Statistical Analysis Plan: I8R-MC-IGBO (Final Version 1.0)

An Open-Label, Multi-Center, Single-Dose Study to Assess the Safety, Tolerability, Pharmacodynamics, and Pharmacokinetics of Nasal Glucagon in Pediatric Patients With Type 1 Diabetes Aged 1 to <4 Years

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STATISTICAL ANALYSIS PLAN

An Open-Label, Multi-Center, Single-Dose Study to Assess the Safety, Tolerability, Pharmacodynamics, and Pharmacokinetics of Nasal Glucagon in Pediatric Patients with Type 1 Diabetes Aged 1 to <4 years

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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
AUC	Area under the concentration versus time curve
BG	Blood glucose
BG_{max}	Maximum observed blood glucose
CGM	Continuous glucose monitoring
C_{max}	Maximum observed drug concentration
CRF	Case Report Form
CSR	Clinical Study Report
ICH	International Conference on Harmonisation
MedDRA	Medical Dictionary for Regulatory Activities
NG	Nasal glucagon
PD	Pharmacodynamic
PG	Plasma Glucose
PK	Pharmacokinetic
SAP	Statistical Analysis Plan
SD	Standard deviation
SOP	Standard Operating Procedure
T1D	Type 1 diabetes
TBG_{max}	Time of maximum observed blood glucose
TEAE	Treatment-emergent adverse event
TFLs	Tables, Figures, and Listings
WHO	World Health Organization

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 19 March 2021).

This SAP describes the planned analysis of the safety, tolerability, 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 with Eli Lilly and Company. A limited amount of information concerning this study (e.g., objectives, study design) is given to help the reader's interpretation. For open-label studies, this SAP must be signed off prior to first patient visit 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 with Eli Lilly and Company 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 Conference 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 Objective

The primary objective is to assess the safety and tolerability of a single dose of nasal glucagon (NG) 3 mg in children aged 1 to <4 years with type 1 diabetes (T1D).

4.2 Secondary Objectives

The secondary objectives are:

- To assess the PD of a single dose of 3 mg NG in children aged 1 to <4 years with T1D
- To assess the PK of a single dose of 3 mg NG in children aged 1 to <4 years with T1D.

4.3 Exploratory Objective

The exploratory objective is to assess the efficacy of a single dose of 3 mg NG in children aged 1 to <4 years with T1D.

5. STUDY ENDPOINTS

5.1 Primary Endpoint

The primary endpoint is the incidence of treatment-emergent adverse events (TEAEs).

5.2 Secondary Endpoints

The secondary endpoints are:

- Change from baseline of maximum blood (plasma) glucose
- The following plasma glucose (PG) parameters:
  - maximum observed blood glucose (BG_{max})
  - area under the concentration-time curve (AUC)
  - time of maximum observed blood glucose (TBG_{max})
- Model-estimated population PK parameters

5.3 Exploratory Endpoint

The exploratory endpoint is the proportion of patients achieving treatment success defined as an increase of PG ≥20 mg/dL (1.11 mmol/L) from baseline within 30 min postdose

6. STUDY DESIGN

Study IGBO is a Phase 1, open-label, multi-center study with a primary objective of assessing safety and tolerability of a single 3 mg dose of NG in pediatric patients aged 1 to <4 years with T1D.

Patients will attend study visits, including screening, in the company of 1 or more parents or legal guardians, and in accordance with local healthcare facility practice.

The study comprises a single cohort, with each patient receiving a single dose of 3 mg NG. At least 9 patients with an approximate maximum of 20 may be enrolled so that 6 evaluable patients complete the study.

For the purposes of this study, a patient completes the study after the conclusion of the second follow-up telephone call on Day 9 (±3).

A study schema can be seen in Figure 1.

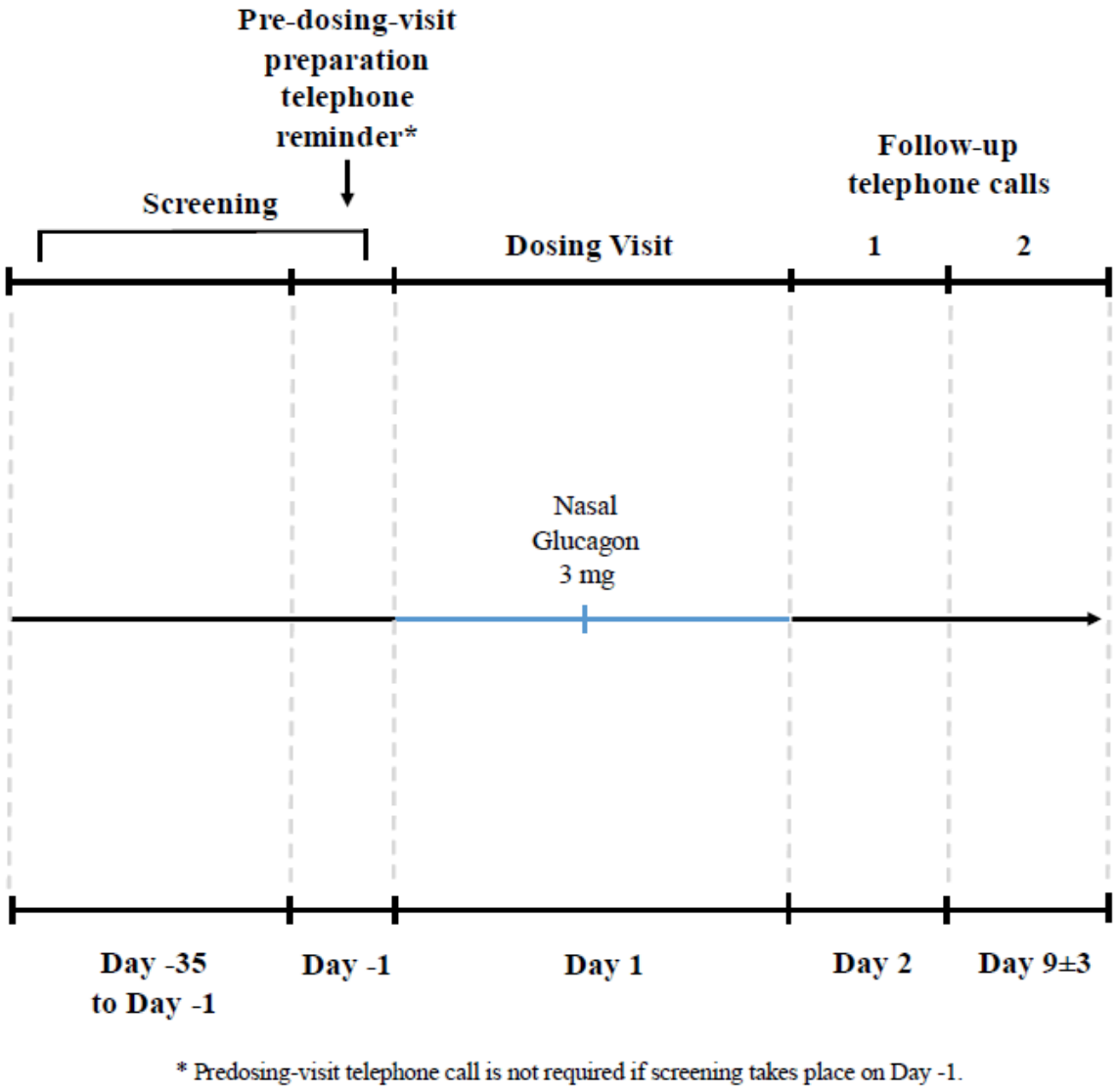

Figure 1: Study Schema for IGBO

7. TREATMENT

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

Study Treatment Name	Treatment order in TFL
3 mg nasal glucagon	1

8. SAMPLE SIZE JUSTIFICATION

At least 9 patients with an approximate maximum of 20 may be enrolled so that 6 evaluable patients complete the study.

The sample size is customary for Phase 1 studies evaluating safety, tolerability, PD, and PK, and is not powered on the basis of statistical hypothesis testing.

The sample size assumes a 33% dropout rate.

Patients who are enrolled but not administered treatment may be replaced to ensure that enough patients may complete the study. Patients that do not have at least 1 PD postbaseline measure may also be replaced.

9. DEFINITION OF ANALYSIS POPULATIONS

The "Efficacy" population will consist of all patients who received at least one dose of NG, and have baseline and at least 1 postbaseline PG measure within 30 minutes after dose administration. For rescued patients, data after the rescue would be excluded from the analysis.

The "Safety" population will consist of all patients who received at least one dose of NG, whether or not they complete all protocol requirements.

The "Pharmacokinetic" population will consist of all patients who received at least one dose of NG and have evaluable PK data. For rescued patients, data after the rescue would be excluded from the analysis.

The "Pharmacodynamic" population will consist of all patients who received at least one dose of NG and have evaluable PD data. For rescued patients, data after the rescue would be excluded from the analysis.

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

10. STATISTICAL METHODOLOGY

10.1 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, min, max and n; for log-normal data (e.g. the PK parameters: AUCs and maximum observed drug concentration [C_{max}]) the geometric mean and geometric coefficient of variation will also be presented. For categorical data, frequency count and percentages will be presented. Data listings will be provided for all patients up to the point of withdrawal, with any patients excluded from the relevant population highlighted. Summary statistics and statistical analyses will generally only be performed for patients 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 patients' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual patient's baseline value from the value at the timepoint. The individual patient's change from baseline

values will be used to calculate the mean change from baseline using a SAS procedure such as Proc Univariate.

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

10.2 Demographics and Patient Disposition

Patient disposition will be listed. The demographic variables age, sex, race, ethnicity, country of enrolment, site ID, body weight, height, screening glycated hemoglobin, and duration of T1D will be summarized and listed. All other demographic variables will be listed only.

10.3 Pharmacokinetic Assessment

10.3.1 Pharmacokinetic Analysis

Glucagon concentration data after NG administration will be analyzed using a population PK approach via nonlinear mixed-effects modeling with the NONMEM software due to limited number of PK samples collected in this study. Model-estimated population PK parameters will be reported. Additional population PK analysis may be performed by combining data from this study with data from other NG studies.

Evaluable PK outcome is defined as having at least 1 postbaseline measure.

Pharmacokinetic concentrations of plasma glucagon by timepoint will be summarized by descriptive statistics and listed. Mean and individual concentration over time plots will also be produced.

Derivation of the PK parameters will be done by Eli Lilly and Company. Eli Lilly and Company will also be responsible for all PK parameter TFLs.

10.3.2 Pharmacokinetic Statistical Methodology

No inferential statistical analyses are planned

10.4 Pharmacodynamic Assessment

10.4.1 Pharmacodynamic Analysis

Due to limited number of PG measurements (5 time points) from the glucose analyzer, a limited number of PD parameters will be estimated. The primary PD parameter is change from baseline of BG_{max}. In addition, other PG parameters, AUC and TBG_{max}, may also be estimated. Actual sampling times will be used for all calculations.

PG AUC will be calculated using the trapezoidal rule. If the first (predose) or last (90 minutes) timepoints are missing, an AUC will not be derived.

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

Other PD parameters of PG may be calculated if required.

Derivation of the PD parameters will be done by Labcorp. Labcorp will also be responsible for all PD TFLs.

10.4.2 Pharmacodynamic Statistical Methodology

The PG PD parameters, as well as the change from baseline for BG_{max}, where baseline is defined as Day 1 Predose, will be summarized and listed.

Individual concentrations of PG, together with changes from baseline (predose), will also be summarized by timepoint using descriptive statistics and listed. Mean, mean changes from baseline, and individual concentration over time plots will be produced.

No inferential statistical analyses are planned

10.5 Efficacy Assessment

Plasma glucose levels will be measured prior to the administration of glucagon, as well as at various time points after administration and will be used to assess the efficacy of NG.

Efficacy of NG will be assessed in terms of "treatment success", in which treatment success is defined as an increase of PG≥20 mg/dL (1.11 mmol/L) from baseline within 30 minutes postdose. The proportion of patients achieving treatment success will be calculated, summarized, and listed. Rescued patients, data after the rescue would be excluded from the analysis, see Section 10.6.2 for further information on rescued patients.

The time to treatment success will be summarized and listed.

A Kaplan-Meier curve will be constructed for the time-to-achieve treatment success.

10.6 Safety and Tolerability Assessments

10.6.1 Adverse events

Where changes in severity are recorded in the Case Report Form (CRF), each separate severity of the adverse event (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 patient has provided written informed consent and is ongoing at consent. A non-TEAE is defined as an AE which starts after informed consent but prior to dosing. A TEAE 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 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 will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 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 by the investigator. Any serious AEs will be listed.

Nasal/respiratory and anosmia AEs (see Appendix 2) will be summarized.

Discontinuations due to AEs will be listed.

10.6.2 Glucose Monitoring and Hypoglycemia

At baseline, during, and after dosing, blood glucose (BG) levels will be measured at the bedside for safety monitoring using an approved point-of-care glucometer. The bedside glucose measurements will be performed for safety monitoring only and will not be databased.

Severe hypoglycemica in children events will be listed and summarized. Severe hypoglycemia in children is defined[3] as follows:

- **Severe hypoglycaemia in children:** because children have limited ability to detect and/or self-treat hypoglycemia, severe hypoglycemia in children is an event in which children have severe cognitive impairment, and require external assistance, are semiconscious or unconscious, or in coma with or without convulsions, and requires another person to actively administer carbohydrates, glucagon, or take other corrective action

The determination of a hypoglycemic event as an episode of severe hypoglycemia, as defined above, will be made by the investigator based on the medical need of the patient to have had hypoglycemia-induced cognitive dysfunction and is not predicated on the report of a patient simply having received assistance.

Further information on patients that experience a hypoglycemic event will be collected using a hypoglycaemia event CRF form, this data will be listed and summarized.

A glucose infusion alternative glucagon therapy, or oral carbohydrate may be used for rescue treatment if a patient's BG level is declining rapidly, or their symptoms become consistent with progression to clinically significant or severe hypoglycemia. A separate listing will be presented for the use of rescue medication used for severe hypoglycaemia.

The following steps will be taken based on the patient's baseline BG level:

- If BG < 70 mg/dL, the investigator will determine whether to proceed with dosing or to use rescue treatment.
- If BG < 54 mg/dL (clinically significant hypoglycemia [Level 2]), site will halt study drug procedure and use rescue therapy to raise BG level. Such patients' visits may be rescheduled for a subsequent visit

10.6.3 Concomitant medication

Concomitant medication will be coded using the WHO drug dictionary (Version March 2021). Concomitant medication will be listed.

10.6.4 Vital signs

Vital signs data will be listed for individual patients.

Changes from baseline (Day 1 predose) will be calculated for vital signs.

10.6.5 Hepatic Monitoring

If a patient experiences elevated laboratory parameters, as detailed in Section 10.4 of the protocol, additional tests will be performed to confirm the abnormality. Additional safety data may be collected if required, as defined in the protocol. Where applicable, the following will be presented.

The patients' liver disease history and associated person liver disease history data will be listed. Any concomitant medications that have potential for hepatotoxicity, including acetaminophen will be listed. Results from any hepatic monitoring procedures, such as a magnetic resonance elastography scan, and biopsy assessments 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 patient data listings.

10.6.6 Nasal Inspection

AEs found during Nasal inspection will be summarized and listed by pre-dose and 90 min post-dose respectively. TEAEs found during nasal inspection will also be summarized and listed.

10.6.7 Other assessments

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

10.6.8 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

11. INTERIM ANALYSES

After 3 patients have completed the study, patient enrollment will be paused and an interim analysis will be conducted, evaluating the data relating to the primary and secondary objectives

After this interim analysis, if there are no clinically significant safety concerns, study enrollment will resume.

12. CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

There were no changes from the protocol specified statistical analyses.

13. 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. Jones TW. Defining relevant hypoglycemia measures in children and adolescents with type 1 diabetes. Pediatr Diabetes. 2018;19(3):354-355. doi:10.1111/pedi.12600

14. DATA PRESENTATION

14.1 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. BG_{max}, should be reported as received. Observed time data, e.g. TBG_{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.

14.2 Missing Data

Missing data will not be displayed in listings.

14.3 Insufficient Data for Presentation

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

15. APPENDICES

Appendix 1: Document History

Status and Version	Date of Change	Summary/Reason for Changes
Final Version 1.0	NA	NA; the first version.

NA = not applicable

Appendix 2: 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

MedDRA Preferred Term Code	MedDRA Preferred Term	MedDRA System Organ Class
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

MedDRA Preferred Term Code	MedDRA Preferred Term	MedDRA System Organ Class
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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