Protocol: I8R-MC-IGBO(a)

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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Title Page

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Protocol Number: I8R-MC-IGBO

Amendment Number: a

Compound: Nasal glucagon

Study Phase: 1

Short Title: A Single-Dose Study to Assess Nasal Glucagon in Pediatric Patients with Type 1 Diabetes aged 1 to <4 years

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

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Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Original Protocol	*19-Mar-2021*

Amendment [a]

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

To revise the existing inclusion criterion for hemoglobin A1c (HbA1c) to align with the observed distribution at study sites so that the study can consider a wider patient population as potential study participants without impacting study participants' safety and study data integrity. Additional clarifications were made as outlined in the table below.

Section # and Name	Description of Change	Brief Rationale
Section 1.1. Synopsis and Section 3. Objectives and Endpoints	In the first secondary endpoint, added predose BG in parenthesis, deleted plasma from parenthesis, and replaced plasma with blood.	To provide additional information and clarification
Section 1.3. Schedule of Activities (SoA)	Included SC injection of insulin as an option for MDI users	Added for consistency with Section 4.1.4.
Section 3. Objectives and Endpoints	In the exploratory endpoint, added predose BG in parenthesis and replaced plasma with blood	To provide additional information and clarification
Section 4.1.4. Day 1: Predose	Included SC injection of insulin as an option for MDI users	Added for flexibility in treatment options for MDI users
Section 4.1.5. Day 1: Dosing	NG will be administered within 5 minutes of baseline BG measurement changed as predose BG measurement	Correction to state that NG administration to be done within 5 minutes of predose BG rather than from baseline BG

Section # and Name	Description of Change	Brief Rationale
Section 5.1. Inclusion Criteria	In inclusion criterion 4, increased the HbA1c level from ≤9.0 to ≤9.5%	To revise the existing inclusion criterion for HbA1c to align with the observed distribution at study sites so that the study can consider a wider patient population as potential study participants without impacting study participants' safety and study data integrity.

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1. Protocol Summary

1.1. Synopsis

Protocol Title: 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

Short Title: A Single-Dose Study to Assess Nasal Glucagon in Pediatric Patients with Type 1 Diabetes aged 1 to <4 years

Rationale: The primary aim of Study I8R-MC-IGBO (IGBO) is to assess the safety and tolerability of a 3 mg dose of NG (commercial drug product) in pediatric participants aged 1 to <4 years with T1D in an inpatient clinical research facility.

Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the safety and tolerability of a single dose of NG 3 mg in children aged 1 to <4 years with T1D	Incidence of treatment-emergent adverse events.
Secondary	
To assess the PD of a single dose of NG 3 mg in children aged 1 to <4 years with T1D	Change from baseline (predose BG) of maximum blood glucose. Other blood glucose parameters: • BGmax • AUC • TBGmax
To assess the PK of a single dose of NG 3 mg in children aged 1 to <4 years with T1D	Model-estimated population PK parameters

Overall 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 participants aged 1 to <4 years with T1D.

Participants 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 participant receiving a single dose of 3 mg NG.

Disclosure Statement: This is a single-arm, open-label pediatric study.

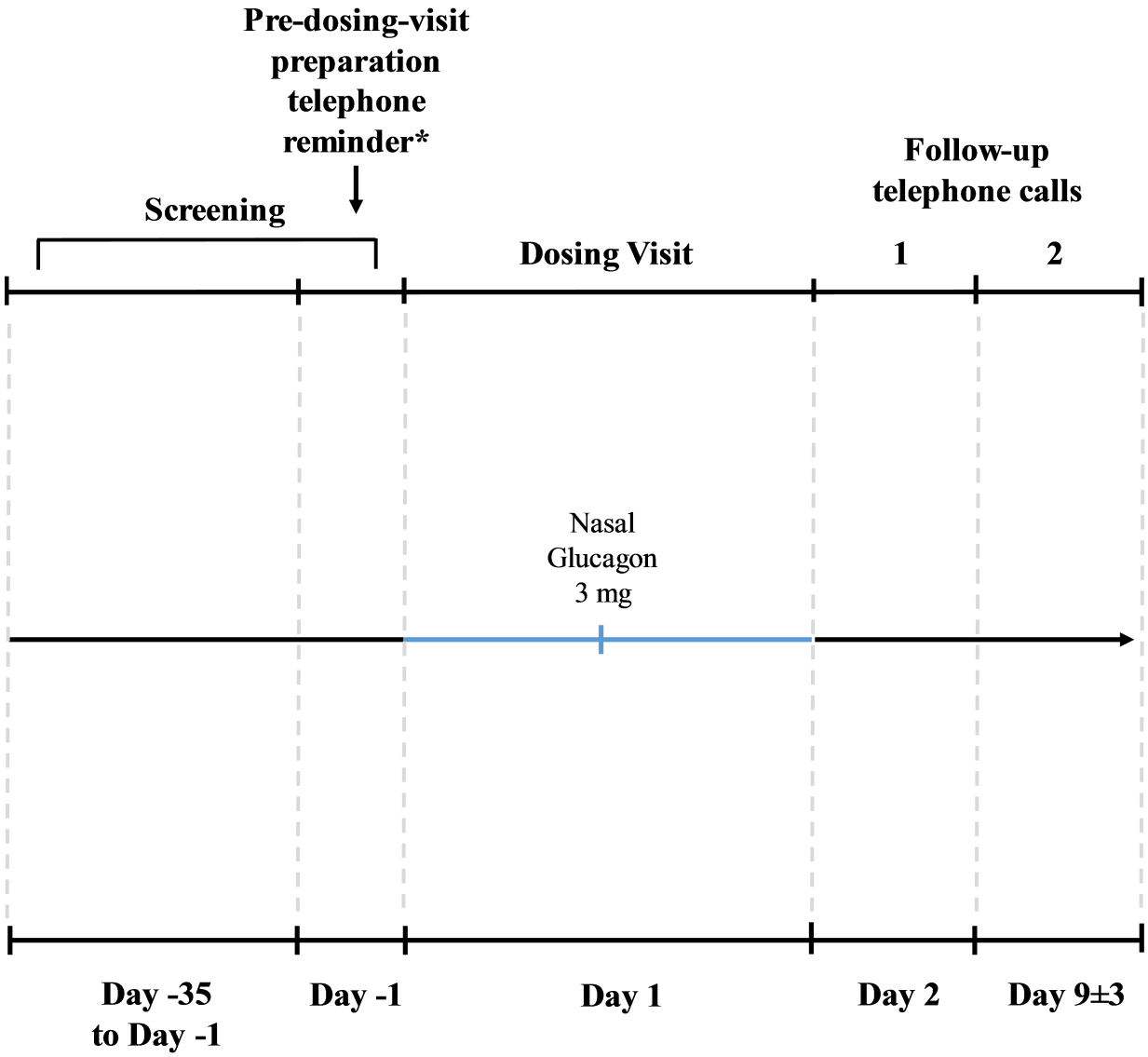
Number of Participants: At least 9 participants with an approximate maximum of 20 may be enrolled so that 6 evaluable participants complete the study.

Intervention Groups and Duration:

Each participant is expected to participate in the study for up to approximately 7 weeks, from screening through follow-up.

Data Monitoring Committee: No

1.2. Schema



* Predosing-visit telephone call is not required if screening takes place on Day -1.

1.3. Schedule of Activities (SoA)

Procedure	Screening Visit	Predosing-visit preparation reminder (telephone)	Dosing Visit	Follow-up (telephone)	Second Follow-up (telephone)	Comments
	Day -35 to Day -1	Day -1	Day 1	Day 2	Day 9±3	
Informed consent	X					Provided by parent/legal guardian. Should be obtained before any study-related procedures are performed. May be obtained during a separate informed consent visit to the site.
Demographics	X					Full date of birth (day, month, year), sex, and ethnicity will be collected, if consistent with local regulations.
Medical history	X					
Education on specifics of dosing visit	X	X				Discussion between site staff and parent/legal guardian on the target blood glucose range and information for dosing visit. See Section 5.1.
Eligibility	X					See Section 5.
Height	X					
Weight	X		X			On Day 1, body weight will be measured predose.

Procedure	Screening Visit	Predosing-visit preparation reminder (telephone)	Dosing Visit	Follow-up (telephone)	Second Follow-up (telephone)	Comments
	Day -35 to Day -1	Day -1	Day 1	Day 2	Day 9±3	
Vital signs (body temperature, blood pressure, pulse rate)	X		X			See Section 8.2.2. On Day 1, vital signs should be measured predose and 45 min postdose. Time points may be added on Day 1 if warranted, at the discretion of the investigator.
Clinical laboratory tests	X					See Appendix 2 (Section 10.2) for details. Participants do not need to fast for laboratory samples. Laboratory tests will be processed at a local laboratory.
Age-appropriate physical examination	X					
Adverse event assessment	X		X	X	X	AE assessment at telephone follow-up requires conversation with parent/legal guardian about any AEs experienced by the participant.
Concomitant medication assessment	X		X	X	X	On Day 1, concomitant medication assessment should be conducted predose.
Pre-admission contact from site to parent/legal guardian			X			Contact parent/legal guardian to check BG levels are suitable for study procedures. Before participant and parent/legal guardian leave home, within approximately 2 hours before dosing.

Procedure	Screening Visit	Predosing-visit preparation reminder (telephone)	Dosing Visit	Follow-up (telephone)	Second Follow-up (telephone)	Comments
	Day -35 to Day -1	Day -1	Day 1	Day 2	Day 9±3	
Admission to site			X			It is recommended that participants have a natural overnight fast if possible, assuming morning dosing. At a minimum, participants should have no food or beverage intake other than water within 3 hours before dosing.
Verification of hypoglycemia history since screening			Predose			See Section 5.2.1.
Allocation of participant enrollment number			X			Once eligibility is confirmed and participant is ready for dosing.
Baseline glucose measurement			X			See Section 4.1.4.

Procedure	Screening Visit	Predosing-visit preparation reminder (telephone)	Dosing Visit	Follow-up (telephone)	Second Follow-up (telephone)	Comments
	Day -35 to Day -1	Day -1	Day 1	Day 2	Day 9±3	
If necessary to achieve target glucose level, adjust basal rate or administer a small bolus via insulin pump; or for MDI, infuse a small correction bolus of insulin diluted in normal saline through IV or by SC injection			Predose			At PI's discretion. See Section 4.1.4.
Nasal inspection	X		Predose, 90 min			Visual nasal inspections. On Day 1, the predose inspection, administration of NG, and postdose inspection (90 min) should all be done by the same person.
Return insulin pump basal rate to pre-study settings			Postdose			For pump users only. If basal rate was adjusted to achieve target blood glucose on the study day, the basal rate must be returned to participant's normal rate prior to discharge.

Procedure	Screening Visit	Predosing-visit preparation reminder (telephone)	Dosing Visit	Follow-up (telephone)	Second Follow-up (telephone)	Comments
	Day -35 to Day -1	Day -1	Day 1	Day 2	Day 9±3	
NG administration			X			Nasal glucagon will be administered only if a participant's baseline glucose level is within target range. See Section 4.1.4.
Sample collection for measurement of plasma glucagon (pharmacokinetics)			10, 30, 60 min			Time points are relative to NG administration.
Bedside glucose safety measurements			X			Measured using a point-of-care blood glucose testing device: either CGM, if applicable, via IV cannulation, or using an approved BG meter. See Section 8.2.4.1. Blood glucose readings will be taken every 5 to 10 min for the first 30 min after dosing, and then every 20 min up to 90 min. Additional measurements may be taken at investigator's discretion. When a planned bedside safety sample coincides with a PD sample, the PD sample may be used for bedside safety assessment.
Sample collection for measurement of plasma glucose (pharmacodynamics)			P, 10, 30, 60, 90 min			Measured with study-approved rapid glucose analyzer (Section 8.6). Timings are relative to NG administration.

Procedure	Screening Visit	Predosing-visit preparation reminder (telephone)	Dosing Visit	Follow-up (telephone)	Second Follow-up (telephone)	Comments
	Day -35 to Day -1	Day -1	Day 1	Day 2	Day 9±3	
Meal			X			Following completion of all study procedures, the participant will be provided a meal including carbohydrates, and the investigator will ensure the participant's plasma glucose is stable prior to discharge.
Discharge from site			X			Participants may be discharged after 4 hours postdose safety monitoring is complete. If required, a participant may remain in clinic for further observation, at the discretion of the investigator.

Abbreviations: AE = adverse event; BG = blood glucose; CGM = continuous glucose monitoring; IV = intravenous; MDI = multiple daily injection; NG = nasal glucagon; P = predose; PD = pharmacodynamics; PI = principal investigator; SC = subcutaneous.

2. Introduction

2.1. Study Rationale

The primary aim of Study I8R-MC-IGBO (IGBO) is to assess the safety and tolerability of a 3 mg dose of NG (commercial drug product) in pediatric participants aged 1 to <4 years with T1D in an inpatient clinical research facility.

2.2. Background

NG (also known as Baqsimi; LY900018) is a drug-device combination product consisting of a single-use nasal dosing device that delivers glucagon powder for absorption through the nasal mucosa. NG provides the same single-chain, 29-amino-acid polypeptide as human glucagon and the recombinant DNA-produced glucagon used in currently marketed glucagon emergency kits (Glucagon Emergency Kit [Eli Lilly and Company] and GlucaGen® HypoKit [Novo Nordisk A/S]). It is approved for use as a treatment for severe hypoglycemia in adults and pediatric patients with diabetes mellitus aged ≥4 years. It has not been studied in children aged <4 years.

The principal action of NG is to increase BG concentration through the action of glucagon in the liver.

The formulation contains 3 mg of glucagon, as well as beta-cyclodextrin (a compendial excipient that works as a filler/bulking agent/absorption enhancer), and dodecylphosphocholine (a novel excipient that works as an absorption enhancer/surfactant).

The same drug-device combination product that is approved for use in patients aged 4 years and older will be used in this study in pediatric participants aged 1 to <4 years.

2.3. Benefit/Risk Assessment

NG is administered by inserting the tip of the device into the nostril and pushing the plunger, which actuates the device to deliver the NG powder into the nasal mucosa. The tip of the device is of similar size with similar drug product volume to other currently marketed devices approved and used for pediatric intranasal spray administration in patients aged <4 years including Nasacort® (Children's Nasacort USPI, 2015), Narcan® Nasal Spray (Narcan Nasal Spray PIL, 2020), Sterimar™ (Sterimar Package Insert, 2019), and Calpol® Saline Nasal Spray (Calpol PIL, 2010).

Due to the insertion of the device into the nostril, there is some risk of local nasal discomfort, irritation, and possibly trauma. To minimize these risks, NG will be administered by healthcare professionals who have been trained on the use of the device and to limit the device insertion depth based on the size and distensibility of the external nare for the individual participant.

NG has been approved as safe and effective for the treatment of severe hypoglycemia in patients with diabetes aged ≥4 years. As part of the clinical development program it was tested in the pediatric population aged between 4 and <17 years in 1 clinical trial and 1 actual-use study. A description and outcomes of these studies are provided in Section 2.3.1.2. The results of this current study will provide information that may contribute toward the approval for the treatment

of severe hypoglycemia with NG in pediatric patients with diabetes aged 1 to <4 years, allowing an additional glucagon formulation treatment option for this population.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of NG may be found in the IB and Baqsimi Package Insert (2019).

2.3.1. Risk Assessment

Risks related to IGBO study procedures, and how they will be mitigated, are described in Section 2.3.1.1. A summary of glucagon safety is in Section 2.3.1.2.

2.3.1.1. Risks and Safety Considerations in Study IGBO

Baseline glucose target level

Prior to dosing, each participant's baseline glucose level should be within a target range of 70 to 140 mg/dL for NG to be administered. This range is based on premeal target glucose values recommended by the ISPAD (DiMeglio et al. 2018) of 70 to 130 mg/dL, with a +10 mg/dL allowance for the upper limit.

Refer to the Study Operations Manual for detailed instructions.

This study avoids the induction of hypoglycemia (defined as BG <70 mg/dL; Abraham et al. 2018), to ensure there is no more than a minimal increase in medical risk for the pediatric population.

The investigator may consider rescue medication to pre-empt or treat clinically significant or severe hypoglycemia if indicated by the baseline BG level.

If a participant's baseline BG level is

- <70 mg/dL, the investigator will determine whether to proceed with dosing or to use rescue treatment (Section 8.3.6).
- <54 mg/dL (clinically significant hypoglycemia [Level 2]), site will halt study drug procedure and use rescue therapy to raise BG level.

If rescue therapy is administered, the participant should remain at the site until stable based on investigator observation and clinical judgment. The visit may be rescheduled for a subsequent day at the investigator's discretion, and according to the Manual of Operations.

If the participant does not return to the site for a subsequent visit in which required study procedures are completed, the participant must be discontinued from the study.

Blood sampling

The number and volume of blood samples for each participant have been minimized to reduce the potential risks and lower the burden of study procedures for pediatric participants.

Glucose safety monitoring

Though hypoglycemia is not induced in this study, there is the potential for a participant to experience hypoglycemia. Participants' BG level will be monitored at the bedside during and after NG administration, and the investigator may consider use of glucose or glucagon to

pre-empt or treat severe hypoglycemia. See Section 8.2.4.1 for details on this bedside glucose safety monitoring, and Section 8.3.6 for detail of the rescue procedure.

Needle punctures

There is a small risk associated with needle punctures for blood sampling, which in some instances may cause bleeding, bruising, discomfort, infections, and/or pain. Use of age-appropriate equipment will be used to minimize risks associated with these procedures. In addition, use of local anesthetics (e.g., Emla® cream) consistent with local prescribing information is permitted during the study visit to ease discomfort associated with venipuncture. To minimize venipuncture and adhere to blood volume restrictions, laboratory tests have been minimized.

2.3.1.2. Historical Summary of Glucagon Safety

Injectable glucagon

There has been extensive patient exposure to recombinant glucagon with injectable administration for approximately 20 years. Side effects noted are generally mild and include nausea and vomiting. Generalized allergic reactions, including urticaria, respiratory distress, and hypotension, have been reported in patients who received glucagon by injection. It is contraindicated in patients with known hypersensitivity to it, or in patients with known pheochromocytoma or insulinoma.

Inclusion and exclusion criteria in this study were designed to mitigate these risks.

Nasal glucagon

NG was approved in the US and Europe in 2019 for the emergency treatment of severe hypoglycemia in patients with diabetes aged 4 years and above.

The NG development program demonstrated that NG is safe in both adult and pediatric patients aged ≥4 years. The program included 10 studies in adults (healthy subjects and patients with diabetes) and 2 studies in pediatric patients with T1D. This program demonstrated that NG has a comparable safety profile to recombinant glucagon, with the exception of additional effects related to its nasal route of administration. The most commonly reported AEs in the NG development program were vomiting, headache, nausea, and “upper respiratory tract irritation” (rhinorrhea, nasal discomfort, nasal congestion, cough, and epistaxis), watery eyes, redness of eyes, sneezing, and itchy nose, throat, and eyes.

The NG formulation in Study IGBO is the commercial drug product, which was also used in adult Studies I8R-MC-IGBI and I8R-MC-IGBJ. Study IGBI was a multi-center, randomized, open-label, 2-treatment, 2-period, single-dose, crossover study in adult patients with T1D that compared glucagon administered through either the nasal route (NG) or the intra-muscular route (GlucaGen) in the recovery from hypoglycemia induced by a controlled insulin infusion. Study IGBJ was a Phase 3, multi-center, randomized, open-label, active comparator, single-dose, 2-period, 2-treatment, crossover study of NG (LY900018) compared to intramuscular glucagon for treatment of insulin-induced hypoglycemia in adult Japanese patients with diabetes mellitus.

Summary of NG safety in pediatric patients

NG was assessed in pediatric patients in Studies I8R-MC-IGBB and I8R-MC-B001 (B001). In total in these studies, 58 patients aged 4 to <18 years received at least 1 dose of NG.

Study IGBB evaluated PK, PD, safety, and tolerability of NG 2 mg and 3 mg in pediatric patients aged 4 to <17 years with T1D. In this study, 36 patients with T1D received NG 3 mg, 23 received NG 2 mg, and 24 received weight-based intramuscular glucagon.

The following table summarizes adverse reactions that occurred in pediatric patients in Study IGBB at an incidence of ≥2%, following NG 3 mg administration.

Adverse Reaction	NG 3 mg n = 36 %
Vomiting	30.6
Headache	25.0
Nausea	16.7
Upper Respiratory Tract Irritation[a]	16.7

Abbreviations: n = number of patients; NG = nasal glucagon.

[a] Upper respiratory tract irritation: nasal discomfort, nasal congestion, sneezing.
Source: Baqsimi Package Insert, 2019.

Nasal and ocular symptoms were also solicited in Study IGBB through a patient questionnaire. A list of these symptoms and their incidence rates is included in the Baqsimi Package Insert (2019).

Study B001 is a real-world study that evaluated the effectiveness and ease-of-use of NG 3 mg in pediatric patients aged 4 to <18 years with T1D. In this study, 22 patients received at least 1 dose of NG 3 mg.

AEs solicited through the Hypoglycemia Episode Questionnaire and the Nasal Score Questionnaire were low to moderate in severity. The most common AEs were nasal discomfort (92.9%), watery eyes (85.7%), headache (71.4%), runny nose (64.3%), nasal congestion (50.0%), sneezing (50%), and redness of eyes (42.9%), with approximately 60% of events resolving within 1 hour.

Three patients who discontinued from Study B001 due to a clinical event reported severe nasal discomfort and 1 patient withdrew consent for reasons not related to a clinical event.

2.3.2. Benefit Assessment

There is no anticipated therapeutic benefit for the participants in Study IGBO.

Study IGBO is expected to help meet an unmet need by contributing to the development of an additional rescue therapy with alternate route of administration for the treatment of severe hypoglycemia in children aged 1 to <4 years.

2.3.3. Overall Benefit: Risk Conclusion

Considering the measures taken to minimize risk to participants of this study, the potential risks identified in association with NG are justified by the contribution of data that may inform further development and provide the benefit of an additional rescue therapy for severe hypoglycemia

that does not require dose adjustment and provides an alternate route of administration for the T1D pediatric population aged between 1 and <4 years.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the safety and tolerability of a single dose of NG 3 mg in children aged 1 to <4 years with T1D	Incidence of treatment-emergent adverse events
Secondary	
To assess the PD of a single dose of NG 3 mg in children aged 1 to <4 years with T1D	Change from baseline (predose BG) of maximum blood glucose. Other blood glucose parameters: • BGmax • AUC • TBGmax
To assess the PK of a single dose of NG 3 mg in children aged 1 to <4 years with T1D	Model-estimated population PK parameters
Exploratory	
To assess the efficacy of a single dose of NG 3 mg in children aged 1 to <4 years with T1D	The proportion of participants achieving treatment success defined as an increase of blood glucose ≥20 mg/dL (1.11 mmol/L) from baseline (predose BG) within 30 min postdose

Abbreviations: AUC = area under the concentration-time curve; BGmax = maximum observed blood glucose; NG = nasal glucagon; PD = pharmacodynamics; PK = pharmacokinetics; T1D = type 1 diabetes; TBGmax = time of maximum observed blood glucose.

4. Study Design

4.1. Overall 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 participants aged 1 to <4 years with T1D.

Participants 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. For simplicity, the term "parent/legal guardian" will be used in the singular throughout this protocol.

The study comprises a single cohort, with each participant receiving a single dose of 3 mg NG. At least 9 participants with an approximate maximum of 20 may be enrolled so that 6 evaluable participants complete the study. See Section 9.4 for definitions of evaluable participants.

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

Study governance considerations are described in detail in Appendix 1, Section 10.1.

Section 1.2 illustrates the study design.

4.1.1. Screening

The screening visit will take place as shown in the SoA.

In addition to screening tests, the screening visit will include an information session for the participant's parent/legal guardian on the target BG range for dosing day, including

- the target range for the participant's BG on dosing day
- how the parent/legal guardian can help achieve this target BG level, including
    - the recommendation that participants have a natural overnight fast if possible, assuming morning dosing. At a minimum, participants should have no food or beverage intake other than water within 3 hours before dosing
    - parent/legal guardian participation in a predosing-visit telephone reminder on Day -1 (if required – see Section 4.1.2), and responding to contact from site on the morning of dosing to verify that the BG level is likely to be in a range appropriate for the scheduled visit.

4.1.2. Predosing-Visit Telephone Reminder

On Day -1, site staff will telephone the participant's parent/legal guardian to give a reminder about the procedure for dosing day, including

- the recommendation that participants have a natural overnight fast if possible, assuming morning dosing. At a minimum, participants should have no food or beverage intake other than water within 3 hours before dosing,
- the target BG level, and

- that site staff will be in contact on the morning of dosing to determine whether the participant's BG level is likely to be in the required range for dosing.

Note that this postscreening call may be omitted if the screening visit was on Day -1.

4.1.3. Day 1: Call/Text on Morning of Dosing

On Day 1, before each participant is expected to leave their home to travel to the site, site staff will call or send a text message to the parent/legal guardian soliciting

- a measurement of the participant's BG level and
- the participant's physical status to participate and attend the visit.

The BG measurement can be taken either via the participant's own CGM device or using an appropriate glucometer, and will be used to determine whether the baseline BG level is likely to be within the target range at the time of dosing at the site.

Based on this information, the PI may decide to proceed or reschedule the visit (Section 4.1.8).

4.1.4. Day 1: Predose

For the dosing visit (Day 1), it is recommended that participants have a natural overnight fast if possible, assuming morning dosing. At a minimum, participants should have no food or beverage intake other than water within 3 hours before dosing.

At the study site, BG will be measured to determine if the participant's baseline BG level is within the target range of 70 to 140 mg/dL (Section 2.3.1.1), and confirm ability to proceed with dosing and other study procedures.

If BG is

- below the target range, rescue treatment may be considered (Section 8.3.6).
- above the target range, the investigator may choose to
    - in the case of pump users, increase the basal insulin rate of the participant's insulin pump, or initiate a small bolus dose, to achieve target BG
    - in the case of MDI users: administer a small correction bolus via SC injection of insulin or IV infusion of insulin diluted in normal saline to achieve target BG
    - wait and allow BG to decrease to target level if BG is already decreasing, or
    - reschedule the visit (Section 4.1.8).

If a bolus dose of insulin is administered via the pump, or insulin is administered to patients on MDI, the dose level will be based on PI discretion.

The basal rate or insulin infusion may be adjusted at the discretion of investigator during study procedures as necessary to protect participant safety.

For pump users only, if the investigator adjusts the pump basal rate setting, it may be returned to pre-study settings after 90 minutes postdose and all PK and PD samples have been collected, at the discretion of investigator. The basal rate setting must be returned to participant's usual setting prior to discharge. Additionally, site staff must confirm the basal settings with the parent/legal guardian before the participant is discharged.

4.1.5. Day 1: Dosing

NG will be administered within 5 minutes of predose BG measurement by site staff with the participant in a recumbent or semi-recumbent position.

The tip of the device is gently inserted in the nostril. At that point, the plunger of the device is pushed firmly until the green line is no longer showing, which indicates that the dose is complete. The drug is absorbed from the nasal cavity; thus the participant does not need to inhale after dosing.

If a participant sneezes immediately after administration, site staff should document this in the eCRF. All postdose assessments, including PK and PD sampling, would still occur in this case.

4.1.5.1. Suspected Administration Failure

If site staff are not able to successfully dose – e.g., due to device malfunction, or the child forcefully moving their head away – there will be a 30-minute period during which safety and PD blood sampling will proceed. At 30 minutes, if PD and safety sampling show that the participant's BG levels are in the target range (Section 2.3.1.1), a second dose may proceed, at the discretion of the PI and participant's parent/legal guardian.

4.1.6. Day 1: Postdose

After dosing, bedside glucose safety measurements will be taken with either the participant's own CGM device, or with an approved point-of-care glucometer using capillary blood samples, as described in Section 8.2.4.1.

Venous blood samples will be taken for PK measurements.

Following study procedures, participants will be given a meal including carbohydrates, and discharged. Discharge may be delayed if the investigator determines that further observation is needed.

4.1.7. Follow-up

Site staff will conduct 2 follow-up telephone calls with the parent/legal guardian to discuss any potential side effects or AEs:

- on Day 2
- on Day 9 (±3 days).

4.1.8. Rescheduling Visits

A participant's dosing visit may be rescheduled, up to a maximum of 2 times, if

- based on the Day 1 communication prior to the participant traveling to site (Section 4.1), the PI determines that the participant's BG level is unlikely to be within the target range in time for dosing, or
- a participant's baseline BG level, as measured on site prior to dosing, is outside the target range and may not be achieved within a time frame suitable for completion of all required visit procedures (Section 4.1.4), or

- a participant has an acute illness such as influenza, ear or respiratory infection, or other illness that in the opinion of the investigator would hinder completion of visit procedures.

Note that if the device malfunctions and no dose is delivered, rescheduling is not required and dosing may proceed with another device. See Section 4.1.5.1.

The dosing visit should be within 35 days of the screening visit. If this is not possible, additional time may be allowed between screening and Day 1 with documented approval from the sponsor.

The dosing day will always be designated as Day 1 and subsequent study days numbered accordingly.

In the event of rescheduled dosing visits, site staff may repeat as needed the postscreening communication prior to the participant traveling to site.

4.2. Scientific Rationale for Study Design

NG 3 mg has demonstrated similar safety and PD responses across all completed adult and pediatric studies (age range 4 to <17 years) in which injectable glucagon was used as an active comparator. Based on these data, Study IGBO was designed without an active comparator, to eliminate unnecessary procedures and minimizes distress and discomfort for study participants.

4.3. Justification for Dose

NG is approved for use in patients with diabetes aged 4 years and above, at a dose level of 3 mg. A single dose of 3 mg NG was supported by the safety, tolerability, efficacy, and PK data generated during the NG development program.

For pediatric patients with diabetes, the selection of a 3 mg dose was based on results from Study IGBB. In that study

- NG 3 mg was administered to all age groups (4 to <8, 8 to <12, and 12 to <17 years). In each group, NG 3 mg rapidly produced a maximal BG increase, similar to that of injectable glucagon doses (0.5 or 1 mg depending on the patient's weight);
- NG 2 mg and 3 mg were administered to the 2 younger age groups (4 to <8 and 8 to <12 years). NG 3 mg produced a slightly higher glucose response than NG 2 mg;
- NG 3 mg in pediatric patients showed similar tolerability and safety to NG 2 mg, and to weight-based injectable glucagon doses.

Although 3 mg NG in 1- to <4-year-old participants is expected to result in higher systemic glucagon concentrations than those observed with 3 mg NG in older pediatric patients, this transient high systemic exposure is expected to be safe. This expectation is based on published data with intravenous-administered glucagon in adults (Graf et al. 1999), which showed exposures that were multiples higher than the projected maximum exposure following NG administration in pediatric patients aged 1 to <4 years, with no safety concerns.

Additionally, this transient high glucagon concentration is expected to ensure that the maximum PD effect of BG excursion is produced, as desired for an emergency-use product.

4.4. End of Study Definition

The end of the study is the date of the second follow-up telephone call shown in the SoA (Section 1.3) for the last participant.

5. Study Population

Eligibility of participants for the study will be based on the results of screening medical history, physical examination, vital signs, and clinical laboratory tests.

The nature of any conditions present at the time of the physical examination and any preexisting conditions will be documented.

Screening may occur up to 35 days prior to enrollment. At the investigator's discretion, with documented approval from the sponsor, participants who have not attended a dosing visit within 35 days of screening may be subjected to an additional medical assessment and/or clinical measurements to reconfirm their eligibility. Laboratory tests previously collected for the screening visit may be used to reconfirm eligibility.

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

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply at screening:

Age

1. Are aged 1 to <4 years, at the time of the ICF being signed and throughout their participation in the study.

Type of participant and disease characteristics

2. have a diagnosis of T1D based on medical history for at least 6 months as previously demonstrated by either documented presence of autoimmune antibodies (glutamic acid decarboxylases; insulin-associated tyrosine phosphatase antibody; insulin autoantibody; islet cell antibody) as per medical records, or diagnosis by an endocrinologist (pediatric or adult), or a physician with expertise in treating pediatric patients with T1D
3. have been receiving insulin therapy via MDI, or continuous subcutaneous insulin infusion using a pump, and have been stable on the therapy and route of administration for at least 3 months prior to screening
4. have a hemoglobin A1c level of ≤9.5% at screening
5. have venous access sufficient to allow for blood sampling as per the protocol
6. are in good general health with no conditions that could influence the outcome of the trial, and in the judgment of the investigator are a good candidate for the study based on review of available medical history, physical examination, and clinical laboratory evaluations with no prior history of choanal atresia, nasal/pharyngeal blockage, or anomaly.

Availability and informed consent

7. participant and their parent/legal guardian are reliable and willing to be available for the duration of the study, and to follow study procedures

8. the participant's parent/legal guardian can provide written informed consent on behalf of the participant.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical conditions

9. have presence or history of hypersensitivity to glucagon or any related products; or severe hypersensitivity reactions, such as angioedema, to any medication
10. have presence or history of any of the disorders in the following list, that in the opinion of the investigator, could significantly alter the absorption, metabolism, or elimination of drugs; constitute a risk when taking the investigational product; or interfere with the interpretation of data:
    - cardiovascular,
    - respiratory,
    - hepatic,
    - renal,
    - gastrointestinal,
    - endocrine (other than T1D),
    - hematological, or
    - neurological disorders
    - suspected low glycogen stores due to chronic low carbohydrate intake or inadequate diet.
11. have a history of pheochromocytoma (i.e., adrenal gland tumor) or insulinoma
12. have a history of epilepsy or seizure disorder
13. have 1 or more congenital anomalies to the anatomy of the nose, or require changes to the anatomy of the nose (e.g., are eligible for nasal pharyngeal surgery)
14. have history or presence of laryngopharyngeal reflux
15. have an abnormal blood pressure and/or pulse rate as determined by the investigator
16. in the 3 months before screening, have had an episode of severe hypoglycemia, defined as a hypoglycemia event with severe cognitive impairment (including coma and convulsions) requiring assistance by another person to actively administer carbohydrates, glucagon, or take other corrective actions (Abraham et al. 2018)
17. have clinically significant multiple or severe drug allergies, or intolerance to topical corticosteroids, or severe posttreatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, or exfoliative dermatitis)
18. have a history of human immunodeficiency virus infection and/or positive human immunodeficiency virus antibodies
19. have a history of hepatitis C and/or positive hepatitis C antibody
20. have a history of hepatitis B and/or positive hepatitis B surface antigen

Prior/concomitant therapy

21. are regularly administered a systemic beta-blocker, indomethacin, warfarin, or drugs classified as anticholinergics, or corticosteroids; or regular use of other medications, pending discussion between the investigator and the study clinical pharmacologist or CRP
22. are using closed-loop insulin therapy, UNLESS such a device is set to 'open loop/manual' mode and the automated low glucose suspend or predictive low glucose suspend are disabled on the day of the dosing visit until all PK and PD samples have been collected.

Prior/concurrent clinical study experience

23. are currently enrolled in a clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study
24. have participated, within the past 30 days, in a clinical study involving an investigational product. If the previous investigational product has a long half-life, 5 half-lives or 30 days (whichever is longer) should have passed.

Other exclusions

25. are related to either a Lilly employee; an employee of a third-party organization involved in this study; or investigative site staff directly affiliated with this study
26. in the opinion of the investigator or sponsor, the participant or their parent/legal guardian is unsuitable for inclusion in the study.

5.2.1. Additional Exclusion Criteria Prior to Dosing Visit (Day 1)

27. have had an episode of severe hypoglycemia, or have had glucagon administered, during the period between the screening visit and the dosing visit. An episode of severe hypoglycemia is defined as a hypoglycemia event with severe cognitive impairment (including coma and convulsions) requiring assistance by another person to actively administer carbohydrates, glucagon, or take other corrective actions (Abraham et al. 2018).

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

It is recommended that participants have a natural overnight fast if possible, assuming morning dosing.

At a minimum, participants should have no food or beverage intake other than water within 3 hours before dosing.

5.4. Screen Failures

Screen failures are defined as participants whose parent/legal guardian consented for them to participate in the clinical study but who are not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) or were required to unexpectedly discontinue from the study during screening or lead-in period (e.g., due to enrollment pause related to the coronavirus disease-19 or other public health emergency) may be re-screened once, at the investigator and sponsor's discretion. In the case of rescreening, the participant's previous screening blood chemistry results may be used if they were taken within the previous 6 months.

Re-screened participants should be assigned a new participant number. Each time re-screening is performed, a new informed consent must be signed.

6. Study Intervention

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to/used by a study participant according to the study protocol.

6.1. Study Intervention Administered

Intervention Name	Nasal glucagon
Type	Drug-Device
Dose Formulation	Powder
Dosage Level(s)	3 mg glucagon
Route of Administration	Nasal
Use	Experimental
investigational medicinal product/noninvestigational medicinal product	investigational medicinal product
Sourcing	Provided centrally by the sponsor
Packaging and Labeling	Nasal glucagon will be provided in nasal delivery devices labeled as required per country requirement
Name(s) or Alias(es)	Baqsimi; LY900018

6.1.1. Administration Details

See Section 4.1.5 for an overview of NG administration. Further detail is in the NG Instructions for Use.

6.2. Preparation/Handling/Storage/Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Unused study materials will remain locked and securely stored until returned to the sponsor or destroyed, according to written instruction from the sponsor. Further guidance and information for the final disposition of unused study materials are provided in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

Not applicable as this is a single-arm study.

6.4. Study Intervention Compliance

Participants will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5. Concomitant Therapy

Participants on stable concomitant medications at the time of study entry, as defined in Section 5.2, Exclusion Criterion 21, should continue their regular, unchanged dose throughout the study.

For participants using CGM, concomitant medications or supplements in doses that may interfere with CGM measurements according to the label should not be taken within 48 hours prior to the dosing visit.

In general, new concomitant medications should be avoided; however, acetaminophen or similar medication may be administered at the discretion of the investigator postdosing for treatment of pain or discomfort. If the need for other concomitant medication arises, inclusion or continuation of the participant may be at the discretion of the investigator in consultation with a Lilly clinical pharmacologist. Any medication used during the course of the study must be documented in the eCRF. All changes in concomitant medications made during the study should be recorded in the eCRF.

6.6. Dose Modification

Dose modification is not allowed in this study.

Due to the design of the NG drug-device, a full 3 mg dose of NG is administered when the tip of the device is inserted into the nostril and the plunger is pressed firmly. It is not possible to modify the dose with the current drug-device.

6.7. Intervention after the End of the Study

Participants will continue their previous insulin regimen after all study procedures have been completed.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

Not applicable as this is a single-dose study.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study

- at any time at his/her own request
- at the request of his/her designee (e.g., parent/legal guardian)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- due to enrollment in any other clinical study involving an investigational product, or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- if their baseline BG is below 54 mg/dL as described in Section 2.3.1.1.

If consent is withdrawn for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant is withdrawn from the study, their parent/legal guardian may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.2.1. Discontinuation of Inadvertently Enrolled Participants

If the sponsor or investigator identifies a participant who did not meet enrollment criteria and was inadvertently enrolled, then safety follow-up should be performed as outlined in Section 1.3 (Schedule of Activities), Section 8.2 (Safety Assessments), and Section 8.3 (Adverse Events and Serious Adverse Events) of the protocol. Such participants would be classified as discontinued.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if the participant's parent/legal guardian is unable to be contacted by the study site for follow-up telephone calls. Site staff are expected to make diligent attempts to contact participants' parent/legal guardian for follow-up.

Discontinuation of specific sites or of the study as a whole is handled as part of Appendix 1 (Section 10.1).

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

Investigators or relevant clinical staff will provide age-appropriate explanations to all children prior to any assessment or procedure as appropriate. Investigators should assess and monitor physical pain and distress at each visit. Clinical staff trained or experienced in pediatric phlebotomy should perform blood draws at the clinic.

Use of local anesthetics (e.g., Emla cream) and other techniques to promote viable ease in blood sampling consistent with local prescribing information are permitted during the study visit to ease discomfort associated with venipuncture. Owing to blood volume restrictions, laboratory tests have been minimized.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1. Efficacy Assessments

Efficacy of NG may be assessed as an exploratory objective, based on PD parameters. See Section 9.4.3.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1. Physical Examinations

An age-appropriate physical examination will be conducted.

8.2.2. Vital Signs

For each participant, vital sign measurements will be conducted according to the SoA (Section 1.3).

Blood pressure and pulse rate should be measured with the participant sitting and relaxed when possible. Blood pressure measurements should be determined using a correctly sized cuff.

Additional vital signs may be measured for participant safety at the dosing visit, at the discretion of the investigator.

8.2.3. Clinical Safety Laboratory Assessments

For each participant, laboratory tests detailed in Section 10.2 should be conducted according to the SoA (Section 1.3).

8.2.4. Safety Monitoring

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

Lilly will review SAEs within time frames mandated by company procedures. The Lilly clinical pharmacologist or CRP will periodically review vital signs, safety, and AEs.

8.2.4.1. Bedside Glucose Safety Monitoring

During and after dosing, BG levels will be measured at the bedside for safety monitoring using an approved point-of-care glucometer. This will be 1 of 2 types, as follows:

- If the participant has been using an approved CGM in accordance with the device label for at least 1 month prior to the dosing visit, this CGM may be used for safety monitoring.
- If the participant has not been using an approved CGM, plasma BG levels for safety will be measured using a study-approved point-of-care glucometer.

In both cases, refer to the Study Operations Manual for details.

Timings of BG measurements are shown in the SoA (Section 1.3).

8.2.5. Monitoring for Hypoglycemia

Severe hypoglycemia will be described using the following ISPAD definition (Jones 2018):

Severe hypoglycemia 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 participant to have had hypoglycemia-induced cognitive dysfunction and is not predicated on the report of a participant simply having received assistance.

All episodes of severe hypoglycemia must be recorded in the eCRF and reported as SAEs.

Use of intravenous glucagon to preempt or treat severe hypoglycemia is described in Section 8.3.6.

8.2.6. Nasal Inspections

A visual nasal inspection will be conducted as specified in the SoA (Section 1.3), and more frequently if deemed necessary by the investigator. The same investigator that conducts the predose inspection should perform the postdose inspection for consistency. Refer to the Study Operations Manual for further details on this procedure.

8.2.7. Hepatic Safety Monitoring

If clinically applicable, the investigator may obtain additional laboratory tests during the study to confirm any hepatic abnormalities that may occur. Specific tests and follow-up procedures are provided in Section 10.4 (Appendix 4).

8.3. Adverse Events and Serious Adverse Events

AEs will be reported by the investigative site staff, or the participant's parent/legal guardian.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention, study device, or device constituent, or study procedures, or that caused the participant to discontinue the study (see Section 7).

A non-SAE that can be attributed or related to study device or device constituent, where the device complaint/deficiency/problem was anticipated, is also referred to as an adverse device effect.

An SAE attributable or related to an anticipated study device or device constituent complaint/deficiency/problem is also referred to as a serious adverse device effect.

An SAE attributable or related to an unknown or unanticipated device or device constituent complaint/deficiency/problem is also referred to as an unanticipated adverse device effect; or unanticipated serious adverse device effect in certain countries.

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

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs will be collected from the signing of the ICF until the completion of the second follow-up phone call.

AEs that begin before the start of study intervention but after signing of the ICF will be recorded on the Adverse Event eCRF.

Although all AEs after signing the ICF are recorded by the site in the CRF/electronic data entry, SAE reporting to the sponsor begins after the participant's parent/legal guardian has signed the ICF and the participant has received study drug. However, if an SAE occurs after signing the ICF, but prior to receiving NG, it needs to be reported ONLY if it is considered reasonably possibly related to study procedures.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3 (Appendix 3).

Care will be taken not to introduce bias while detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant, participant's parent/legal guardian, and investigator assessment are the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow up with each participant's parent/legal guardian at subsequent visits/contacts. All SAEs will be followed up until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3 (Appendix 3).

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

Not applicable for this study.

8.3.6. Rescue Treatment

Rescue treatment may be considered to preempt or treat clinically significant or severe hypoglycemia based on BG measures taken at baseline (Section 2.3.1.1), or as part of bedside glucose safety monitoring during and after dosing (Section 8.2.4.1).

8.3.6.1. Criteria for Considering Rescue Treatment

In general, the investigator may decide to start a glucose infusion if a participant's BG level is declining rapidly, or their symptoms become consistent with progression to clinically significant or severe hypoglycemia.

In addition, specific BG thresholds for considering rescue treatment at baseline and during bedside glucose safety monitoring are as follows:

Baseline criteria for rescue

If a participant's baseline BG level is

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

8.3.6.2. Rescue Procedure

Oral or intravenous glucose or glucagon may be given as appropriate to the clinical situation. If NG was administered, any remaining blood samples will be collected, if possible, according to the SoA.

Further details will be provided to the site in the Study Operations Manual.

8.3.7. Product Complaints

A product complaint is any written, electronic, or oral communication that alleges a deficiency related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a Lilly product after it is released to the study. When the ability to use the product safely is impacted, the following are also product complaints:

a. Deficiencies in labeling information, and
b. Use errors for device or combination products due to ergonomic design elements of the product.

The sponsor collects product complaints on investigational products, medical devices, and drug delivery systems used in clinical studies to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Complaints are also collected on comparators and other materials supplied, as required and instructed for the study.

Participants' parent/legal guardian will be instructed to contact the investigator as soon as possible if they have a complaint or problem with the investigational product, medical device, or delivery system, so that the situation can be assessed.

Product complaints will be reported by the investigator to the sponsor per instructions provided on the study-specific Product Complaint Form.

With each complaint related to a medical device or delivery system, the investigator will assess and indicate on the complaint form whether the product complaint could have led to an SAE had precautions not been taken.

8.4. Treatment of Overdose

For the purposes of this study, an overdose of NG is considered any dose higher than the planned 3 mg dose.

In case of suspected overdosing, serum potassium levels may decrease and should be monitored and corrected if needed. If the participant develops a marked increase in blood pressure, blood pressure medication appropriate to the child's age may be administered, e.g., phentolamine mesylate for children aged 3+ years (OraVerse USPI, 2018; Baqsimi USPI, 2019).

Refer to the Product Label for additional details.

8.5. Pharmacokinetics

At the times specified in the SoA, venous blood samples of approximately 2 mL each will be collected to determine the plasma concentrations of glucagon.

Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded. Sites may use topical anesthetics to minimize pain or discomfort associated with sample collection.

8.5.1. Bioanalysis

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

Concentrations of glucagon will be assayed using a validated liquid chromatography with tandem mass spectrometry method.

Bioanalytical samples collected to measure investigational product concentrations will be retained for a maximum of 1 year following last participant visit for the study.

8.6. Pharmacodynamics

At the times specified in the SoA, blood samples will be collected for use in a study-approved rapid glucose analyzer (YSI or equivalent) to determine the plasma concentrations of glucose.

Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

8.7. Genetics

Genetics will not be evaluated in this study.

8.8. Biomarkers

Biomarkers will not be evaluated in this study.

8.9. Immunogenicity Assessments

Not applicable.

8.10. Health Economics

Not applicable.

9. Statistical Considerations

9.1. Statistical Hypotheses

Not applicable.

9.2. Sample Size Determination

At least 9 participants with an approximate maximum of 20 may be enrolled so that 6 evaluable participants 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.

Participants who are enrolled but not administered treatment may be replaced to ensure that enough participants may complete the study.

9.3. Populations for Analyses

A detailed description of participant disposition will be provided.

The participants' baseline characteristics and demographics will be obtained at entry and will be summarized for all enrolled participants who proceed to the dosing visit.

9.4. Statistical Analyses

Statistical analysis of this study will be the responsibility of 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.

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

Unless otherwise specified, efficacy analyses will be conducted on all enrolled participants who receive the study drug and have an evaluable efficacy outcome (based on PD parameters, see Section 9.4.3).

PK and PD analyses will be conducted on data from all enrolled participants who receive the study drug and have evaluable PK or PD data. See Section 9.4.2 for definitions of evaluable PD and PK data.

Safety analyses (Section 9.4.1) will be conducted for all enrolled participants who receive at least 1 dose of the study drug, whether or not they complete all protocol requirements.

Additional exploratory analyses of the data will be conducted as deemed appropriate.

9.4.1. Primary Endpoint: Safety

9.4.1.1. Clinical Evaluation of Safety

All investigational product and protocol procedure AEs will be listed, and if the frequency of events allows, safety data will be summarized using descriptive methodology.

The incidence of symptoms will be presented by severity and by association with investigational product as perceived by the investigator. Symptoms reported to occur prior to enrollment will be distinguished from those reported as new or increased in severity during the study. Each symptom will be classified by the most suitable term from the Medical Dictionary for Regulatory Activities.

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

Nasal/respiratory and anosmia AEs will be identified using preferred terms and summarized. The details will be provided in the SAP.

9.4.1.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include safety laboratory parameters and vital signs. The parameters will be listed or summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data. Details will be provided in the SAP.

9.4.2. Secondary Endpoints: Pharmacodynamics and Pharmacokinetics

9.4.2.1. Pharmacodynamics

9.4.2.1.1. Pharmacodynamic Parameter Estimation

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

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. Individual concentrations and PD parameters of PG will be summarized using descriptive statistics.

9.4.2.1.2. Pharmacodynamic Statistical Summary

The PD parameters (such as change from baseline of BGmax, BGmax, AUC parameters, and TBGmax) will be summarized using standard descriptive statistics.

Evaluable PD data are defined as having baseline and at least 1 postbaseline measure. For rescued participants, data after the rescue would be excluded from the analysis.

See Section 9.4.3 for details on the exploratory efficacy objective based on PD parameters.

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

9.4.2.2. Pharmacokinetics

9.4.2.2.1. Pharmacokinetic Parameter Estimation

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. For rescued participants, data after the rescue would be excluded from the analysis.

9.4.3. Exploratory Endpoint: Efficacy

PG levels will be measured prior to the administration of glucagon, as well as at various time points after administration (SoA, Section 1.3), and may be used to assess efficacy of NG.

Efficacy of NG will be assessed in terms of "treatment success." This is defined as an increase of PG ≥20 mg/dL (1.11 mmol/L) from baseline within 30 minutes postdose. The proportion of participants achieving treatment success will be calculated.

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

Evaluable efficacy outcome is defined as having baseline and at least 1 postbaseline measure within 30 minutes after dose administration. For rescued participants, data after the rescue would be excluded from the analysis.

The details will be provided in the SAP.

9.5. Interim Analyses

After 3 patients have completed the study, participant enrollment will be paused and an interim analysis will be conducted, evaluating the data relating to the primary and secondary objectives (Section 9.4).

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

The SAP will describe the planned interim analyses in greater detail.

9.6. Data Monitoring Committee

Not applicable.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- The investigator will be responsible for reporting cases of suspected child abuse and/or neglect according to local regulations including local medical association (e.g., American Academy of Pediatrics, EU Academy of Pediatrics) or Health Department guidelines).
- This study will be conducted in accordance with the protocol and with the following:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
    - Applicable ICH GCP Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
    - Notifying the IRB/IEC of SAEs (and/or unanticipated adverse device effects) or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- Investigator sites are compensated for participation in the study as detailed in the clinical trial agreement.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial

certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant's parent/legal guardian and answer all questions regarding the study.
- The participant's parent/legal guardian must be informed that participation in this study is voluntary. The participant's legally acceptable representative, parent, or legal guardian will be required to provide a statement of informed consent that meets the requirements of 21 Code of Federal Regulations 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that consent from the legally acceptable representative, parent(s), or legal guardian was obtained before the participant was enrolled in the study and the date the written consent was obtained. The medical record should also describe how the clinical investigator determined that the person signing the ICF was the participant's legally acceptable representative, parent(s), or legal guardian. The site staff obtaining the informed consent must also sign the ICF.
- The participant's legally acceptable representative, parent(s), or legal guardian must be reconsented to the most current version of the ICF(s) during their child's participation in the study.
- A copy of the ICF(s) must be provided to the participant's legally acceptable representative, parent(s), or legal guardian.

Prior to rescreening, the legally acceptable representative, parent(s), or legal guardian must sign a new ICF prior to any further study procedures.

Assent from study participants is not required due to the very young age of the participants.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets, or samples that are transferred to the sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.
- The participant's legally acceptable representative, parent(s), or legal guardian must be informed that the participant's personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the legally acceptable representative, parent(s), or legal guardian who will be required to give consent for their data to be used as described in the informed consent.

- The participant's legally acceptable representative, parent(s), or legal guardian must be informed that the participant's medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The sponsor has processes in place to ensure data protection, information security, and data integrity. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

10.1.5. Dissemination of Clinical Study Data

The sponsor will disclose a summary of study information, including tabular study results, on publicly available websites where required by local law or regulation.

10.1.6. Data Quality Assurance

All participant data relating to the study will be recorded on eCRF unless transmitted to the sponsor or designee electronically (e.g., PK data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The investigator must maintain accurate source documentation that supports all information entered in the eCRF. Source data may include laboratory tests, medical records, and clinical notes.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques are provided in the Monitoring Plan.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

The sponsor assumes accountability for actions delegated to other individuals (e.g., CRO).

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site staff are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the clinical trial agreement unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

In addition, the sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by the

sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data capture system

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor.

An electronic data capture system will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided electronic data capture system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

Data collected via the sponsor-provided data capture system(s) will be stored at a third party. The investigator will have continuous access to the data during the study and until decommissioning of the data capture system(s). Prior to decommissioning, the investigator will receive an archival copy of pertinent data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system and reports will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the sponsor data warehouse.

Data from complaint forms submitted to the sponsor will be encoded and stored in the global product complaint management system.

10.1.7. Source Documents

Source documents are defined in Section 10.1.6.

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.8. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to

- failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- inadequate recruitment of participants by the investigator
- discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant's parent/legal guardian, and assure appropriate participant therapy and/or follow-up.

10.1.9. Publication Policy

In accordance with the sponsor's publication policy, the results of this study will be submitted for publication by a peer-reviewed journal if the results are deemed to be of significant medical importance.

10.1.10. Investigator Information

Physicians with experience in pediatric clinical studies, and in treating pediatric patients with diabetes, will participate as investigators in this clinical trial.

10.2. Appendix 2: Clinical Laboratory Tests

The following tests will be performed by the local laboratory.

- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Investigators must document their review of each laboratory safety report.

Safety Laboratory Tests

Hematology	**Clinical Chemistry**
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count (RBC)	Chloride
Mean cell volume	Glucose
Mean cell hemoglobin	Blood urea nitrogen (BUN)
Mean cell hemoglobin concentration	Albumin
Leukocytes (WBC)	Total bilirubin
Platelets	Alkaline phosphatase (ALP)
Differential WBC % of:	Aspartate aminotransferase (AST)
Neutrophils	Alanine aminotransferase (ALT)
Lymphocytes	Creatinine
Monocytes	Magnesium
Eosinophils	Bicarbonate
Basophils	Phosphorus
	HbA1c

Abbreviations: HbA1c = glycated hemoglobin; RBC = red blood cell; WBC = white blood cell.

10.3. Appendix 3: Adverse Events: Definitions, and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., electrocardiogram, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdose should be reported regardless of sequelae. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted to hospital for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- The investigator will consider any AEs, SAEs, and clinically important laboratory abnormalities as related to the study intervention unless there is clear evidence that the event is not related.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor or designee.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the sponsor or designee. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in the SAE Report.

10.4. Appendix 4: Liver Safety: Suggested Actions and Follow-up Assessments

At the PI's discretion, in the event of suspected hepatic impairment of a study participant, close or comprehensive monitoring may be conducted.

Close hepatic monitoring

Laboratory tests (Appendix 2, Section 10.2), including ALT, AST, ALP, TBL, as well as direct bilirubin, gamma glutamyltransferase, and creatine kinase, should be conducted.

These should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if 1 or more of these conditions occur:

If a participant with baseline results of ...	develops the following elevations:
ALT or AST <1.5x ULN	ALT or AST ≥3x ULN
ALP <1.5x ULN	ALP ≥2x ULN
TBL <1.5x ULN	TBL ≥2x ULN (except for patients with Gilbert's syndrome)
ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline
ALP ≥1.5x ULN	ALP ≥2x baseline
TBL ≥1.5x ULN	TBL ≥2x baseline (except for patients with Gilbert's syndrome)

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated medical monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, recent illnesses (e.g., heart failure, systemic infection, hypotension, or seizures), recent travel, history of concomitant medications (including over-the-counter), herbal and dietary supplements, history of alcohol drinking and other substance abuse.

Initially, monitoring of symptoms and hepatic biochemical tests should be done at a frequency of 1 to 3 times weekly, based on the participant's clinical condition and hepatic biochemical tests. Subsequently, the frequency of monitoring may be lowered to once every 1 to 2 weeks, if the participant's clinical condition and laboratory results stabilize. Monitoring of ALT, AST, ALP, and TBL should continue until levels normalize or return to approximate baseline levels.

Comprehensive hepatic evaluation

A comprehensive evaluation should be performed to search for possible causes of liver injury if one or more of these conditions occur:

If a participant with baseline results of...	develops the following elevations:
ALT or AST <1.5x ULN	ALT or AST ≥3x ULN with hepatic signs/symptoms*, or ALT or AST ≥5x ULN
ALP <1.5x ULN	ALP ≥3x ULN
TBL <1.5x ULN	TBL ≥2x ULN (except for patients with Gilbert's syndrome)
ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline with hepatic signs/symptoms*, or ALT or AST ≥3x baseline
ALP ≥1.5x ULN	ALP ≥2x baseline

TBL ≥1.5x ULN	TBL ≥1.5x baseline (except for patients with Gilbert's syndrome)

*** Hepatic signs/symptoms are severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.**

At a minimum, this evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for prothrombin time-international normalized ratio; tests for viral hepatitis A, B, C, or E; tests for autoimmune hepatitis; and an abdominal imaging study (e.g., ultrasound or computed tomography scan).

Based on the participant's history and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for hepatitis D virus, cytomegalovirus, Epstein-Barr virus, acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and serum phosphatidylethanol. Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, cardiac echocardiogram, or a liver biopsy.

Additional hepatic data collection (hepatic safety CRF) in study participants who have abnormal liver tests during the study

Additional hepatic safety data collection in hepatic safety CRF should be performed in study participants who meet 1 or more of the following 5 conditions:

1. Elevation of serum ALT level to ≥5x ULN on 2 or more consecutive blood tests (if baseline ALT <1.5x ULN)
    - In participants with baseline ALT level ≥1.5x ULN, the threshold is ALT level ≥3x baseline on 2 or more consecutive tests
2. Elevation of TBL level to ≥2x ULN (if baseline TBL level <1.5x ULN) (except for cases of known Gilbert's syndrome)
    - In participants with baseline TBL level ≥1.5x ULN, the threshold should be TBL level ≥2x baseline
3. Elevation of serum ALP level to ≥2x ULN on 2 or more consecutive blood tests (if baseline ALP <1.5x ULN)
    - In participants with baseline ALP level ≥1.5x ULN, the threshold is ALP level ≥2x baseline on 2 or more consecutive blood tests
4. Hepatic event considered to be an SAE
5. Discontinuation of study drug due to a hepatic event

Note: the interval between the consecutive blood tests should be at least 2 days.

10.5. Appendix 6: Blood Sampling Summary

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

Protocol I8R-MC-IGBO Sampling Summary for full sampling

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening chemistry and hematology[a]	3	1	3
Bedside point-of-care glucose monitoring[b]	-	9	0.01
Pharmacokinetics (plasma glucagon)	2	3	6
Pharmacodynamics (plasma glucose)	0.1	5	0.5
Blood discard for cannula patency	1	5	5
Total			14.51
Total for clinical purposes [rounded up to the nearest 10 mL]			20

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

b Applies only to participants for whom a point-of-care blood glucometer will be used, i.e., this is not needed for participants who are using their own continuous glucose monitoring equipment (see Section 8.2.4.1). The volume of each glucose measurement using a point-of-care blood glucometer is estimated at 0.3 to 1.5 µL (0.0003 to 0.0015 mL; ADA 2020).

10.6. Appendix 7: Abbreviations

Term	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BG	blood glucose
BGmax	maximum observed BG
CGM	continuous glucose monitoring
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CRF	case report form
CRO	contract research organization
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
eCRF	electronic case report form
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
GCP	good clinical practice
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee

informed consent	A process by which a participant, or their parent or legal guardian, voluntarily confirms their willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IRB	Institutional Review Board
ISPAD	International Society for Pediatric and Adolescent Diabetes
IV	intravenous
MDI	multiple daily injection
NG	nasal glucagon
participant	Equivalent to CDISC term “subject”: an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
PG	plasma glucose
PI	principal investigator
PK/PD	pharmacokinetics/pharmacodynamics
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SoA	schedule of activities
T1D	type 1 diabetes
TBGmax	time of maximum observed blood glucose
TBL	total bilirubin
ULN	upper limit of normal

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Approval	PPD Medical Director 28-Jul-2022 14:43:40 GMT+0000

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