (Day 1 predose of each period) QTcF interval relative to plasma LY900018. BLQ

LY900018 concentration data will be imputed to 50% of the LLOQ for the purposes of the analysis. The analysis will be performed by plotting change from baseline QTcF against LY900018 concentrations, including all post dosing timepoints. The plot will be produced separately for each treatment and diabetes type.

A mixed effects analysis model will be performed on the change from baseline QTcF values and will include LY900018 concentration as a covariate and subject as a random effect. The results of the model and associated 90% CI will be fitted on the plot and the p-value for the slope reported.

### 9.6.6 Injection-site assessment

Injection-site assessment data (erythema, induration, categorical pain, pruritus and edema) will be listed and summarized in frequency tables.

### 9.6.7 Hepatic Safety

If a study patient experiences elevated alanine aminotransferase (ALT) ≥3× upper limit of normal (ULN), alkaline phosphatase (ALP) ≥2× ULN, or elevated total bilirubin (TBL) ≥2× ULN, liver tests (Protocol Appendix 4) should be repeated to confirm the abnormality and to determine if it is increasing or decreasing.

The subjects' liver disease history and associated person liver disease history data will be listed. Any concomitant medication of acetaminophen/paracetamol will be listed. Results from any hepatic monitoring procedures, such as a magnetic resonance elastography scan, and a biopsy assessment will be listed, if performed.

Hepatic risk factor assessment data will be listed. Liver related signs and symptoms data will be summarized by treatment and listed. Alcohol and recreational drug use data will also be listed.

All hepatic chemistry, hematology, coagulation, and serology data will be listed. Values outside the reference ranges will be flagged on the individual subject data listings.

### 9.6.8 Nasal Inspection

Nasal inspections will be performed for safety monitoring purposes only and will not be presented.

### 9.6.9 Hypoglycemic episodes

Hypoglycemic event data will be listed and summarized by hypoglycemia category, treatment and diabetes type as defined in the Protocol (Section 9.5.5.1).

Severe hypoglycemic events will be reported separately as SAEs.

### 9.6.10 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 the plasma glucose analysis.

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.

### 9.6.11 Edinburgh Hypoglycemia Scale: Experimental Hypoglycemia

The Edinburgh Hypoglycemia Scale data will be analyzed in the same way as the nasal questionnaire data for the ARS.

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

### 9.6.12 Immunogenicity

The frequency and percentage of patients with pre-existing (baseline) ADA, ADA at any time point after baseline, and patients with TE ADA to glucagon will be tabulated if available.

Treatment-emergent ADA are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution of the assay, if no ADA were detected at baseline; or those with a 4-fold (2 dilutions) increase in titer compared to baseline, if ADA were detected at baseline. For patients with TE ADA, the distribution of maximum titers will be tabulated if available. The frequency of neutralizing antibodies will also be tabulated if available.

If there is antibody presence, the relationship between the presence (or absence) of antibodies and clinical parameters (AEs, efficacy measures, and so on) will be assessed. Likewise, the relationship between the presence of antibodies and the PK/PD parameters to LY900018 will be assessed.

### 9.6.13 Other assessments

All other safety assessments not detailed in this section will be listed but not summarized or statistically analyzed.

### 9.6.14 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

## 10. INTERIM ANALYSES

Access to the safety data, including AEs, SAEs, vital signs, ECGs, and safety laboratory tests, is scheduled to occur after the first 6 patients complete Period 2. The purpose of the safety reviews is to ensure that the study procedures and treatment are safe enough to proceed with the remaining patients. The investigator and the Lilly sponsor team will make the determination to proceed with randomization of the remaining patients based upon their review of the safety and tolerability data.

A primary database lock will be conducted after last patient discharge from the CRU. The aim of the primary database lock is to enable data analysis to assess the primary/secondary objectives, and may include assessment of exploratory objectives. The primary database lock will include all study data, except for immunogenicity data, up to the last patient discharge from the CRU.

If patients need additional follow-up for TE ADA, an additional database lock may be conducted to develop the CSR. The database lock may contain all patients' data up to the follow-up visit, except for immunogenicity data. The final database lock is planned after all patients complete the follow-up period and additional follow-up for TE ADA (if needed).

## 11. CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

There were no changes from the protocol specified statistical analyses.

## 12. REFERENCES

1. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.

2. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.

3. 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.

# 13. DATA PRESENTATION

## 13.1 Derived Parameters

Individual derived parameters (e.g. PK parameters) and appropriate summary statistics will be reported to three significant figures. Observed concentration data, e.g. $C_{max}$, should be reported as received. Observed time data, e.g. $t_{max}$, should be reported as received. N and percentage values should be reported as whole numbers. Median values should be treated as an observed parameter and reported to the same number of decimal places as minimum and maximum values.

## 13.2 Missing Data

Missing data will not be displayed in listings.

## 13.3 Insufficient Data for Presentation

Some of the TFLs may not have sufficient numbers of subjects or data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the centre of the table, such as, "No serious adverse events occurred for this study."

# 14. APPENDIX

## 14.1 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 |
| 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 |
| 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 |