CLINICAL REVIEW

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Reviewer Name(s)	Andreea O Lungu
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Established/Proper Name	Glucagon
(Proposed) Trade Name	BAQSIMI
Applicant	Lilly
Dosage Form(s)	Nasal powder
Applicant Proposed Dosing Regimen(s)	3 mg
Applicant Proposed Indication(s)/Population(s)	Treatment of severe hypoglycemia
Recommendation on Regulatory Action	Approve
Recommended Indication(s)/Population(s) (if applicable)	Treatment of severe hypoglycemia

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BG	blood glucose
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CG	control glucagon
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
DMEPA	Division of Medication Errors Prevention and Analysis
ECG	electrocardiogram
FDA	Food and Drug Administration
GCP	good clinical practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NG	nasal glucagon
NDA	new drug application
NME	new molecular entity
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report

PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

The nasal glucagon (NG) is being developed for the treatment of severe hypoglycemia. The drug substance in NG is synthetic glucagon, which is the same as recombinant glucagon used in the currently marketed glucagon emergency kits, also identical to human glucagon. The NG drug product is a (b) (4) powder consisting of synthetic glucagon (3 mg), DPC as a (b) (4), and beta-cyclodextrine (β-CD) as a (b) (4) The drug product powder is to be marketed in a prefilled device for nasal delivery.

The applicant is proposing only one dose for marketing, 3 mg.

The proposed trade name for NG is BAQSIMI.

The applicant proposed the following indication for the NG:

> *BAQSIMI is an antihypoglycemic agent indicated for the treatment of severe hypoglycemia.*

1.2. Conclusions on the Substantial Evidence of Effectiveness

The NG phase 3 development program is comprised of 5 studies. Three of the studies were in adults, of which 2 were phase 3 controlled studies, and one a real use study; and 2 in pediatrics (one controlled, and one real-use study).

The clinical trials conducted to support efficacy of NG were conducted in adults with type 1 diabetes (T1DM) or type 2 diabetes (T2DM), and children with T1DM. The controlled studies used insulin to induce lowering of glucose (to <60 mg/dL range in adults, and to < 80 mg/dL in children), and used one of the approved injectable glucagon products as control glucagon (CG). The dose studied in the adult efficacy studies was 3 mg NG, while the pediatric controlled study evaluated 2 and 3 mg NG. The real use trial(s) studied in both adults and children were conducted in T1DM patients, and were uncontrolled. The outcome used to define treatment success was different in different studies. In the two controlled studies in adults, the primary outcome was success/failure, with success defined as an increase in blood glucose to ≥70 mg/dL or an increase of ≥20 mg/dL from nadir within 30 minutes after receiving study glucagon, without receiving additional actions to increase the blood glucose level such as intravenous glucose, additional glucagon, or exogenous carbohydrates. Both studies achieved the primary endpoint. The pediatric controlled study was designed with a primary pharmacokinetic (PK)

and pharmacodynamic (PD) outcome, but efficacy could be assessed post hoc as the proportion of patients with an increase in blood glucose ≥20 mg/dL from nadir at 5, 10, 15, 20, 30, 40, 60, and 90 minutes post glucagon administration. For the real use studies, success was defined as the proportion of patients who were awake or returned to normal status 30 minutes after NG administration, and efficacy was demonstrated here as well, although these studies had multiple major protocol violations, and both studies had one site closed for Good Clinical Practices (GCP) non-compliance, limiting the number of evaluable events.

It is also notable that the product underwent manufacturing changes over the course of the clinical program, partly because of changes in ownership, and partly for product improvement. The only study performed with the to-be-marketed drug product was study IGBI, which was considered the pivotal study in the FDA assessment of efficacy, with the additional studies considered as supportive.

Additionally, NG appears to be delayed in increasing blood glucose (BG) by 1-4 minutes (depending on the study), while still meeting the primary endpoint at 30 minutes, in comparison to approved injectable glucagon products. Since the currently approved glucagon products require reconstitution prior to injection, it is likely that this delay with the NG is not clinically relevant.

In summary, NG was shown to be efficacious in treating hypoglycemia in adults with T2DM, as well as adults and pediatric patients with T1DM. Although very few events were severe hypoglycemia in adults, and there were no events of severe hypoglycemia in children, it is generally adequate in clinical trials to show a sustained increase in blood glucose following insulin infusion, or a spontaneous moderate or severe hypoglycemic episode, as the response to glucagon does not appear to depend on the starting blood glucose.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Severe hypoglycemia is a serious condition occurring in patients with diabetes, and occurs with higher frequency in patients with T1DM. The incidence of severe hypoglycemia increases with age, disease duration for patients with T1DM, and insulin therapy duration for patients with T2DM. Severe hypoglycemia affects approximately 30% (range, 22% to 46%) of patients with T1DM annually, at a frequency of 30 to 320 events per 100 patient-years. In insulin-treated patients with T2DM, severe hypoglycemia affects 7% to 25% at a frequency of 10 to 80 events per 100 patient-years. Currently available outpatient treatment for severe hypoglycemia is limited to injectable glucagon. The goal of glucagon treatment is to increase blood glucose levels rapidly, to the point where the patient with severe hypoglycemia regains sufficient cognitive function to safely consume oral carbohydrates. The currently approved injectable products need to be reconstituted (b) (4) and then injected, by the caregiver of the patient experiencing a severe hypoglycemic event. Either because of the need for reconstitution, or the need to administer an injection, or both, the currently available glucagon products appear to be underutilized. Nasal glucagon was developed as an alternative to currently available glucagon products.

The NG phase 3 development program is comprised of 5 studies. Three studies were conducted in adults, which included 2 phase 3 controlled studies, and one real use study. Two studies were conducted in pediatric subjects, one was a controlled study and one was a real-use study. The nasal glucagon was shown to increase blood glucose level, and the efficacy endpoints were met in all adult and pediatric studies. While the evidence from the real use studies was less rigorous due to the nature of these studies, and protocol violations that led to a large proportion of unevaluable events, the totality of data is supportive of efficacy for the 3 mg NG dose for the treatment of severe hypoglycemia in patients age 4 and above.

The safety of NG was evaluated based on spontaneous adverse events (AEs) and questionnaires which specifically assessed for issues related to the nasal delivery (nasal and ocular symptoms). There was one death reported, and 2 serious adverse events (SAEs) were reported from the entire development program, none related to the study drug. As expected with glucagon drug products, nausea and vomiting were common AEs. Headache, nasal, and ocular AEs were reported more commonly with the NG, but none were SAEs. These events were further characterized based on the questionnaires, and it appears that the nasal and ocular symptoms peak at 15 minutes post-dose, and then slowly decline. While some symptoms were recorded as severe in intensity (not SAEs) at 15 minutes, none were reported as severe at the last assessment, 90 minutes after the dose.

The clinical benefit appears to outweigh the risks associated with the NG. NG was shown to be efficacious in treating hypoglycemia, although

with 1-4 minutes delay compared to the control glucagon (CG). This time to effect difference is likely mitigated by the need for reconstitution and injection with the currently approved glucagon, which can be reasonably assumed to delay the administration of the product, although there is no data to support this assumption. The safety profile of NG, which is similar to the currently approved glucagon formulation, is also associated with additional common treatment-emergent AEs (TEAEs) related to the route of administration, in the form of increase in headache, and nasal, and ocular AEs. While these AEs are relevant and should be documented in the prescribing information, none of them were a SAE, and they were transient. NG is a product for emergency use where lack of treatment could result in death. In this context, the NG product offers an alternative for caregivers who are not comfortable administering an injection.

I recommend approval of nasal glucagon for treatment of severe hypoglycemia.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Serious condition occurring in patients with diabetes • More common in T1DM • Affects approximately 30% of patients with T1DM annually	• Severe hypoglycemia is a serious condition that can lead to death
Current Treatment Options	• Glucagon 0.5 and 1 mg	• The only outpatient treatment for severe hypoglycemia is glucagon • All currently marketed glucagon products require reconstitution and are injectable
Benefit	• The NG 3 mg drug product was effective in delivering glucagon and increasing blood glucose in both adults and pediatric patients, and in clinical research center conditions, as well as real-use conditions	• Because of the delivery route, and lack of need to reconstitute and administer an injectable product, it offers a reasonable, and possibly easier to administer, alternative for the caregivers of patients with diabetes

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• The safety of NG was evaluated in both adults and pediatric patients • The safety of NG showed similarity with the currently marketed glucagon, with the most frequent treatment emergent AEs being nausea and vomiting. • The use of NG was associated with increased incidence of headache compared to currently marketed glucagon formulations • The use of NG was associated with an increase in nasal and ocular AEs, sometimes rated as severe by the patients (but not SAEs), although some led to treatment discontinuation • The time to treatment success was slightly delayed between 1-4 minutes when compared to currently marketed rescue products	• The safety of NG can be adequately represented in the prescribing information • While the NG increase in glucose is delayed compared to currently marketed glucagon, it is reasonable to assume this delay matched the delay created by the need for reconstitution and injection of the currently marketed glucagon

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☒	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☒	Clinical outcome assessment (COA) data, such as		
		☒	Patient reported outcome (PRO)	Nasal Questionnaire
		☒	Observer reported outcome (ObsRO)	Hypoglycemia Questionnaire
		☒	Clinician reported outcome (ClinRO)	Nasal and Non-Nasal Questionnaire
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.			

Reviewer comment: Notably, none of these questionnaires was validated with the FDA, but, because most of them collected specific adverse events, they were considered in the assessment of safety.

2. Therapeutic Context

Severe hypoglycemia is a significant complication of diabetes treatment, occurring more frequently in patients with T1DM, but also in patients with T2DM, particularly patients taking insulin and oral medications that increase insulin secretion. Severe hypoglycemia is characterized by neurological impairment that, if left untreated, can lead to loss of consciousness, seizures, coma, adverse cardiovascular outcomes, and even death. Glucagon increased blood glucose concentration by activating hepatic gluconeogenesis, and has been used in the treatment of hypoglycemia since the 1950s. There are multiple injectable glucagon products approved by the FDA for the treatment of severe hypoglycemia. The need for product reconstitution and the route of administration for the currently available glucagon formulations is somewhat limiting for their use in clinical practice. The applicant developed a nasal glucagon formulation intended for the treatment of severe hypoglycemia in adult and pediatric patients with diabetes. The drug product is a drug-device combination, 3 mg dose of ready-to-use NG (b) (4) powder, administered by inserting the tip of the single use device into the patient's nostril, and depressing the plunger to expel the glucagon powder into the nostril where it is passively absorbed in the anterior nasal mucosa.

2.1. Analysis of Condition

Severe hypoglycemia is an episode of hypoglycemia that causes neurological impairment and requires the assistance from another person to actively administer carbohydrates, glucagon, or take other corrective actions. It is a serious condition occurring in patients with diabetes, occurring with higher frequency in patients with T1DM. The incidence of severe hypoglycemia increases with age, disease duration for patients with T1DM, and insulin therapy duration for patients with T2DM.

Severe hypoglycemia affects approximately 30% (range, 22% to 46%) of patients with T1DM annually, at a frequency of 30 to 320 events per 100 patient-years. In insulin-treated patients with T2DM, severe hypoglycemia affects 7% to 25% at a frequency of 10 to 80 events per 100 patient-years.

2.2. Analysis of Current Treatment Options

Currently available treatments for severe hypoglycemia are limited to intravenous dextrose and injectable glucagon. Intravenous dextrose requires administration by trained personnel within a hospital or emergency medical setting; thus, injectable glucagon is the only treatment option for caregivers in outpatient settings. The goal of glucagon treatment is to increase blood glucose levels rapidly, to the point where the patient with severe hypoglycemia regains

sufficient cognitive function to safely consume oral carbohydrates. Injectable glucagon is not currently available in a ready-to-use formulation, (b) (4) Therefore, the currently available glucagon formulations have to be reconstituted, which adds a delay to an emergency treatment, and then injected, which may add an additional level of complexity for the caregiver. As a result, there is literature to suggest that caregivers without medical training find it difficult to administer injectable glucagon in an emergency. This may contribute to the underutilization of injectable glucagon. The currently approved glucagon products are summarized below.

Table 1 Summary of Treatment Armamentarium Relevant to Proposed Indication

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments (e.g., subpopulation not addressed
FDA Approved Treatments						
Glucagon (GlucaGen – Novo Nordisk, Glucagon-Lilly and other manufacturers)	Treatment of severe hypoglycemia	1998	Subcutaneous, intramuscular, or intravenous	Approved for use in adults (1mg), and children (1 mg or 0.5 mg, weight based)	Common adverse events include nausea, vomiting, and temporary increase in blood pressure and pulse	Requires reconstitution before administration

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Nasal glucagon was originally developed by A.M.G Medical Inc. (AMG Medical) and later by Locemia Solutions (Locemia) prior to acquisition by Lilly in 2015. The clinical program is comprised of 11 clinical trials, 10 of which have been conducted prior to the time of acquisition by Lilly. The prespecified analyses were conducted by AMG Medical/Locemia, however Lilly performed post-hoc analyses in some instances to provide additional clarification and to align to the Lilly standards for data review. Additionally, the FDA required that Lilly perform a bridging study since Lilly changed the manufacturing process of the drug product.

3.2. Summary of Presubmission/Submission Regulatory Activity

The design of the pivotal study IGBC, including the choice of endpoints and non-inferiority margin (NIM), was agreed on November 18, 2013 with the US FDA via a Special Protocol Assessment (SPA). Per the agreement, demonstration of non-inferiority in percentage of patients achieving treatment success and a similar glucose response to injectable glucagon in pivotal studies would be appropriate to support the use of nasal glucagon (NG) for the indication of severe hypoglycemia.

The pivotal pediatric study in patients with T1DM (IGBB) was different in design from the pivotal adult study because of ethical concerns of inducing hypoglycemia in children. The pediatric study design was agreed upon with US FDA (December 13, 2013) during review of the Agreed initial Pediatric Study Plan (iPSP). At the time of the agreement, the applicant and the FDA agreed that studies in patients (b) (4) should be deferred.

Per the applicant, phase-appropriate changes were made to the NG manufacturing process throughout development, starting with a small-scale manual process and progressing to a full-scale commercial process, with automated device filling and assembly processes. The clinical bridging and confirmatory study (IGBI), which used a design similar to that of study IGBC following agreement with FDA (Meeting Minutes, December 9, 2016), was the first study conducted with the commercial drug product. The purpose of this study was to demonstrate comparability to results of Study IGBC, thereby bridging to previously-generated clinical data, and to confirm the efficacy and safety profile of commercial NG drug product.

3.3. Foreign Regulatory Actions and Marketing History

The NG product is not marketed in any country.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

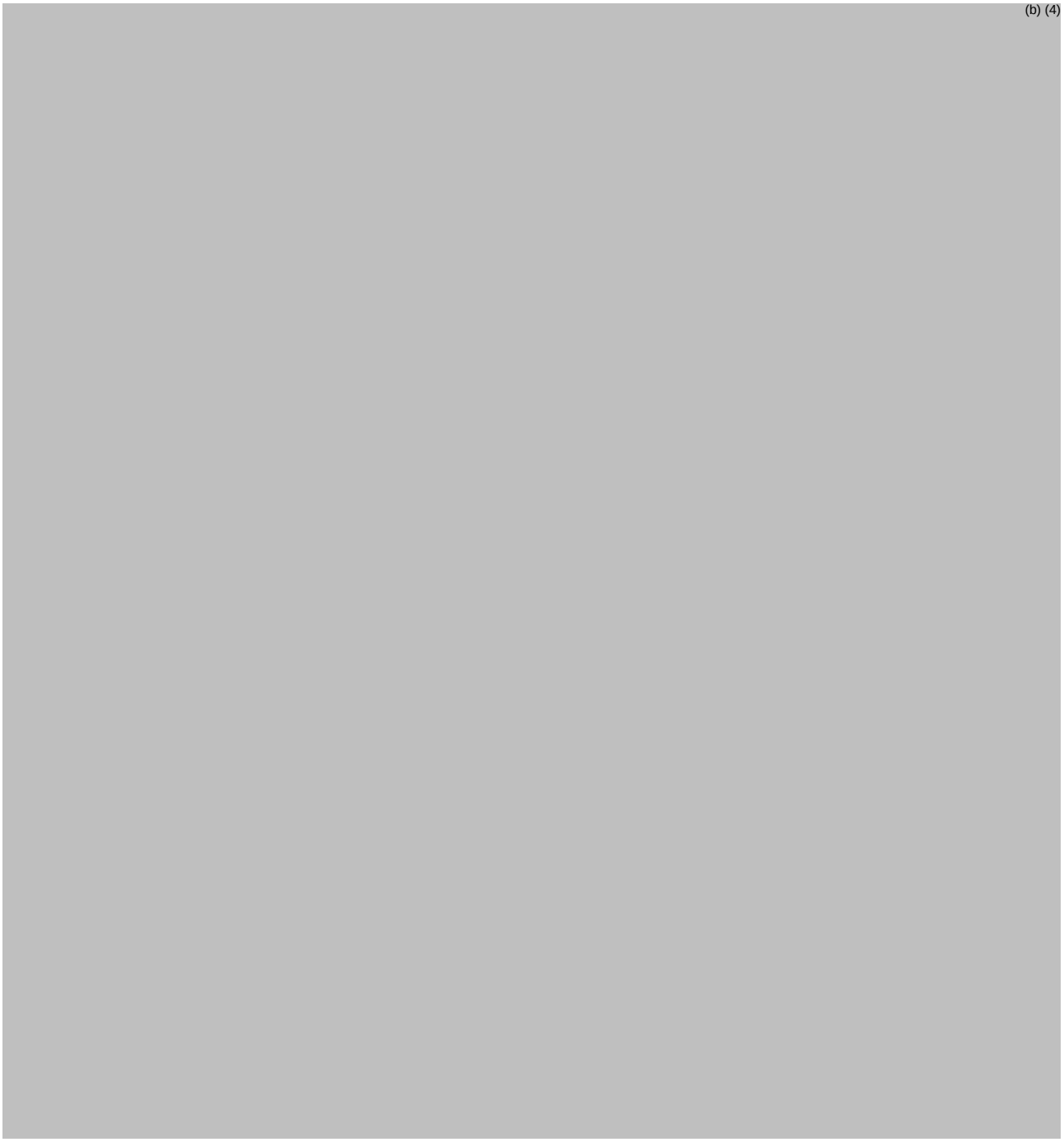
4.1. Office of Scientific Investigations (OSI)

The FDA inspection for this new drug application (NDA) consisted of two domestic clinical sites (representing three study sites) as well as the applicant and contract research organization (CRO). The inspection of the applicant, CRO and the clinical investigators revealed no regulatory violations.

Based on the inspections of the two clinical sites, the CRO and the applicant, the inspectional findings support validity of data as reported by the applicant under this NDA.

(b) (4)

(b) (4)



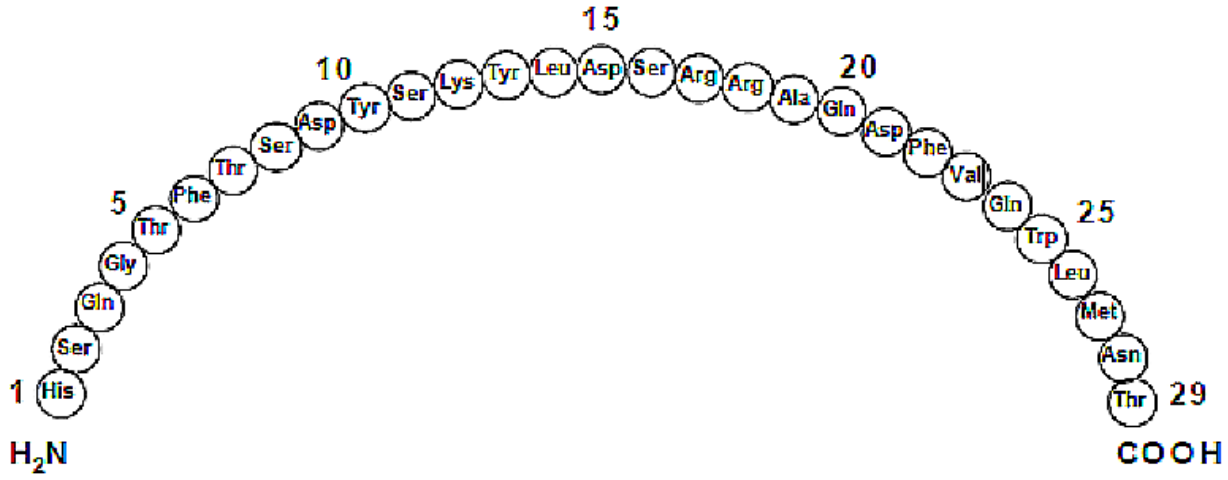
Please see OSI review by Dr Cynthia Kleppinger for details.

4.2. Product Quality

Drug Substance

Glucagon is a single-chain polypeptide that contains 29 amino acid residues and has the molecular weight of 3483. The drug substance in NG is synthetic glucagon, which is the same as recombinant glucagon used in the currently marketed glucagon emergency kits, also identical to human glucagon. The chemical structure of glucagon is represented in Figure 1 below.

Figure 1 Chemical Structure of Glucagon



Source: Figure 2.7.1.1 Biopharmacology Summary

Drug Product

Nasal glucagon is a (b) (4) powder consisting of synthetic glucagon (3 mg), dodecylphosphocholine (DPC) as a (b) (4) and beta-cyclodextrine (β-CD) as a (b) (4)

The formulation used to support all of the clinical trials contained glucagon, DPC, and β -CD. The composition of the NG drug powder is represented in Table 2 below.

Table 2 Unit Formula for Nasal Glucagon Drug Powder

Ingredient	Quantity (mg/unit dose)	Function	Reference to Standards
Active Ingredient			
Glucagon (Synthetic)	3.0	Active ingredient	(b) (4)
Other Ingredients			
β-Cyclodextrin			
Dodecylphosphocholine (DPC)			
(b) (4)			

(b) (4)

Abbreviations: Ph.Eur. = European Pharmacopoeia; USP-NF = United States of Pharmacopoeia and National Formulary.

[a] (b) (4)

Source: Table 2.3.P.1-1 Drug Product Document

Excipients

DPC is a novel excipient used as (b) (4), which is present at (b) (4)% in the (b) (4) formulation. Nuclear magnetic resonance studies show that the phospholipid structure of DPC interacts with several amino acids in glucagon, which may help to inhibit the aggregation of glucagon.

β-CD, which is present in the formulation at (b) (4)%, is used to (b) (4)

(b) (4) is used to dissolve all the components in the drug product formulation.

Product variability throughout the development program

The adult clinical bridging and confirmatory study, study IGBI, was conducted to allow an assessment of clinical comparability between the commercial and clinical trial drug products, through indirect comparison with study IGBC. Phase-appropriate changes were made to the

NG manufacturing process during development to facilitate the production of larger quantities of material to supply product for the clinical trials and commercialization. (b) (4)

(b) (4)

(b) (4) These changes resulted in batches with different drug product.

While the proposed drug for the drug product is 3 mg, the actual dose that can be potentially delivered along the shelf life of the drug product is a range. Per the CMC review, "The combination product is labeled to dispense a mean of 3 mg glucagon per actuation. At the end of shelf-life, the mean dose dispensed from the device can be as low as (b) (4) mg glucagon with an understanding 90% of the samples tested will have a potency of (b) (4) mg and the potency of the remaining of the sample population may lie between (b) (4) mg". The efficacy of the 2 mg dose is discussed in section 7.1.4.

The CMC reviewer granted an 18 months shelf life when stored at (b) (4) 30°C for the combination product packaged in shrink-wrapped secondary packaging.

Please see CMC review by Dr Muthukumar Ramaswamy for details.

4.3. Clinical Microbiology

Please see CMC review by Dr Muthukumar Ramaswamy for details.

4.4. Nonclinical Pharmacology/Toxicology

The nonclinical testing strategy for nasal glucagon, including the approved excipient β-CD and novel excipient DPC, followed a development pathway of a short-term usage (i.e. ≤7 days), biotherapeutic intended as treatment for severe hypoglycemia in patients with diabetes mellitus and is consistent with current regulatory guidance.

The systemic toxicity of glucagon has been well characterized for the marketed injectable glucagon products. The nasal glucagon toxicology program characterized not only the local effects of this glucagon drug product but also the systemic effects following nasal administration.

Because the pharmacological properties of glucagon are well known, the nonclinical pharmacology program was limited to an assessment of glucagon PK and glucose PD after a single intranasal (IN) administration of nasal glucagon to dogs using the single-use nasal dosing

device and comparing this PK/PD response with the PK/PD response of subcutaneous injected recombinant human glucagon. Overall, the PK and PD of intranasally administered nasal glucagon and SC glucagon were comparable with both demonstrating rapid absorption and elevation in serum glucose concentration. Safety pharmacology studies of nasal glucagon and DPC did not raise concerns for alterations in cardiovascular, respiratory, or CNS function. In the toxicology program of nasal glucagon, no adverse effects of nasal glucagon were noted in any of the in-life observations, and no systemic target organ toxicity was identified in rats and dogs at glucagon serum exposures up to 1748x and 11611x the human AUC, respectively, following a therapeutic dose of nasal glucagon. No systemic target organ toxicity was associated with a dose multiple of ≥26x for β-CD and an AUC-based exposure multiple of ≥16x for DPC in the 28-day toxicology studies. Reversible inflammation of olfactory epithelial lamina propria and erosion/ulceration of the olfactory epithelia in rats and atrophy/degeneration of the olfactory epithelia in dogs were produced by nasal glucagon primarily due to synthetic glucagon. When the nasal glucagon dosing regimen in dogs was limited to a single 20-mg dose of nasal glucagon drug product local nasal changes were limited to minimal inflammation, but no atrophy/degeneration of the olfactory epithelia was observed suggesting the local nasal changes in the olfactory epithelia were a cumulative effect. DPC and β-CD produced minimal local nasal irritation. Furthermore, DPC did not produce genotoxicity, reproductive toxicity, or developmental toxicity.

The applicant argues that the local irritation observed in non-clinical studies is unlikely to be a clinically meaningful issue in humans because the nasal irritation appeared to be a cumulative effect following 28 days of dosing in animals, which differs from single dose treatment of severe hypoglycemia in humans. Additionally, the applicant states that the local irritation in animals was mild, and fully reversible.

Please see Pharmacology and Toxicology review by Dr Dongyu Guo for details.

4.5. Clinical Pharmacology

The aim of the NG clinical pharmacology program was to assess the safety, tolerability, PK, and PD of NG, and thereby identify a dose of NG that produces a rapid and near maximal glucose response that is well tolerated both in adult and pediatric patients. The studies that collected clinical pharmacology parameters are summarized in Table 3 below.

Table 3 Index of Clinical Studies of Nasal Glucagon with PK and PD Results

Brief Description of Study	Trial Alias
Dose Selection Studies	
Single dose (0.5, 1, 2 mg NG; 1 mg SCG) in healthy adult subjects	IGBD
Single dose (1, 2, 3 mg NG; 1 mg SCG) in adult T1D	IGBA
Single (3 mg NG) and double dose (6 mg NG) in adult T1D and T2D	IGBG
Single dose (2, 3 mg NG; 0.5/1 mg IMG) in pediatric T1D	IGBB
Dose Confirmation Studies	
Single dose (3 mg NG; 1 mg IMG) in adult T1D and T2D	IGBC
Single dose (3 mg NG; 1 mg IMG) clinical bridging and confirmatory study in adult T1D	IGBI
Supportive Studies Providing Other PK/PD Information	
Single dose (3 mg NG) in otherwise healthy adult subjects with common cold symptoms	IGBE

Abbreviations: IMG = intramuscular glucagon; NG = nasal glucagon; PD = pharmacodynamic; PK = pharmacokinetic; SCG = subcutaneous glucagon; T1D = type 1 diabetes; T2D = type 2 diabetes.

Source: Table 2.7.2.1 Clinical Pharmacology Summary

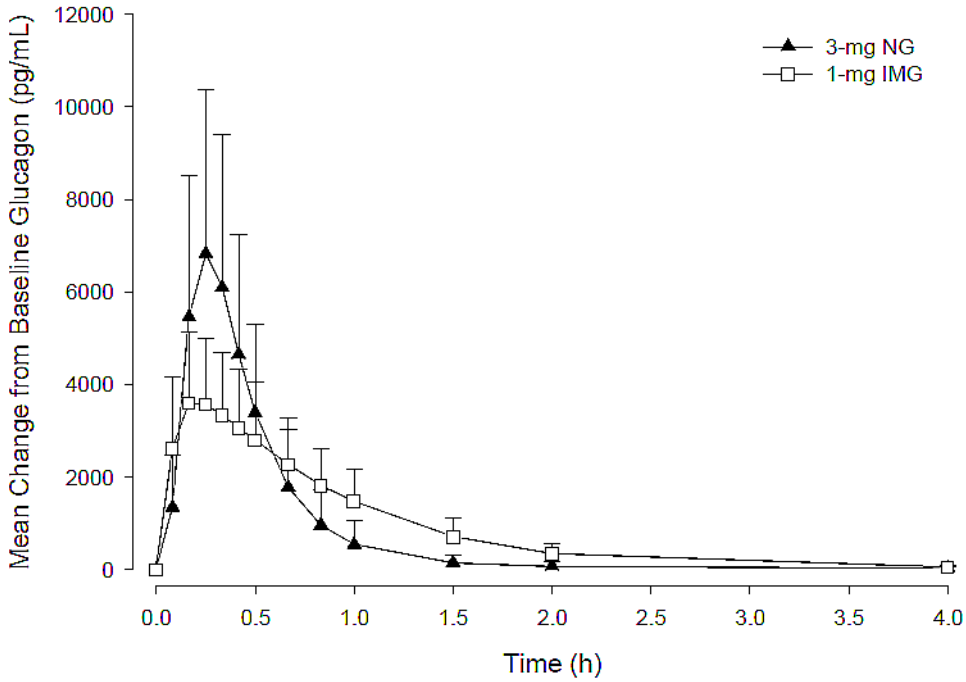
Six clinical studies informed the dose selection, and investigated doses ranging from 0.5 mg to 6 mg.

The applicant states that the 3 mg dose was determined to be the appropriate dose and is proposed for registration, based on the clinical observations and dose-response relationship.

PK and PD Characterization

Th PK and PD parameters of the NG were variable throughout the clinical development, potentially related to the changes in the drug product pertaining to particle size of the glucagon powder, as well as delivery device. Study IGBI was designed as a bridging study and is the only study that was performed using a to-be-marketed formulation of the NG drug product. The dose studied in study IGBI was 3 mg NG, which is the dose proposed for marketing. Glucagon was rapidly absorbed following NG administration, and achieved a geometric mean maximum concentration (Cmax) of 6130 pg/ml, which was observed at about 15 minutes after dosing. Area under the concentration-time curve (AUC[0-tlast]) was 2740 pgxh/ml.

Figure 2 Mean Change in Glucagon Concentration Over Time – Study IGBI

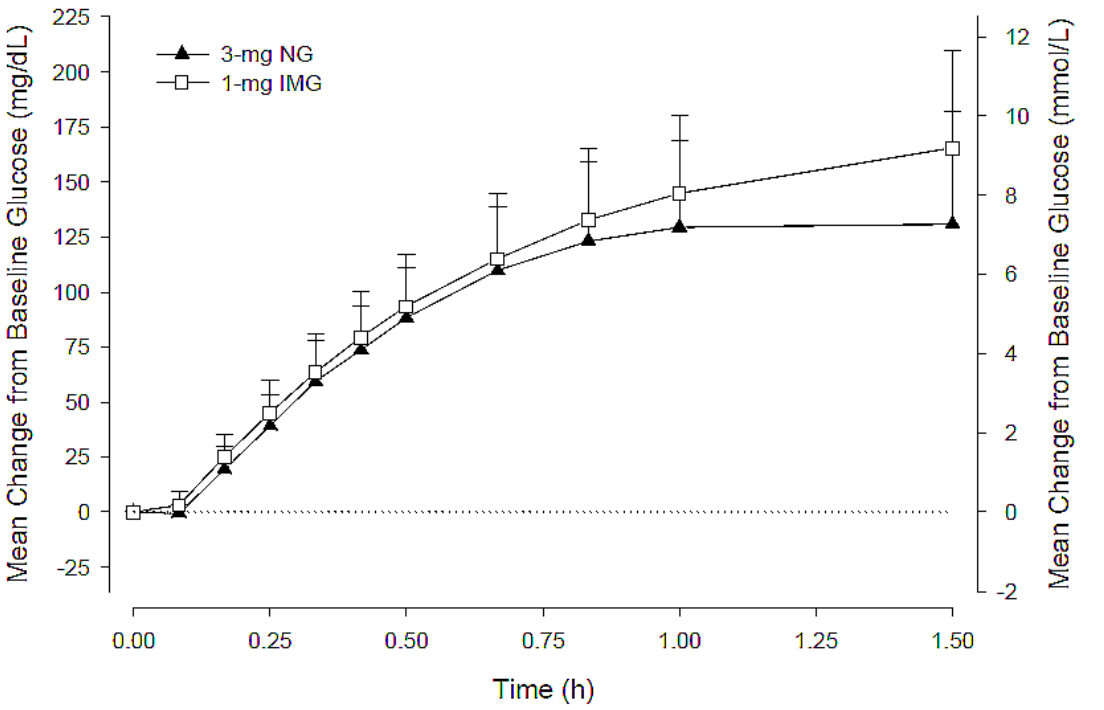


Abbreviations: IMG = intramuscular glucagon; NG = nasal glucagon; SD = standard deviation.

Source: Figure 2.7.2.18 Clinical Pharmacology Summary

NG 3 mg administration resulted in an increase in blood glucose, with ΔBGmax of 132 mg/dL.

Figure 3 Mean Change in Glucose Concentration Over Time – Study IGBI



Abbreviations: IMG = intramuscular glucagon; NG = nasal glucagon; SD = standard deviation.

Source: Figure 2.7.2.19 Clinical Pharmacology Summary

NG/IMG Comparison: Maximum glucagon concentrations were attained by 15 minutes post-dose with both NG and IMG routes of administration. While NG had a higher Cmax compared to IMG (6130 pg/mL vs. 3750 pg/mL), it had a lower AUC(0-tlast) (2740 pgxhour/mL vs. 3320 pgxhour/mL) and appeared to be cleared faster. There was no apparent delay in initiation of glucagon absorption following NG administration, relative to IMG. Glucose responses of NG 3 mg and IMG 1 mg were similar for the first 40 minutes post-dose. While a continuous increase of blood glucose up to 1.5 hours was observed for IMG 1 mg, a plateau was reached for NG 3 mg by 60 minutes

Figure 4 Summary of PK and PD Parameters – Study IGBI

	Change from Baseline Glucagon (PK) Parameters			Glucose (PD) Parameters		
Treatment (N_{PK}/N_{PD})	C_{max}[a] (pg/mL)	AUC(0-t_{last})[a] (pg.h/mL)	T_{max}[a] (hours)	BG_{max}[a] (mg/dL)	ΔBG_{max}[a] (mg/dL)	T_{BGmax}[a] (hours)
3 mg NG (63/68)	6130 [74]	2740 [68]	0.25 (0.17, 0.50)	192 [24]	132 [36]	1.00 (0.42, 1.50)
1 mg IMG (65/69)	3750 [44]	3320 [40]	0.25 (0.08, 0.50)	220 [20]	161 [29]	1.50 (0.83, 1.50)

Abbreviations: AUC(0-t_{last}) = area under the concentration curve from time 0 to the last quantifiable concentration (C_{last}); BG_{max} = maximum observed blood glucose concentration; ΔBG_{max} = maximum change from baseline blood glucose concentration; C_{max} = maximum observed concentration; NG = nasal glucagon; N_{PD} = number of subjects in the PD analysis; N_{PK} = number of subjects in the PK analysis; PD = pharmacodynamics; PK = pharmacokinetics; T_{BGmax} = time to maximum drug concentration; T_{max} = time to maximum drug concentration.

[a] Geometric mean [% coefficient of variation] is presented for C_{max}, BG_{max}, ΔBG_{max}, and AUC(0-t_{last}). Median (minimum, maximum) is presented for T_{max} and T_{BGmax}.

Source: Table 2.7.2.8 Clinical Pharmacology Summary

The drug products used during the clinical development were at times different in terms of PK parameters, likely due to particle size distribution. All the above data is presented for the to-be-marketed drug product used in study IGBI. While the glucagon maximum concentration (Cmax) was higher for NG 3 mg compared to IMG 1 mg in Study IGBI as shown in the above table, a lower glucagon Cmax was observed for NG 3 mg compared to IMG 1 mg in Study IGBC, and other studies that did not use the to-be-marketed drug product.

Table 4 Summary of Cmax Ratio and AUC Ratio between NG and IMG

STUDY	N	C_{max} Ratio (90% CI)	AUC(0-t_{last}) Ratio (90% CI)
IGBC (NG_CT/IMG)	80	0.783 (0.644, 0.951)	0.691 (0.589, 0.812)
IGBI (NG_Commercial/IMG)	68	1.560 (1.33, 1.82)	0.804 (0.689, 0.938)

Abbreviations: AUC(0-tlast) = area under the concentration-time curve from time 0 to last quantifiable concentration (Clast); CI = confidence interval; Cmax = maximum observed concentration; commercial = commercial drug product; CT = clinical trial drug product; IMG = intramuscular glucagon; NG = nasal glucagon.

Source: Table 2.7.2.10 Summary of Clinical Pharmacology

The applicant concluded that the AUCs of the NG 3 mg for the two studies were comparable because the 90% CIs overlapped. The Cmax of NG 3 mg in Study IGBI was 56% higher than IMG 1 mg and 22% lower than IMG 1 mg in Study IGBC. The 90% CIs of the Cmax ratio (NG/IMG) for the 2 studies do not overlap, indicating that NG 3 mg commercial drug product produced a higher Cmax than NG 3 mg clinical trial drug product. This did not appear to impact the efficacy or safety of the drug product.

Please see Clinical Pharmacology review by Dr Sury Sista for details.

4.6. Devices and Companion Diagnostic Issues

The primary container closure for nasal glucagon is a (b) (4) A diagram of the primary container closure is provided below.

Figure 5 Primary Container Closure

(b) (4)

Source: Figure 3.2.P.7.1.1-1 Container Closure Document

In addition to the primary container closure, the nasal glucagon delivery device consists of (b) (4)

Figure 6 Nasal Glucagon Delivery Device

Source: Figure 3.2.P.7.1.2-1 Container Closure Document

Both the primary container closure and the delivery device were modified throughout the development program. The changes that occurred during development are outlined in Table 5 below.

Table 5 Delivery Device Change Summary

(b) (4)

Source: Table 3.2.P.2.4-2 Container Closure System Document

The only phase 3 study where the final version of the device was used was IGBI.

The Center for Devices and Radiological Health (CDRH) review recommended the following:

Device Constituents Parts of the Combination Product are Approvable with a (b) (4) month

shelf life. If the sponsor would like to extend the shelf life to (b) (4) month, as originally proposed, we recommend that they submit a shelf-life extension protocol to propose the device performance testing that would be needed to extend the shelf life as a part of a supplement.

For review issues regarding the device, please see CDRH review by Dr Matthew Ondeck.

4.7. Consumer Study Reviews

Human factors studies conducted to evaluate the usability of the device were reviewed by Dr. Ariane Conrad from the Division of Medication Error Prevention and Analysis (DMEPA). The initial human factors study did not adequately demonstrate the device usability, and further changes to the container and device label were requested, as well as a repeat human factors study with the new labels. This study is ongoing at the time of this review. Please see review by Dr Ariane Conrad for details.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

NG was evaluated in 11 clinical studies, 9 in adults, and 2 in children. All clinical studies in the NG development program are summarized below.

Table 6 Listing of Clinical Trials

Study Identifier	Type of Study	Study Objective	Study Design	Dose	Patients Enrolled/Completed	Patient population
Adults						
Phase 3						
IGBI	Efficacy and Safety	NG vs marketed injectable glucagon	Multicenter, randomized, open label, cross-over	NG: 3 mg CG: 1 mg	70/69	Adults with T1DM
IGBC	Efficacy and Safety	NG vs marketed injectable glucagon	Multicenter, randomized, open label, cross-over	NG: 3 mg CG: 1 mg	83/82	Adults with T1DM or T2DM
B002	Real use, uncontrolled	Effectiveness of NG in real world setting	Multicenter, open-label, actual-use	NG: 3 mg	129/101	Adults with T1DM
Dose finding						
IGBA	PK and PD	NG vs marketed injectable glucagon	Single-center, randomized, open label, cross-over	NG: 1, 2, and 3 mg CG: 1 mg	18/18	Adults with T1DM
Other						
IGBD	PK and PD	NG vs marketed injectable glucagon	Single-center, randomized, open label, cross-over	NG: 0.5, 1, and 2 mg CG: 1 mg	16/13	HV
IGBE	PK and PD	Evaluate effects of common cold and nasal decongestant on NG	Single-center, open label, parallel	NG: 3 mg NG: 3 mg with nasal decongestant	36/35	Adults with upper respiratory infection, no diabetes
IGBF	Immunogenicity	NG vs marketed injectable glucagon	Single-center, randomized, open label, parallel	NG: 3 mg CG: 1 mg	75/73	Adults with T1DM or T2DM
IGBG	PK and PD	Single vs repeated administration of NG	Single-center, randomized, open label, cross-over	NG: 3, and 6 mg (repeated dose of 3 mg)	32/25	Adults with T1DM or T2DM

IGBH	PK and PD	Single vs repeated administration of NG	Single-center, randomized, open label, cross-over	NG: 3, and 6 mg (repeated dose of 3 mg)	12/0[a]	Adults with T1DM or T2DM
Pediatrics						
IGBB	PK and PD Efficacy and Safety	NG vs marketed injectable glucagon	Multicenter, randomized, cross-over	NG: 2, and 3 mg CG: 0.5, and 1 mg (weight based)	48/47	Pediatric patients with T1D
B001	Real use, uncontrolled	Effectiveness of NG in real world setting	Multicenter, open-label, actual-use	NG: 3 mg	26/12	Pediatric patients with T1D

Abbreviations: CG = control glucagon; NG = nasal glucagon; PK = pharmacokinetic; PD = pharmacodynamic; T1D = type 1 diabetes mellitus; T2D = type 2 diabetes mellitus.

[a] Study IGBH was terminated early due to potential sub-target dosing and was repeated under a new trial alias, Study IGBG.

5.2. Review Strategy

Four adult studies, including the dose finding study, and two pediatric studies were included in the analysis of efficacy by the applicant. My efficacy analysis will not include the dose finding study, instead, focusing on the two adult, and one pediatric efficacy studies, as well as the two real use studies. Since the to-be-marketed drug product was only used in study IGBI, I considered IGBI to be the pivotal study and IGBC to be supportive. The efficacy for the 2 mg dose as studied in the dose finding study IGBA, and study IGBB will be briefly reviewed in section 7.1.4 Dose and Dose-Response.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. IGBI

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

6.1.1. Study Design

Overview and Objective

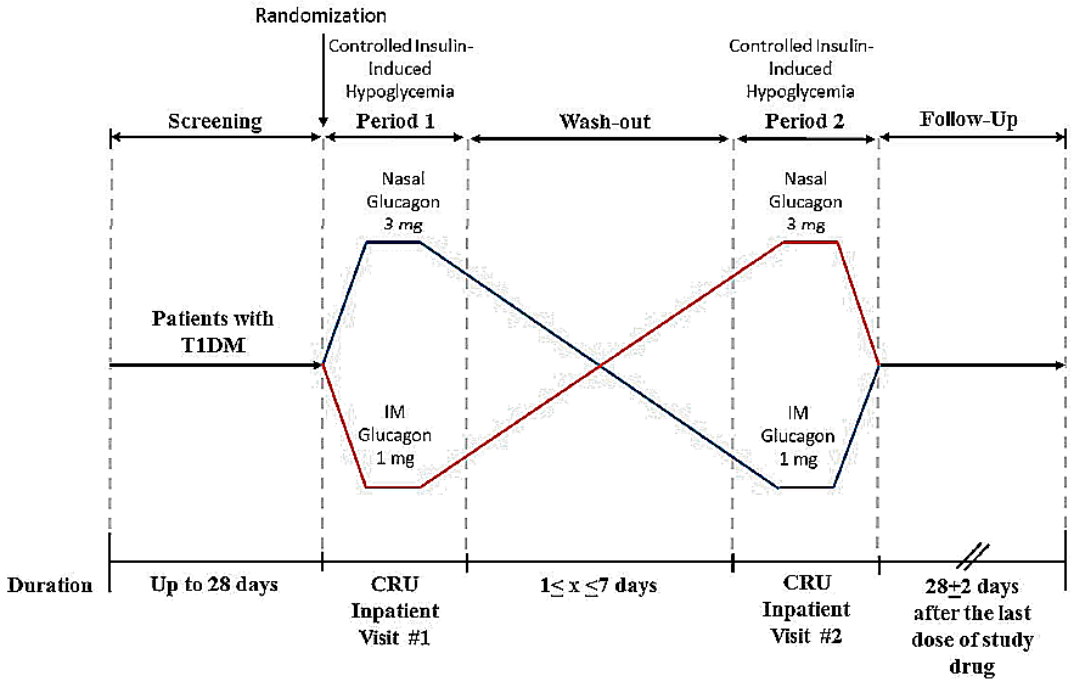
This study was the only study conducted with the to-be-marketed glucagon formulation. It was designed as an efficacy bridge between the to-be-marketed NG and the currently marketed Glucagen (control glucagon - CG). The primary objective was to compare NG vs CG in the percentage of adult patients with T1DM who achieve treatment success during controlled insulin-induced hypoglycemia.

Secondary objectives were to assess the safety and tolerability, and to characterize the PK and PD profile of NG vs CG.

Trial Design

Study IGBI was a multicenter, randomized, open-label, 2-treatment, 2-period, single-dose crossover study in patients with T1DM.

Figure 7 Study Design for Study IGBI



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

Source: Figure IGBI.5.1 CSR

Although this was an open-label study, the patients' treatment assignments were not shared with the site staff responsible for evaluating the treatment response, and that included deciding whether additional measures to raise the patient's plasma glucose (PG) concentration were necessary after glucagon dosing. A study investigator or qualified designee was at bedside for clinical assessment of patients during induction of hypoglycemia and for at least 90 minutes following glucagon administration.

Inclusion/Exclusion Criteria

Inclusion criteria included:

- Patients with T1DM aged 18-64, HbA1C ≤10%, insulin dose ≤1.5 units/kg, no severe hypoglycemia in the 1 month prior to enrollment, no history of epilepsy or seizure disorder, and did not use beta-blockers, indomethacin, warfarin, or anti-cholinergic drugs on a daily basis.

Exclusion criteria included: patients on above-listed medications, history of insulinoma, or history of epilepsy or seizure disorder.

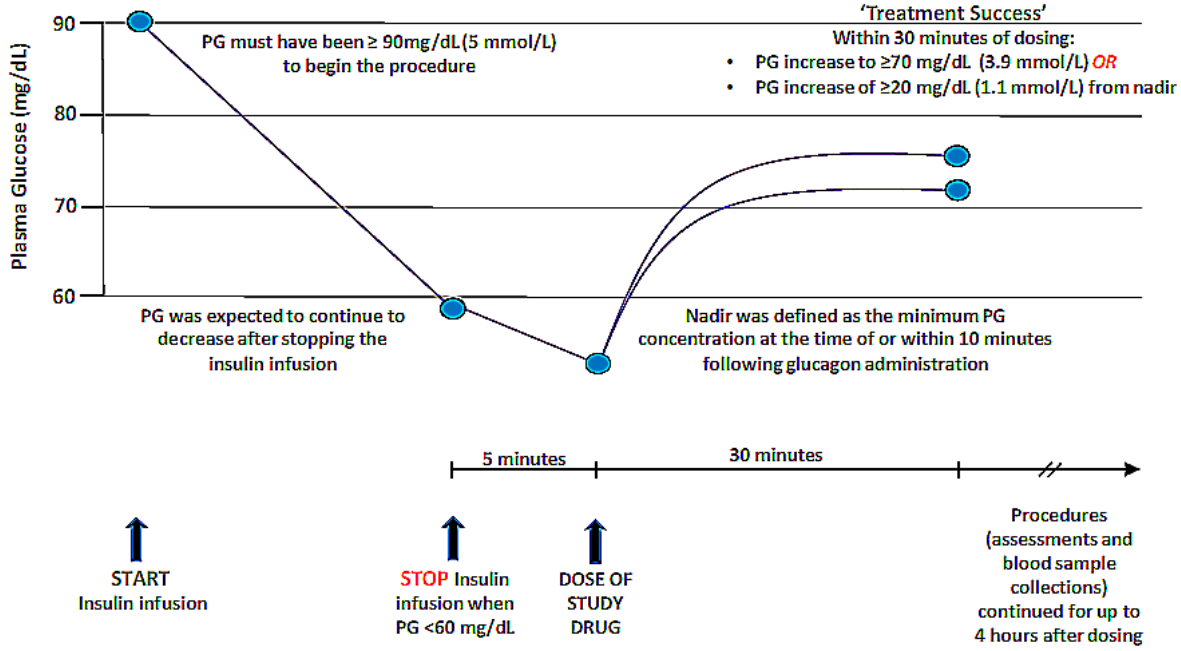
Please see study protocol for full inclusion and exclusion criteria.

Study procedures

Insulin-induced hypoglycemia

Testing was preceded by an 8 hour fast, and glucose had to be at least 90 mg/dL to begin the hypoglycemia procedures. To begin the procedure, 15 units of Humalog were diluted in saline to 0.3 U/mL and infused at a variable rate to lower PG concentrations to <60 mg/dL in a controlled manner. Once the PG concentration was <60 mg/dL, the insulin infusion was stopped. Study drug was administered approximately 5 minutes after the insulin infusion was stopped.

Figure 8 Insulin-Induced Hypoglycemia Protocol Schematic Representation Study IGBI



Abbreviation: PG = plasma glucose.
NOTE: This diagram is for descriptive purposes only; not based on actual data.

Source: Figure IGBI.5.2 CSR

Procedures for administering glucagon

- NG was administered with the patient lying in a fully reclined lateral position on the opposite side of the nostril being administered.

- IM glucagon was administered in the deltoid muscle of the participant's non-dominant

arm, with the participant lying in a fully reclined lateral position on the opposite side of the arm being administered.

Study assessments

Glucose was measured both at bedside and by laboratory pre-dose, and at 5, 10, 15, 20, 25, 30, 40, 50, 60, and 90 minutes post-dose.

Glucagon was measured pre-dose, and at 5, 10, 15, 20, 25, 30, 40, 50, 60, 90, 120, and 240 minutes post dose.

The patients-reported hypoglycemia symptoms during the induction of hypoglycemia, and after glucagon administration, were assessed using the Edinburgh Hypoglycemia Scale.

Nasal and ocular symptoms were assessed using the Nasal and Non-Nasal Questionnaire at baseline and various post-dosing timepoints.

The patients remained in the clinical research unit until 6 hours post-dosing.

Treatments

Nasal glucagon: supplied as (b) (4) powder contained within the nasal delivery device, single 3 mg dose

GlucaGen: supplied as GlucaGen HypoKit, single 1 mg dose

Study Endpoints

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

Secondary endpoints included summary of AEs, nasal and non-nasal symptoms, vital signs, various PK and PD parameters.

Statistical Analysis Plan

Five different populations were defined for analyses.

- All Entered Set (AES): all patients who signed consent and entered the study
- All Randomized set (ARS) patients randomized and enrolled into the study

- Full Analysis set (FAS): randomized patients that received at least one dose of study drug
- Efficacy Analysis Set (EAS)Patients who completed both treatment visits with evaluable data
- PK/PD Population: Patients in the FAS with evaluable PK/PD data

Of these, the EAS was used for the primary efficacy analyses.

A sample size of 66 patients completing both treatments was required to achieve the primary objective with 90% power using the following assumptions:
- Treatment success rate of 98% for both treatments
- Non-inferiority margin of 10%
- 2-sided alpha level of 0.05
- A within-patient correlation of zero between 2 treatment visits

Assuming a 5% dropout rate, the study planned to enroll 70 patients.

The non-inferiority margin of 10% was based upon data from a simulated emergency study in which 10% of the participants (parents of children and adolescents with T1DM) failed entirely to administer injectable glucagon (Harris et al. 2001).

Patients who had at least one treatment visit in which the BG nadir was ≥70 mg/dL were considered non-evaluable, and data was excluded from the primary efficacy analysis.

If a central laboratory measurement was missing, then the bedside glucose measurement from that time point was used.

Protocol Amendments

The original protocol was created on May 8, 2017. There were 2 protocol amendments, both made relatively minor changes.

Protocol amendment 1 was dated August 16, 2017.
- Removed area under the effect concentration-time curve from the exploratory PD parameters
- Made clarifications regarding blood sampling during and after study treatment

Protocol amendment 2 was dated October 12, 2017.
- Excluded patients with stable psychiatric disease
- Clarified that patients in CRU should have continuous venous access
- Clarified that AEs should be followed until restoration or until a stable condition has been achieved, and that follow-up should not be interrupted, even if there is a reasonable explanation for the event.

6.1.2. Study Results

Compliance with Good Clinical Practices

The applicant states that the study was conducted according to Good Clinical Practices guidelines.

Financial Disclosure

See section 13.2 for details.

Patient Disposition

A total of 70 patients entered the study, and 69 completed both study periods. One patient, a 24 year old female, was discontinued from the study due to an adverse event (vomiting) following administration of 3 mg NG in period 1, and did not wish to return for period 2. The applicant stated that this patient was evaluated at a follow-up visit 27 days post-dose, and did not report any adverse events at that time.

Protocol Violations/Deviations

The applicant reported only one important protocol deviation that was reported due to missing PK and PD samples at pre-dose in Period 1 for one patient. These samples were not collected due to cannula problems. This deviation resulted in this patient being excluded from the PK analysis, and the safety PD sample was used to impute the missing PD sample for analysis related to the primary efficacy outcome.

Demographic Characteristics

Patient demographics and baseline characteristics, including diabetes history are presented in Table 7 below. All 70 patients had T1DM, with a mean duration of 19.8 years. The mean age of the study participants was 41.7 years, and the mean HbA1c was 7.34%. All participants were white, and 61.4% were male.

Table 7 Table of Demographic Characteristics Study IGBI

Number of patients studied		70
Age (years)	Mean (SD)	41.7 (12.7)
	Median	41.0
	Minimum - Maximum	20 - 64
Sex	Male	43 (61.4%)
	Female	27 (38.6%)
Ethnicity	Hispanic or Latino	0 (0%)
	Not Hispanic or Latino	70 (100%)
Race	White	70 (100%)
Weight (kg)	Mean (SD)	78.79 (13.28)
	Median	78.65
	Minimum - Maximum	52.8 – 114.4
Height (cm)	Mean (SD)	175.21 (8.43)
	Median	175.0
	Minimum - Maximum	154.0 – 192.0
Body mass index (kg/m^2)	Mean (SD)	25.53 (2.97)
	Median	25.40
	Minimum - Maximum	19.6 – 34.5
Duration of diabetes (years)	Mean (SD)	19.8 (10.6)
	Median	20.0
	Minimum - Maximum	3 - 43
Baseline HbA1c (%)	Mean (SD)	7.34 (0.87)
	Median	7.35
	Minimum - Maximum	5.5 – 9.7
Baseline Clarke Hypoglycemia Awareness status	Aware	51 (72.9%)
	Intermediate	8 (11.4%)
	Reduced	11 (15.7%)

Source: Excerpted from Table IGBI.6.1 CSR

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The study treatment was administered in the clinic, and compliance was expected to be 100%. Oral or parenteral carbohydrates could to be administered as needed per the study investigator.

Efficacy Results – Primary Endpoint

Three patients were excluded from the primary efficacy analysis because they had nadir glucose above 70 mg/dL in one treatment visit. As a result, the primary efficacy analysis included only 66 patients. All of these 66 patients (100%) in both NG and CG treatment groups achieved the primary endpoint as defined in the protocol.

The 4 patients not included in the primary analysis had efficacy results as follows:

- Patient (b) (6) withdrew after receiving one dose of NG due to vomiting. Nadir glucose was 61 mg/dL, increased to >70 mg/dL at 10 minutes, and increased by 20 mg/dL at 15 minutes.

- Patient (b) (6)
  - CG: nadir glucose 59 mg/dL, >70 mg/dL at 10 minutes, increase by >20 mg/dL at 15 minutes
  - NG: nadir glucose 72 mg/dL

- Patient (b) (6)
  - CG: nadir 54 mg/dL, >70 mg/dL, and increase by 20 mg/dL at 10 minutes
  - NG: nadir glucose 74

- Patient (b) (6)
  - CG: nadir 72 mg/dL
  - NG: nadir 59 mg/dL, >70 mg/dL, and increase by 20 mg/dL at 10 minutes

In summary, all patients who received either NG or CG, met the study definition of treatment success for the treatment visit where BG was below 70 mg/dL at baseline.

Data Quality and Integrity

I did not identify any issues regarding data quality and integrity.

Efficacy Results – Secondary and other relevant endpoints

Plasma glucose

Plasma glucose was measured at baseline, and at set intervals up to 90 minutes post-dose. The comparison of absolute glucose values between treatments is presented in the Table 8 below for each timepoint. No significant differences are observed between the treatment group up to 40 minutes post-dose. While the LS mean glucose was statistically significantly different for the 50, 60, and 90 minutes timepoints, it is unlikely that this difference is clinically relevant as the mean BG was above 150 mg/dL for both treatment groups for these timepoints.

Table 8 Statistical Analysis of Central Laboratory Plasma Glucose (mg/dL) FAS – Study IGBI

Time Point	Treatment	N	LS Mean (SE)	Difference of LS Means (95% CI) (3 mg Nasal Glucagon – 1 mg GlucaGen®)	Between Treatment p-value
Absolute Values					
Baseline	1 mg GlucaGen®	69	56.75 (3.34)	3.18 (-2.64, 9.00)	0.2817
	3 mg Nasal Glucagon	68	59.93 (3.36)		
5 minutes postdose	1 mg GlucaGen®	68	60.20 (3.40)	-0.82 (-6.93, 5.29)	0.7911
	3 mg Nasal Glucagon	66	59.38 (3.42)		
10 minutes postdose	1 mg GlucaGen®	69	82.48 (3.43)	-3.70 (-9.98, 2.59)	0.2473
	3 mg Nasal Glucagon	68	78.78 (3.45)		
15 minutes postdose	1 mg GlucaGen®	69	102.18 (3.46)	-4.18 (-10.59, 2.23)	0.1997
	3 mg Nasal Glucagon	68	98.00 (3.47)		
20 minutes postdose	1 mg GlucaGen®	69	120.20 (3.48)	-2.27 (-8.74, 4.20)	0.4895
	3 mg Nasal Glucagon	68	117.93 (3.49)		
25 minutes postdose	1 mg GlucaGen®	69	136.78 (3.51)	-4.85 (-11.45, 1.75)	0.1491
	3 mg Nasal Glucagon	67	131.93 (3.53)		
30 minutes postdose	1 mg GlucaGen®	69	151.22 (3.48)	-4.04 (-10.50, 2.43)	0.2199
	3 mg Nasal Glucagon	68	147.19 (3.49)		
40 minutes postdose	1 mg GlucaGen®	69	172.17 (3.46)	-4.27 (-10.68, 2.14)	0.1908
	3 mg Nasal Glucagon	67	167.91 (3.48)		
50 minutes postdose	1 mg GlucaGen®	69	189.65 (3.44)	-8.08 (-14.36, -1.80)	0.0120
	3 mg Nasal Glucagon	68	181.57 (3.45)		
60 minutes postdose	1 mg GlucaGen®	69	201.59 (3.41)	-13.81 (-19.90, -7.71)	<0.0001
	3 mg Nasal Glucagon	68	187.79 (3.41)		
90 minutes postdose	1 mg GlucaGen®	69	222.70 (3.36)	-32.65 (-38.46, -26.83)	<0.0001
	3 mg Nasal Glucagon	68	190.06 (3.36)		

Model: Result = baseline + patient + treatment + timepoint + period + treatment*timepoint + random error
Baseline = last non-missing value collected prior to glucagon administration at each treatment visit
Patients with missing baseline were excluded from the analysis
A repeated statement with a toeplitz covariance structure was used

Source: Table IGBI.7.4 CSR

The mean change from baseline in plasma glucose is presented in the Table 9 below.

Table 9 Statistical Analysis of Central Laboratory Plasma Glucose (mg/dL) FAS– Change from Baseline- Study IGBI

Time Point	Treatment	N	LS Mean (SE) [p-value]	Difference of LS Means (95% CI) (3 mg Nasal Glucagon – 1 mg GlucaGen®)	Between Treatment p-value
Change from Baseline Values					
5 minutes postdose	1 mg GlucaGen®	68	2.39 (3.54) [0.5009]	-0.43 (-6.36, 5.49)	0.8852
	3 mg Nasal Glucagon	66	1.96 (3.57) [0.5841]		
10 minutes postdose	1 mg GlucaGen®	69	25.13 (3.59) [<0.0001]	-3.32 (-9.48, 2.85)	0.2899
	3 mg Nasal Glucagon	68	21.81 (3.60) [<0.0001]		
15 minutes postdose	1 mg GlucaGen®	69	45.14 (3.61) [<0.0001]	-3.95 (-10.25, 2.35)	0.2182
	3 mg Nasal Glucagon	68	41.19 (3.63) [<0.0001]		
20 minutes postdose	1 mg GlucaGen®	69	63.38 (3.65) [<0.0001]	-2.15 (-8.61, 4.30)	0.5115
	3 mg Nasal Glucagon	68	61.23 (3.66) [<0.0001]		
25 minutes postdose	1 mg GlucaGen®	69	79.50 (3.67) [<0.0001]	-4.60 (-11.17, 1.96)	0.1684
	3 mg Nasal Glucagon	67	74.90 (3.69) [<0.0001]		
30 minutes postdose	1 mg GlucaGen®	69	93.77 (3.67) [<0.0001]	-3.95 (-10.51, 2.61)	0.2361
	3 mg Nasal Glucagon	68	89.82 (3.69) [<0.0001]		
40 minutes postdose	1 mg GlucaGen®	69	114.88 (3.65) [<0.0001]	-4.16 (-10.63, 2.30)	0.2059
	3 mg Nasal Glucagon	67	110.71 (3.66) [<0.0001]		
50 minutes postdose	1 mg GlucaGen®	69	132.44 (3.62) [<0.0001]	-8.01 (-14.31, -1.71)	0.0130
	3 mg Nasal Glucagon	68	124.44 (3.63) [<0.0001]		
60 minutes postdose	1 mg GlucaGen®	69	144.72 (3.60) [<0.0001]	-13.72 (-19.89, -7.55)	<0.0001
	3 mg Nasal Glucagon	68	131.00 (3.60) [<0.0001]		
90 minutes postdose	1 mg GlucaGen®	69	165.81 (3.55) [<0.0001]	-32.76 (-38.67, -26.84)	<0.0001
	3 mg Nasal Glucagon	68	133.05 (3.56) [<0.0001]		

Abbreviations: CI = confidence interval; FAS = full analysis set (randomized patients who received at least 1 dose of study drug); LS = least squares; N = number of patients; SE = standard error

Model:Change from baseline = baseline + patient + treatment + timepoint + period + treatment*timepoint + random error

Baseline = last non-missing value collected prior to glucagon administration at each treatment visit

A repeated statement with a toeplitz covariance structure was used

Least squares means p-values are calculated based on the null hypotheses: LSmean = 0

Source: Table IGBI.7.4 CSR

Dose/Dose Response

Not applicable as only one dose of intranasal glucagon was studied.

Durability of Response

Not applicable

Persistence of Effect

Not applicable.

Additional Analyses Conducted on the Individual Trial

Time to treatment success

The time to success was faster by approximately 1-2 minutes with CG when compared to NG as shown in Table 10 below, regardless of the glucose outcome used (increase by at least 20 mg/dL, glucose ≥70 mg/dL, or both).

Table 10 Time to Treatment Success – Study IGBI

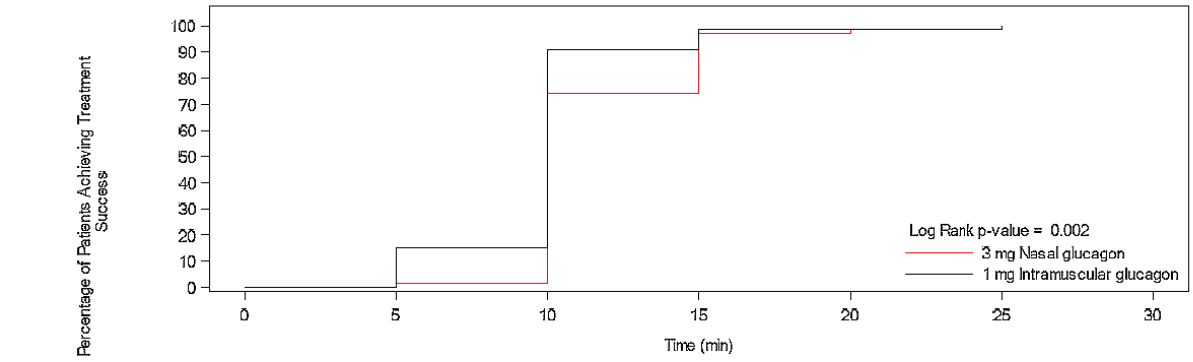
PG Response	Treatment N=66	Mean [SD] Time to Response (minutes)
Treatment Success: Increase to ≥70 mg/dL ***OR*** increase of ≥20 mg/dL within 30 minutes of dosing	3 mg Nasal Glucagon	11.44 [3.01]
	1 mg GlucaGen®	9.85 [3.03]
Increase to ≥70 mg/dL within 30 min of dosing	3 mg Nasal Glucagon	11.59 [3.18]
	1 mg GlucaGen®	10.00 [3.51]
Increase of ≥20 mg/dL within 30 minutes of dosing	3 mg Nasal Glucagon	12.42 [3.19]
	1 mg GlucaGen®	11.21 [2.64]
Increase to ≥70 mg/dL ***AND*** increase of ≥20 mg/dL within 30 minutes of dosing[a]	3 mg Nasal Glucagon	12.58 [3.31]
	1 mg GlucaGen®	11.36 [3.11]

Abbreviations: PG = plasma glucose; SD = standard deviation

[a] If both criteria for treatment success were achieved (that is, PG increase to ≥70 mg/dL AND PG ≥20 mg/dL from nadir), then the earlier time point was used.

Source: Excerpted from Table IGBI.7.3 CSR

Figure 9 Kaplan-Meier Curve for the Time to Treatment Success (an Increase in PG to ≥70 mg/dL or a PG Increase of ≥20 mg/dL from Nadir) within 30 Minutes Following 3 mg NG and 1 mg CG Treatment in the EAS Population – Study IGBI



Cumulative no. of event no. of patients at risk

1 mg IM glucagon	0:66	10:56	60:6	65:1	65:1	66:0
3 mg nasal glucagon	0:66	1:65	49:17	64:2	65:1	66:0

Cox proportional hazard model p-value = <.001

Status of Program: Production
Program Location: /cvn/projects/prj/ecb/programs/000000154927/dev/figures/f_lsucckm.sas
Date/Time Report Produced: 09FEB2018 5:16

Abbreviations: EAS = efficacy analysis set (patients who completed both treatment visits with evaluable data); IM = intra-muscular; PG = plasma glucose.

Source: Figure IGBI.7.1 CSR

Regardless of the outcome used, there was a statistically significant difference between treatments in the time to achieve treatment success as defined in the study. At early time points, there was a higher proportion of patients in the 1 mg CG treatment group achieving treatment success. The difference between NG and CG was less than 2 minutes.

Reviewer comment: While the difference in time to success is clinically significant, especially in an emergency which is the type of situation where the NG product will be used if approved, the CG drug product needs to be reconstituted and then injected, which should conceivably add time to the time to success, and this was not accounted for in the study analyses.

Treatment success in different study populations

Secondary analyses evaluated treatment success for different study populations. The results are summarized in Table 11 below.

Table 11 Treatment Success in Different Study Populations – Study IGBI

PG Response	Treatment	N	n	%
EAS Population				
Increase to ≥70 mg/dL within 30 minutes of doing	1 mg GlucaGen®	66	66	100.0
	3 mg Nasal Glucagon	66	66	100.0
Increase of ≥20 mg/dL from nadir within 30 minutes of dosing	1 mg GlucaGen®	66	66	100.0
	3 mg Nasal Glucagon	66	66	100.0
Increase to ≥70 mg/dL ***AND*** increase of ≥20 mg/dL from nadir within 30 minutes of dosing	1 mg GlucaGen®	66	66	100.0
	3 mg Nasal Glucagon	66	66	100.0
EAS Population with Nadir <50 mg/dL in Both Periods				
Treatment Success: Increase to ≥70 mg/dL ***OR*** increase of ≥20 mg/dL from nadir within 30 minutes of dosing	1 mg GlucaGen®	3	3	100.0
	3 mg Nasal Glucagon	3	3	100.0
Increase to ≥70 mg/dL within 30 minutes of dosing	1 mg GlucaGen®	3	3	100.0
	3 mg Nasal Glucagon	3	3	100.0
Increase of ≥20 mg/dL from nadir within 30 minutes of dosing	1 mg GlucaGen®	3	3	100.0
	3 mg Nasal Glucagon	3	3	100.0
Increase to ≥70 mg/dL ***AND*** increase of ≥20 mg/dL from nadir within 30 minutes of dosing	1 mg GlucaGen®	3	3	100.0
	3 mg Nasal Glucagon	3	3	100.0
ARS Population				
Treatment Success: Increase to ≥70 mg/dL ***OR*** increase of ≥20 mg/dL from nadir within 30 minutes of dosing	1 mg GlucaGen®	69	69	100.0
	3 mg Nasal Glucagon	70	70	100.0
Increase to ≥70 mg/dL	1 mg GlucaGen®	68	68	100.0
	3 mg Nasal Glucagon	68	68	100.0
Increase of ≥20 mg/dL from nadir	1 mg GlucaGen®	69	69	100.0
	3 mg Nasal Glucagon	70	70	100.0
Increase to ≥70 mg/dL ***AND*** increase of ≥20 mg/dL from nadir	1 mg GlucaGen®	68	68	100.0
	3 mg Nasal Glucagon	68	68	100.0

Abbreviations: % = percent of patients; ARS = all randomized set (patients who were randomized to study treatment and enrolled into the study); EAS = efficacy analysis set (patients who completed both treatment visits with evaluable data); N= number of patients; n = number of successes; PG = plasma glucose.
Source Location: lillyce (\\statsclstr)\prd\ly900018\i8r_mc_igbi\csr1\output\shared\t_asucc2 and lillyce (\\statsclstr)\prd\ly900018\i8r_mc_igbi\csr1\output\shared\t_asucc3

Source: Table IGBI.7.2 CSR

As seen above, all patients in all treatment groups, and all study populations, achieved the outcome at the 30 minute timepoint as defined in the study protocol.

6.2. IGBC

6.2.1. Study Design

Study Title: Efficacy and Safety of Intranasal Glucagon for Treatment of Insulin Induced Hypoglycemia in Adults with Diabetes.

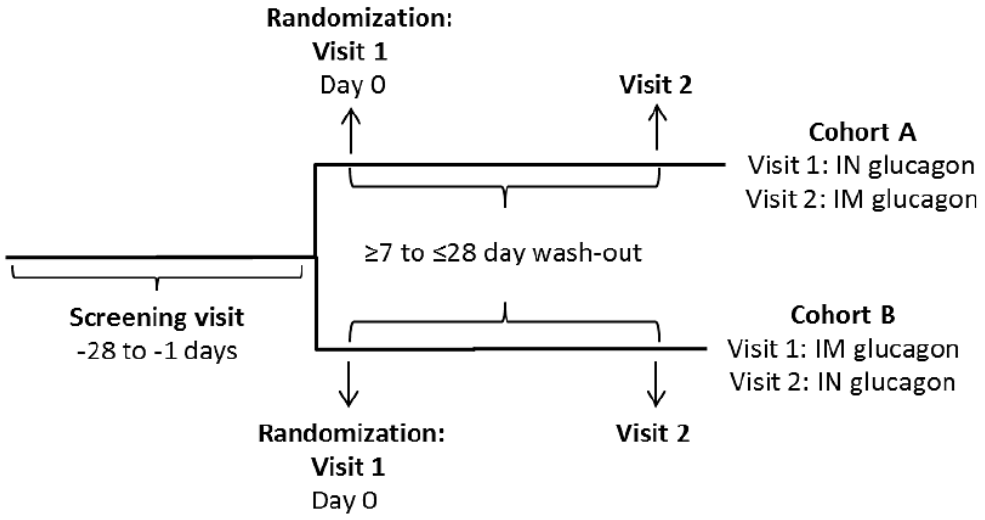
Overview and Objective

The main objective of this study was to assess the efficacy and safety of 3 mg glucagon administered intranasally in comparison with commercially-available intramuscular glucagon (CG) in reversing insulin-induced hypoglycemia in patients with T1 and T2DM. In addition, the PK and PD parameters of NG and CG were evaluated.

Trial Design

Phase III, multi-center, randomized, open-label, cross-over trial. The study design is presented below.

Figure 10 Study Design for Study IGBC



Source: Figure 9.1.1 IGBC CSR

The study design was similar to study IGBI. The investigational products were administered during two outpatient procedures (Study Visit 1 and Study Visit 2), performed at a clinical research center (CRC). Each study visit lasted about 6 hours, during which a single dose of glucagon was administered either intranasally or intramuscularly under fasting and insulin-induced hypoglycemia conditions. The study visits were separated by at least 7 calendar days, and a maximum of 28 calendar days.

Each glucagon dosing visit was conducted after an overnight fast of at least 8 hours with a starting blood glucose ≥90 mg/dL. For participants using an insulin pump, the continuous subcutaneous insulin infusion was suspended during the procedure. The participants using multiple daily injections of insulin took their last long-acting insulin dose the day before testing.

Study Procedures

Procedures prior to inducing hypoglycemia included:

- If glucose >300 mg/dL, ketones were checked, if moderate or greater, the visit was postponed
- Assessment for hypoglycemia since the screening visit
- Assessment for pregnancy
- If glucose <90 mg/dL, oral or intravenous (IV) glucose was given to raise glucose level to 90 mg/dL or above
- If glucose ≥200 mg/dL, 2-4 units of IV insulin were given
- Physical examination including nasal inspection
- Assessment of nasal symptoms (including rhinorrhea, nasal stuffiness/congestion, nasal itching, and sneezing) and non-nasal symptoms (itching/burning eyes, tearing/watering eyes, redness of eyes, and itching of ears or palate), individually graded using a 4-point scale (Nasal and Non-Nasal Questionnaire)
- Assessment of hypoglycemia symptoms using the Edinburgh Hypoglycemia Scale

Procedures for inducing hypoglycemia included:

- Hypoglycemia was induced by an IV infusion of regular insulin diluted in normal saline at a rate of 2 mU/kg/min. The infusion rate may have been adjusted as necessary up to a rate of 3 mU/kg/min to reach the target nadir glucose level of <50mg/dL. Once the plasma glucose level reached <90 mg/dL, the infusion rate may have been decreased at the investigator's discretion to 1.5 or 1.0 mU/kg/min.

- Plasma glucose levels were measured using a bedside rapid glucose analyzer (YSI or equivalent). During the insulin infusion to induce hypoglycemia, glucose levels were measured no more than 10 minutes apart while the glucose level was >100 mg/dL and no more than 5 minutes apart when the plasma glucose level was <100 mg/dL.

- Hypoglycemia symptoms were assessed using the Edinburgh Hypoglycemia Scale

- Once the plasma glucose level was <60 mg/dL, the insulin infusion was stopped and the Edinburgh Hypoglycemia Scale was repeated.

- A blood sample was collected for PK (glucagon), PD (glucose), and insulin 5 minutes after the insulin infusion was stopped (immediately prior to glucagon administration, T=0).

- If the plasma glucose level reached < 60 mg/dL after receiving insulin for at least 3

hours, the assigned glucagon for the visit was administered and all post-administration procedures described below were followed.

Procedures for administering glucagon

- NG was administered with the patient lying in a fully reclined lateral position on the opposite side of the nostril being administered.

- IM glucagon was administered in the deltoid muscle of the participant's non-dominant arm, with the participant lying in a fully reclined lateral position on the opposite side of the arm being administered.

Procedures following glucagon administration

- Plasma glucose (rapid glucose analyzer and blood sample), and glucagon concentration, were measured 5 minutes after the insulin infusion was stopped, immediately prior to glucagon administration (T=0), and 5, 10, 15, 20, 25, 30, 40, 50, 60, and 90 minutes following administration of glucagon. Blood samples for insulin were collected at 30 and 60 minutes.

- Nasal and non-nasal scores assessment at 15, 30, 60, and 90 minutes

- Hypoglycemia assessment using the Edinburgh Hypoglycemia Scale at 15, 30, 45, and 60 minutes

- Nasal or intramuscular administration site inspection at 90 minutes

- Vital signs measurement at 45 minutes

Procedures for insufficient response to glucagon administration

- If a participant's glucose level remained <55 mg/dL at 30 minutes or <60 mg/dL at 45 minutes following administration of the glucagon, oral carbohydrate or IV glucose were given

- If at anytime the glucose level was <40 mg/dL or the participant was experiencing severe symptoms of hypoglycemia, at investigator discretion, oral or IV glucose may have been given.

- If at any time symptoms suggestive of hypoglycemic seizure developed, IV glucose was given, and if unresolved, was followed by IV lorazepam or equivalent emergency benzodiazepine according to institutional policy.

If oral or IV glucose was given or additional glucagon was given, any remaining blood samples for the admission were still collected.

Clinic personnel contacted the participant by phone on the day following the CRC visit to discuss any side effects or other potential AEs that may have occurred.

Treatments

- Treatment 1 (reference product): Glucagon (GlucaGen, Novo Nordisk), 1 mL of 1mg/mL solution for injection
- Treatment 2 (test product): AMG 504-1, (b) (4) powder/intranasal, 3 mg glucagon (b) (4) mg AMG 504-1)

Primary outcome:

The primary outcome, same as in study IGBI, was success/failure, with success defined as an increase in blood glucose to ≥70 mg/dL or an increase of ≥20 mg/dL from nadir within 30 minutes after receiving study glucagon, without receiving additional actions to increase the blood glucose level such as intravenous glucose, additional glucagon, or exogenous carbohydrates.

Other Outcomes

- Time from treatment to return of blood glucose to ≥70 mg/dL or an increase of ≥20 mg/dL

- Safety and tolerability observations, including nausea/vomiting and nasal symptoms/signs

- Recovery from clinical symptoms of hypoglycemia if present as documented using the hypoglycemia symptoms questionnaire

Safety and tolerability were evaluated through assessment of adverse events, physical examination, nasal examination, standard laboratory evaluations, glycemia measurements, vital signs, ECG and nasal and non-nasal scores for patient clinical symptoms.

Inclusion/Exclusion Criteria

Male and female patients, of at least 18 years of age but not older than 65 years, with a clinical diagnosis of either T1DM receiving daily insulin since the time of diagnosis for at least 2 years or T2DM receiving multiple daily insulin doses for at least 2 years, with a BMI between 20-35 kg/m2, and weighing at least 110 lbs were included in the study.

Please see study protocol for full inclusion and exclusion criteria.

Statistical Analysis Plan

The non-inferiority of NG compared to CG in terms of treatment success was assessed using a non-inferiority margin of 10%, for the same reasons outlined in the statistical analysis plan for study IGBI.

Protocol Amendments

There was only one protocol amendment, dated September 27, 2013. The changes in this amendment were as follows:

- Increase in sample size from a total of 45 to a total of 82 to address the change in the non-inferiority margin requested by the FDA (from 15% to 10%)
- Modification of the primary outcome to add an increase of >20 mg/dL to the increase in glucose to ≥70 mg/dL to account for the starting glucose being lower than 50 mg/dL in some patients.
- Prespecified plan for treatment of hypoglycemic seizures added to the protocol at FDA's request
- Modifications to the statistical methods to account for the change in the non-inferiority margin and change in sample size

6.2.2. Study Results

Compliance with Good Clinical Practices

The applicant states that the studies were performed in compliance with Good Clinical Practices.

Financial Disclosure

See section 13.2 for details.

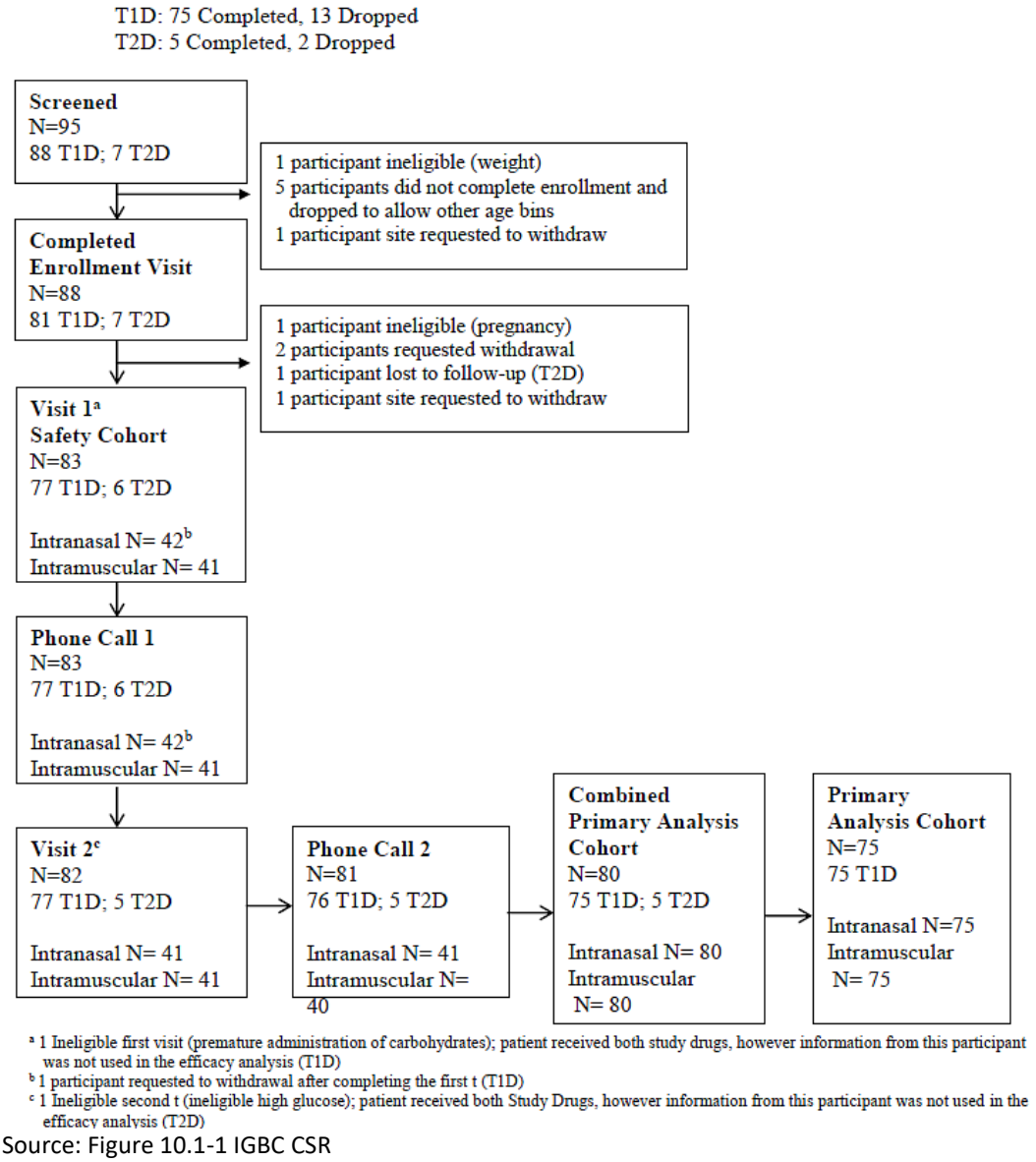
Patient Disposition

A total of 95 patients were screened, 88 with T1DM, and 7 with T2DM. Of these, 7 patients with T1DM did not complete the enrollment visit, one was ineligible due to pregnancy, and 2 requested withdrawal. Of the patients with T2DM, one was lost to follow up and one requested withdrawal. A total of 83 patients received at least one dose of study drug, 77 with T1DM, and 6 with T2DM.

The primary analysis cohort included 75 of the 77 patients with T1DM: one patient was excluded because of premature administration of carbohydrates during the first dosing visit, and another patient requested withdrawal prior to study/dosing visit 2.

The combined primary analysis cohort included the primary analysis cohort, and 5/6 patients with T2DM (one patient excluded because of out of range glucose readings during study/dosing visit 2).

Figure 11 Patient Disposition Study IGBC



Source: Figure 10.1-1 IGBC CSR

The per protocol cohort only included 63 patients as follows:

- Excluded 5 patients because only in-window central lab blood glucose values were included
- Excluded 11 patients where insulin was stopped prior to the central lab blood glucose reaching ≤60 mg/dL
- Excluded one patient who did not have an in-window central lab blood glucose value at 30 minutes.

Table 12 Summary of Analysis Populations for Study IGBC

			T1D		T2D	
	Overall patients	Overall visits	IN	IM	IN	IM
Safety Cohort[‡]	83	165	77	76	6	6
Primary Analysis Cohort[†]	75	150	75	75	-	-
Combined Primary Analysis Cohort[¶]	80	160	75	75	5	5
Per Protocol Cohort[∫]	63	126	63	63	-	-

[‡]The Safety Cohort consisted of all T1D and T2D patients who were randomized and received at least one dose of the Study Drug
[†]The Primary Analysis Cohort consisted of all T1D patients who received both doses of the Study Drug with eligible glucose and glucagon concentrations
[¶]The Combined Primary Analysis Cohort included both T1D and T2D patients who received both doses of the Study Drug with eligible glucose and glucagon concentrations
[∫]The following restrictions were implemented for the per protocol analysis: include only in-window central lab blood glucose values (5 values removed), remove observations where insulin was stopped prior to central lab blood glucose reaching ≤60 mg/dL (11 observations removed), remove observations without an in-window central lab blood glucose value at the 30 minute time point (1 observation removed)

Source: Table 10.1-1 IGBC CSR

Protocol Violations/Deviations

A total of 131 protocol deviations were reported, all of which were deemed by the applicant not to have any impact on the assessment of the study objectives. Patients with protocol deviations were considered in safety and efficacy analyses. All deviations are presented in the Table 13 below.

Table 13 Protocol Deviations Study IGBC

Protocol Deviation Group and Descriptions	N, (%)*
Lab	
Incorrect amount of aprotinin added to central lab samples	1 (0.8)
Incomplete urinalysis results	3 (2.3)
Samples stored in freezer with deviations from acceptable range of -70 to -85C	22 (16.8)
Incorrect timing of QC sample collection	2 (1.5)
Incorrect sample processing procedure	1 (0.8)
Total	29 (22.1)
Testing Procedure	
Improper reference glucose monitoring during insulin administration period	31 (24.8)
Edinburgh Hypoglycemia Scale not done	11 (8.4)
Incorrect timing of administration of Edinburgh Survey	1 (0.8)
Starting insulin infusion rate was not 2 mU/kg/min	14 (10.7)
Blood draw not done	3 (2.3)
More than 4 units of IV insulin given for priming dose.	4 (3.1)
Nasal and Non-Nasal Questionnaire not done	2 (1.5)
Improper timing of glucagon administration	4 (3.1)
Plasma glucose <60 mg/dL not obtained prior to glucagon administration	1 (0.8)
Insulin stopped prior to target glucose level of <60 mg/dL	2 (1.5)
Improper timing of vital signs assessment	1 (0.8)
Insulin infusion stopped based on HGM result	1 (0.8)
Improper timing of blood sample collection	2 (1.5)
Incorrect timing of administration of Nasal and Non-Nasal Questionnaire	2 (1.5)
Total	79 (60.3)
Visit Completion	
Protocol visit completed out of window	15 (11.4)
Protocol phone call completed out of window	2 (1.5)
Protocol phone call missed	1 (0.8)
Informed Consent	
Signature/date discrepancy (patient)	3 (2.3)
Patient signed prior ICF version	1 (0.8)
Eligibility (Enrollment)	
Ineligible patient- minor	1 (0.8)
Total	131

*Proportions based on total number of protocol deviations reported

Source: Table 14.1-1 IGBC CSR

Demographic Characteristics

Demographic characteristics, including diabetes history and treatment for patients with T1DM, and T2DM included in the safety cohort are presented in Table 14 below. The mean age was lower for the T1DM group compared to T2DM (32.9 years vs 47.8 years), more than half of the participants were females (58% of the T1DM patients, and 67% of the T2DM patients). Patients reported having diabetes for about 18 years, mean HbA1c was 8.3% for patients with T1DM, and 8% for patients with T2DM, and most patients did not report reduced awareness to hypoglycemia.

Table 14 Table of Demographic Characteristics Study IGBC

	T1D N=77	T2D N=6
Age (years) – *n(%)*		
18 to <25	28 (36%)	1 (17%)
25 to <35	23 (30%)	0
35 to <45	10 (13%)	1 (17%)
45 to <55	11 (14%)	3 (50%)
≥55	5 (6%)	1 (17%)
Median (25th, 75th percentile)	31.0 (21.6, 41.5)	52.8 (41.4, 54.6)
Mean ±SD	32.9 ± 12.3	47.8 ± 14.7
Female – *n(%)*	45 (58%)	4 (67%)
Race/ethnicity – *n(%)*		
White Non-Hispanic	74 (96%)	1 (17%)
Black Non-Hispanic	1 (1%)	2 (33%)
Hispanic or Latino	1 (1%)	1 (17%)
Other Race/Ethnicity	1 (1%)	2 (33%)
Duration of diabetes (years) – *n(%)*		
<10	27 (35%)	0
10 to <20	16 (21%)	4 (67%)
20 to <30	20 (26%)	1 (17%)
≥30	14 (18%)	1 (17%)
Median (25th, 75th percentile)	17.6 (8.6, 24.6)	15.7 (12.7, 26.0)
Mean ±SD	18.1 ± 11.2	18.8 ± 7.8
Primary insulin modality – *n(%)*		
Insulin pump	57 (74%)	1 (17%)
Multiple daily insulin injections	20 (26%)	5 (83%)
Total daily insulin (units/kg) - median (25th, 75th percentile)	0.58 (0.46, 0.68)	0.81 (0.57, 1.22)
Most recent severe hypoglycemic event[a] – *n(%)*		
Never	46 (60%)	4 (67%)
≤30 days	0	0
31 to 90 days	4 (5%)	1 (17%)
91 to 180 days	0	0
181 to 365 days	2 (3%)	0
>365 days	25 (32%)	1 (17%)
HbA1c[b] – *n(%)*		
≤7%	21 (27%)	1 (17%)
7.1 to 8.0%	22 (29%)	2 (33%)
8.1 to 9.0%	15 (19%)	2 (33%)
9.1 to 10.0%	8 (10%)	1 (17%)
>10.0%	11 (14%)	0
Mean ±SD	8.3 ± 1.8	8.0 ± 0.8
Clarke hypoglycemia unawareness score[c] – *n(%)*		
Reduced awareness	10 (13%)	1 (17%)
Intermediate	10 (13%)	2 (33%)
Aware	57 (74%)	3 (50%)

[1]The Safety Cohort consisted of all T1D and T2D patients who were randomized and received at least one dose of the Study Drug
[a]Severe hypoglycemic event defined as an episode that required third party assistance for treatment
[b]HbA1c performed locally
[c]Reduced awareness = 4 or more reduced responses; Intermediate = 3 reduced responses; Aware= 2 or fewer reduced responses

Source: Table 11.2-1 IGBC CSR

Sixty-nine (83.1%) patients reported at least another medical condition in addition to diabetes, 13 (15.7%) patients reported hypertension, 16 (19.3%) patients reported psychiatric disorders, 21 patients reported hyperlipidemia/hypercholesterolemia/dyslipidemia. Generally, very few patients reported diabetes microvascular or macrovascular complications, and only 2 patients were obese.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Compliance is not an issue for this study as the study drug is administered in CRC setting.

All 83 patients reported the use of at least one concomitant medication. Of these, 25 patients (30.1%) began use of an additional non-study medication post-study start.

Most patients in the combined primary analysis cohort (n=77, 96.3%) received their second dose of study drug within the 7-28 days dosing window, with a median of 15.5 days. The remaining 3 patients were dosed at days 29, 33, and 47, respectively.

Efficacy Results – Primary Endpoint

The primary efficacy analysis was a treatment group comparison of the primary outcome in Primary Analysis cohort, composed of all T1DM patients having completed both Study/Dosing Visits with eligible glucose and glucagon levels.

The primary efficacy outcome, treatment success, was defined as either an increase in blood glucose to ≥70 mg/dL or an increase of ≥20 mg/dL from glucose nadir within 30 minutes after receiving study glucagon, without receiving additional actions to increase the blood glucose level. Due to the residual activity of circulating insulin, glucose nadir was defined as the minimum glucose measurement at the time of, or within 10 minutes following glucagon administration.

As seen in the table below, all patients were successfully rescued with CG, and all but one patient were rescued with NG.

Table 15 Proportion of Patients with Increase in BG to ≥70 mg/dL or an Increase of ≥20 mg/dL from Nadir within 30 Minutes after Administration of Glucagon - Primary Analysis Cohort† - Study IGBC

	Intranasal Glucagon N=75	Intramuscular Glucagon N=75
N with success[a]	74	75
Proportion with success[a]	0.987	1.000
Success criterion met[b] – *n(%)*		
≥70 mg/dL	72 (97%)	74 (99%)
Increase by ≥20 mg/dL from nadir	74 (100%)	75 (100%)
Both	72 (97%)	74 (99%)
Difference in proportion with success[c]		
Unadjusted difference (1-sided upper 97.5% confidence limit)[d]	0.013 (0.040)	
Adjusted difference (1-sided upper 97.5% confidence limit)[e]	0.015 (0.043)	

†The Primary Analysis Cohort consisted of all T1D patients who received both doses of the Study Drug with eligible glucose and glucagon concentrations

[a] Success defined as an increase in central lab blood glucose to ≥70 mg/dL or an increase of ≥20 mg/dL from nadir within 30 minutes after glucagon is administered

[b] Proportion based on total number meeting success (N=74 for intranasal and N=75 for intramuscular)

[c] Difference in proportion with success defined as (proportion with success with Intramuscular treatment) – (proportion with success with Intranasal treatment)

[d] 1-sided confidence interval (CI) from a 1-sample mean of the paired differences in occurrence of outcome; non-inferiority margin = 0.1

[e] Difference and 1-sided CI from a Poisson regression model adjusted for treatment period and blood glucose value immediately before administration of glucagon

Source: Table 11.4-1 IGBC CSR

The one patient who failed intranasal treatment achieved both glucose threshold levels at 40 minutes. Blood glucose values for this one patient are presented below.

Table 16 Description of Lab Glucose Values (mg/dL) at Both Visits for 1 Patient who Failed Intranasal Treatment in the Primary Analysis Cohort† - Study IGBC

		Time Point (minutes)										
Treatment	**Outcome**	**0**	**5**	**10**	**15**	**20**	**25**	**30**	**40**	**50**	**60**	**90**
Intranasal	Failure	50	47	48	53	57	62	65	72	75	79	81
Intramuscular	Success	48	55	60	72	86	98	103	113	142	139	131

†The Primary Analysis Cohort consisted of all T1D patients who received both doses of the Study Drug with eligible glucose and glucagon concentrations

Source: Table 11.4-2 IGBC CSR

Three of the patients achieved a glucose increase ≥20 mg/dL at 30 minutes, but did not achieve glucose levels above 70 mg/dL at 30 minutes. Two of these patients received intranasal glucagon, and one received intramuscular glucagon. The description of lab blood glucose values for these 3 patients are presented in Table 17 below. For the two patients who received

intranasal glucagon, both had a nadir glucose at 5 minutes post dose (36, and 37 mg/dL, respectively), and both required administration of oral carbohydrates, but not in the 30 minutes following glucagon administration (at 40, and 68 minutes post-dose, respectively). In both cases, there was a downward trend in glucose prior to carbohydrate administration. The one patient exposed to intramuscular glucagon had a very low starting blood glucose (28 mg/dL), nadir at 26 mg/dL 5 minutes post-dose, and did not require additional therapies to bring the blood glucose over 70 mg/dL (achieved at 40 minutes post-dose).

Table 17 Description of Lab Glucose Values (mg/dL) for 3 Patients with Successful Treatment (Increase in Glucose ≥20 mg/dL) where Lab Glucose <70 mg/dL at 30 Minutes in the Primary Analysis Cohort†

	Time Point (minutes)										
Treatment	0	5	10	15	20	25	30	40	50	60	90
Intranasal[a]	55	36	37	43	59	59	62	59	59	79	122
Intranasal[b]	43	37	44	54	59	64	66	64	63	59	92
Intramuscular	28	26	27	44	56	50	53	73	74	73	83

†The Primary Analysis Cohort consisted of all T1D patients who received both doses of the Study Drug with eligible glucose and glucagon concentrations

[a]Received carbohydrates (8g glucose tabs) 40 minutes after glucagon was administered
[b]Received carbohydrates (4oz juice) 68 minutes after glucagon was administered

Source: Table 11.4-3 IGBC CSR

A total of 6 patients with T1DM received oral carbohydrates, including the two patients mentioned above. All these 6 patients received oral carbohydrate following administration of intranasal glucagon. Notably only one patient received oral carbohydrates before the 30 minutes timepoint for the primary endpoint. Details regarding these 6 patients are presented in Table 18 below.

Table 18 Patients who Received Oral Carbohydrates in Study IGBC

Patient ID	Glucose at nadir (mg/dL)	Glucose at 30 minutes (mg/dL)	Time to carbohydrate administration (minutes)	Lab glucose prior to carbohydrate administration (mg/dL)	Fingerstick glucose prior to carbohydrate administration (mg/dL)
(b) (6)	44	70	76	63	50
	53	80	50	80	68
	36	62	40	59	51
	39	123	3	43	39
	39	94	81	71	63
	37	66	68	59	57

Source: Individual efficacy response data Study IGBC

The Combined primary cohort and per protocol cohort efficacy analyses yielded similar results.

Table 19 Combined Primary Cohort and Per Protocol Population Analyses – Study IGBC

	Combined Primary Cohort		Per Protocol Cohort	
	NG N=80	**CG N=80**	**NG N=63**	**CG N=63**
N with Success	79	80	62	63
Proportion with success	98.8%	100%	98.4	100%

Source: Tables 11.4-4 and 11.4-6 IGBC CSR

Data Quality and Integrity

Datasets and study documents appear adequate; I did not identify any issues.

Efficacy Results – Secondary and other relevant endpoints

The proportion of patients with treatment success at 15, 20, and 25 minutes is presented in Table 20 below.

Table 20 Proportion of Patients with Study-Defined Treatment Success Over Time – Primary Analysis Population, Study IGBC

Time	**10 minutes**		**15 minutes**		**20 minutes**		**25 minutes**	
Treatment	**NG N=75**	**CG N=75**	**NG N=75**	**CG N=75**	**NG N=75**	**CG N=75**	**NG N=75**	**CG N=75**
N with success	14	39	54	69	66	75	73	75
Proportion with success	0.19	0.52	0.72	0.92	0.88	1.00	0.97	1.00

Source: Excerpted from table 11.4-8 IGBC CSR

Dose/Dose Response

Not applicable as only one dose of the study drug was evaluated in this study.

Durability of Response

As this is a single dose treatment, this is not generally applicable. However, it is notable that more patients in the NG group required administration of oral carbohydrates 40-80 minutes after the administration of glucagon compared to patients receiving injectable glucagon (6 vs 0), which may suggest that the NG may not be as durable. However, it is unclear whether such a conclusion can be drawn in this context, and the NG did meet its primary endpoint set for 30

minutes, and this is sufficient to allow for patients to consume oral carbohydrates in an emergency, which is the goal of the treatment. It is also possible that it is more an issue of potency rather than durability of the effect.

Persistence of Effect

See durability of response.

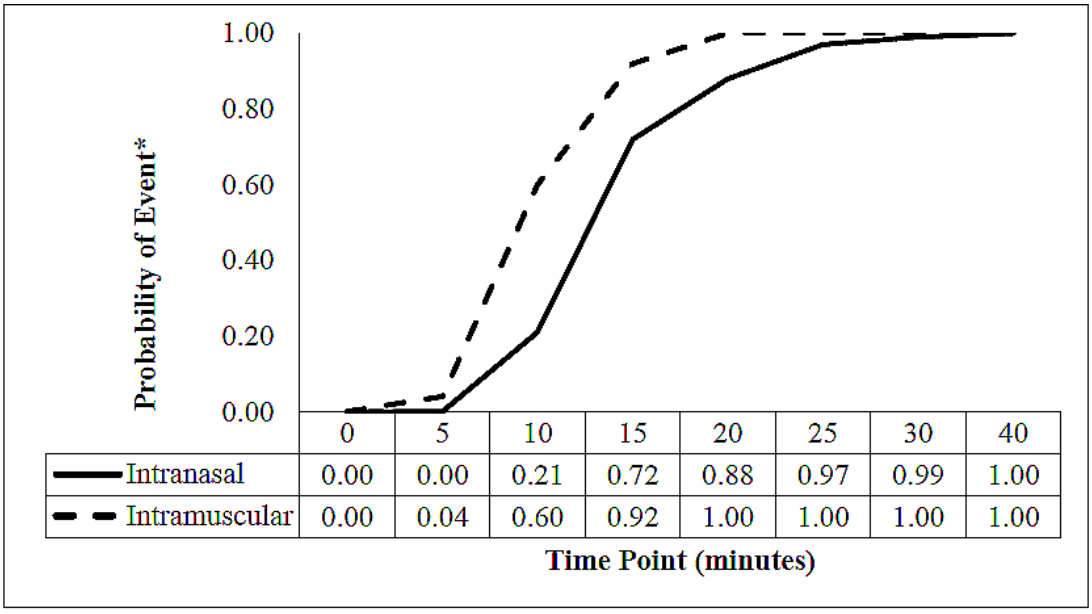
Additional Analyses Conducted on the Individual Trial

Time to treatment success

For both the time to increase blood glucose to ≥70 mg/dL, and increase of ≥20 mg/dL over baseline, or a combination of the two, intramuscular glucagon was faster compared to the intranasal glucagon as shown in the figures below.

For the combined endpoint, the mean time to outcome was 16.2 minutes in the NG treatment arm and 12.2 minutes in the CG treatment arm (P<0.001).

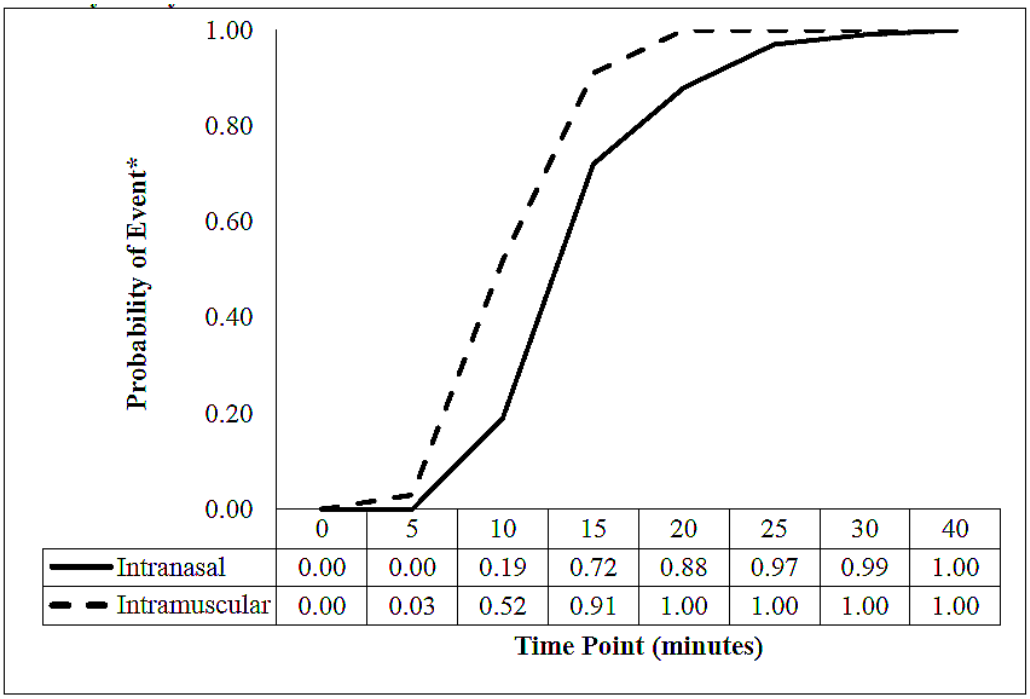
Figure 12 Time from Treatment to Increase in Blood Glucose to ≥70 mg/dL or an Increase of ≥20 mg/dL from Nadir in the Primary Analysis Cohort† - Study IGBC



	0	5	10	15	20	25	30	40
Intranasal	0.00	0.00	0.21	0.72	0.88	0.97	0.99	1.00
Intramuscular	0.00	0.04	0.60	0.92	1.00	1.00	1.00	1.00

†The Primary Analysis Cohort consisted of all T1D patients who received both doses of the Study Drug with eligible glucose and glucagon concentrations
P<0.001 from the marginal Cox proportional hazard model for clustered data adjusted for central lab nadir glucose and treatment period
Source: Figure 11.4-1 IGBC CSR

Figure 13 Time from Treatment to Blood Glucose Increase of ≥20 mg/dL in the Primary Analysis Cohort†, Study IGBC



	0	5	10	15	20	25	30	40
Intranasal	0.00	0.00	0.19	0.72	0.88	0.97	0.99	1.00
Intramuscular	0.00	0.03	0.52	0.91	1.00	1.00	1.00	1.00

†The Primary Analysis Cohort consisted of all T1D patients who received both doses of the Study Drug with eligible glucose and glucagon concentrations
P<0.001 from the marginal Cox proportional hazard model for clustered data adjusted for central lab nadir glucose and treatment period

Source: Figure 11.4-2 IGBC CSR

The mean time to both outcome analyses was 16.3 minutes in the NG treatment arm and 12.7 minutes in the CG treatment arm (P<0.001).

Similarly, for the subgroup of patients with blood glucose nadir below 50 mg/dL, the mean time to both outcomes was 16.3 minutes in the NG group, and 13.2 minutes in the CG group.

6.3. IGBB

Study Title: Assessment of Intranasal Glucagon in Children and Adolescents with Type 1 Diabetes

6.3.1. Study design

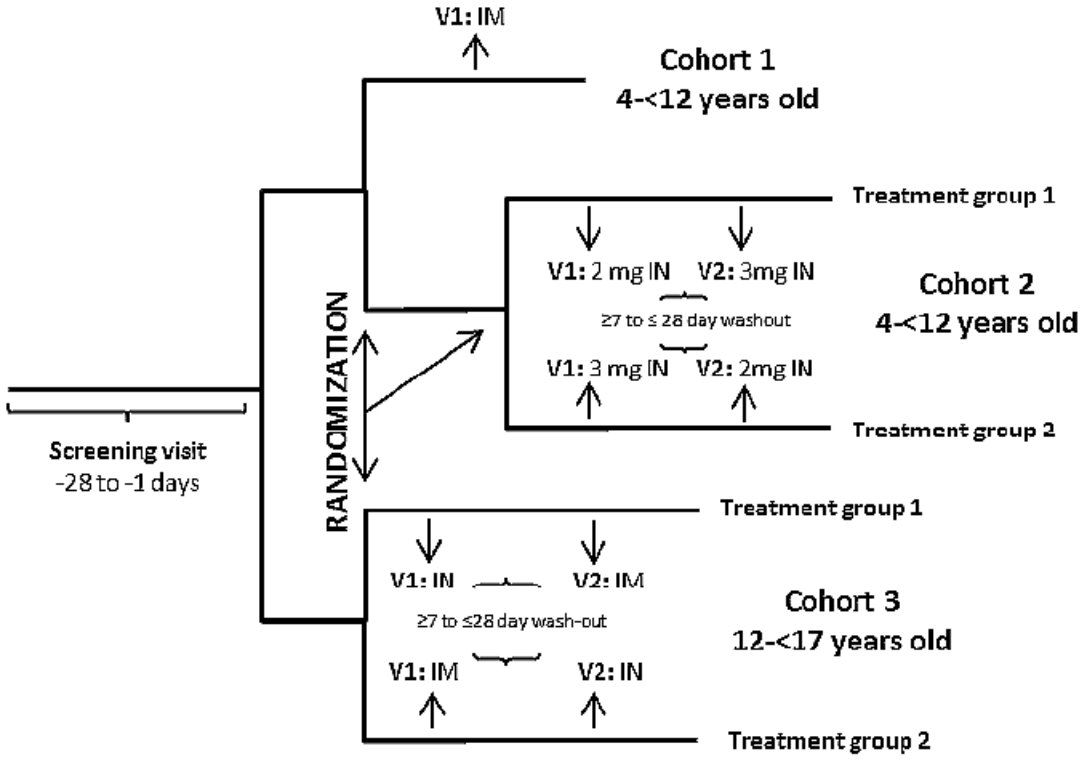
Overview and Objective

The primary objective of study IGBB was to assess, in a pediatric population of T1DM patients, the PK and PD of glucagon administered intranasally in comparison with commercially-available intramuscular (IM) glucagon. The secondary objective was to evaluate safety and tolerability of NG in pediatric T1DM patients.

Trial Design

This was a phase III, randomized, quasi-blinded quasi-crossover design study in pediatric patients (ages 4-17 years) with T1DM. Quasi-crossover means that not all patients had a cross over design, there was a subset of 4 to <12 year olds (cohort 1) who only had one study visit scheduled. While the entire study was not blinded due to inherent differences in the delivery method, the nasal glucagon product doses (2 and 3 mg) were blinded. The study design is outlined in the figure below.

Figure 14 Study Design Study IGBB



Source: Figure 9.1-1 CSR

Treatments

- GlucaGen HypoKit 1 mg powder and solvent for solution for ingestion – 1 mg (1mL) administered to patients weighing at least 55 lbs, and 0.5 mg (0.5 mL) for patients below 55 lbs. The product was administered in the quadriceps muscle with the patient lying on the side.

- AMG504-1 2 mg glucagon administered in the nostril of patients, using a prefilled delivery device (b) (4)

- AMG504-1 3 mg glucagon administered in the nostril of patients, using a prefilled delivery device (b) (4)

Study procedures

Procedures prior to administering the glucagon

- Patients fasting for at least 8 hours arrived at the clinical center in AM.

- Glucose level was checked, if >300 mg/dL, ketones were checked, and if moderate or greater, the visit was postponed.

- Assessment of hypoglycemic events since the screening visit, if any event in the 2 weeks prior to admission, the visit was postponed

- Pregnancy test was performed

- Physical examination including nasal inspection, vital signs

- Assessment of nasal scores and non-nasal symptoms, graded using a 4-point scale

- Intravenous (iv) catheter placement

- Collection of blood sample for local hematocrit assessment, central laboratory assessment of HbA1c, c-peptide, glucose, and diabetes autoantibodies (first visit only), and samples for storage in the T1DM Exchange Biobank.

- Insulin infusion: for patients using insulin pumps, the basal rate was increased 25-50% to provide a gradual decrease in glucose (a priming bolus equivalent to one hour basal dose may have been given at the investigator's discretion, also additional increase in the basal rate and/or additional boluses were allowed as needed). For patients in multiple daily injections, if starting glucose was >200 mg/dL, a priming dose of 2-4 units of iv insulin may have been given. An iv infusion of regular insulin diluted in normal saline at a rate of 1 mU/kg/min was administered. The infusion rate was adjusted as necessary to reach the target glucose level of <80 mg/dL. Glucose levels were measured using a

bedside blood glucose analyzer (Analox, YSI, of equivalent). Measurements were no more than 10 minutes apart while the plasma glucose was >100 mg/dL, and no more than 5 minutes apart below 100 mg/dL. Once a plasma glucose level of <80 mg/dL was reached, the basal rate was returned to normal for participants using an insulin pump and the insulin infusion was stopped for participants using insulin injections. A blood sample was collected for PK analysis (glucagon) and PD analysis (glucose).

- When the starting plasma glucose was <80 mg/dL, no additional insulin was given and the procedures to administer glucagon were followed.

- The glucagon was administered 5 minutes after the basal rate returned to normal or the insulin infusion was stopped.

Post glucagon administration procedures

- Plasma glucose levels were measured using a rapid glucose analyzer (YSI or equivalent device) for safety and serial blood sampling was performed for pharmacokinetics (glucagon) and pharmacodynamics (glucose) assessments 5, 10, 15, 20, 30, 40, 60, and 90 minutes following administration of glucagon. A reduced scheme of draws may have been completed for patients not of sufficient weight to accommodate the blood volume required. The ending time window for completion of each blood draw for inclusion in analyses was the midpoint between consecutive planned measurements. Any sample not drawn by this time was considered missed.

- Nasal and non-nasal scores were assessed at 15, 30, 60, and 90 minutes after glucagon administration.

- Vital signs were assessed at 45 minutes after glucagon administration.

- Examination of the injection site or nasal inspection were performed approximately 90 minutes after glucagon administration.

- Severe hypoglycemia was not expected with this study design, however, the protocol allowed for iv glucose and/or iv lorazepam if needed, at the discretion of the investigator.

Inclusion criteria included

- Patients with T1DM age 4-<17, otherwise in general good health

Exclusion criteria include

- History of severe hypoglycemia in the month prior to enrolling in the study

- History of epilepsy or seizure disorder
- History of pheochromocytoma,
- Use of daily systemic beta-blocker, indomethacin, warfarin or anticholinergic drugs.

See study protocol for full inclusion and exclusion criteria.

Study Endpoints

The primary efficacy variables for the study are the PK (glucagon) and PD (glucose) parameters calculated using both the raw and adjusted concentrations of glucagon and glucose, respectively.

Statistical Analysis Plan

The applicant stated that due to the lack of available data on children, a sample size of 48 participants was selected as a convenience sample based on the FDA guidance for pediatric PK studies which indicates that the standard approach is to administer either single or multiple doses of a drug to a relatively small (e.g., 6-12) group of participants.

Primary analysis

The population for the primary analysis (PK and PD) included all participants who provided evaluable data for at least one of the treatments.

The analysis was stratified by age cohort (4-<8, 8-<12, and 12-<17 years old), except where otherwise indicated. The analyses for the 4-<8 and 8-<12 years old cohorts may have been pooled if the data suggests homogeneity of effect.

The 2mg and 3mg intranasal glucagon treatment arms may have been pooled if the data suggests homogeneity of effect.

Post-hoc analyses

The assessment of the proportion of patients with an increase in blood glucose ≥20 mg/dL from nadir at 5, 10, 15, 20, 30, 40, 60, and 90 minutes post glucagon administration was performed post-hoc.

Protocol Amendments

The initial protocol was dated July 23, 2013, and was amended on October 15, 2013 (protocol amendment #1) to satisfy the FDA's request that both doses of NG (2 mg and 3 mg) were to be studied. This protocol amendment also increased the number of patients from 40 to 48.

Protocol amendment #2, dated June 18, 2014 removed the minimum weight requirement, and clarify that the number of blood draws was to be modified for patients who did not weigh enough (to limit the blood collected to 5% of the total body volume).

6.3.2. Study results

Compliance with Good Clinical Practices

The applicant states that the clinical trial was conducted in compliance with Good Clinical Practices.

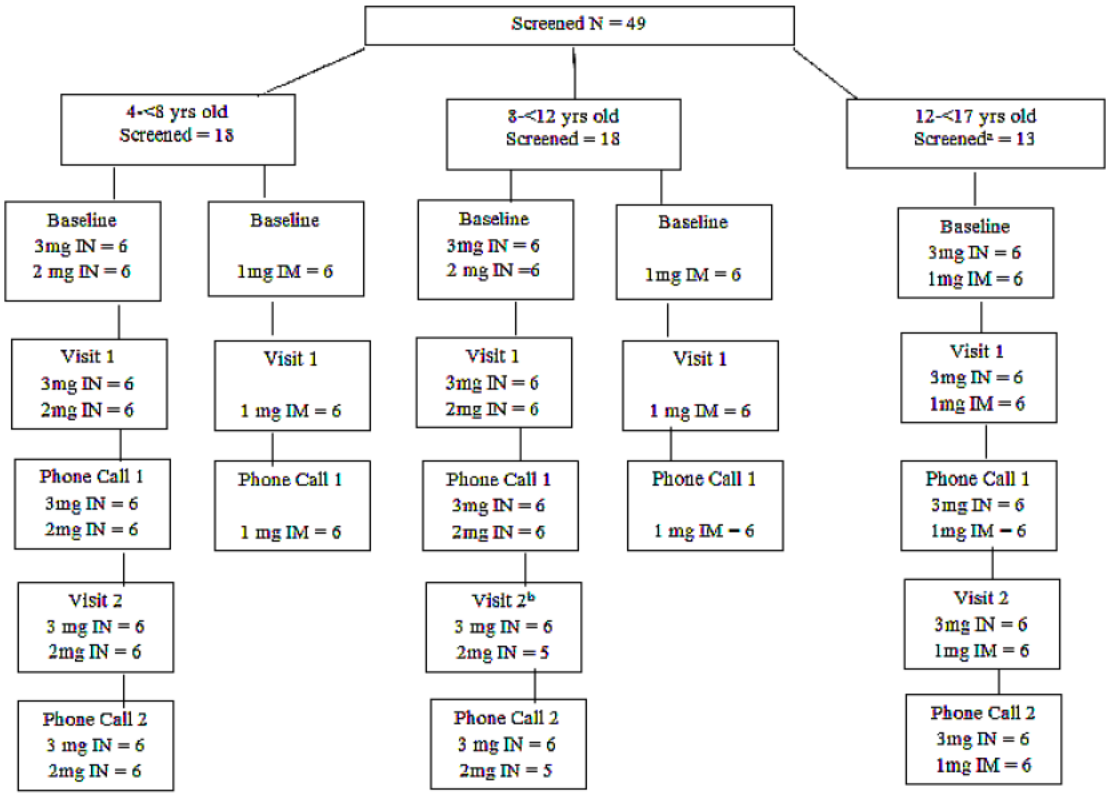
Financial Disclosure

See section 13.2 for details.

Patient Disposition

A total of 49 patients were screened, 18 of which were 4-<8 years of age, 18 were 8-<12, and 13 were 12-<17. One of the patients in the 8-<12 age group requested withdrawal before the second dose of study drug (received 3 mg NG in the first visit). One other patient from the 12-<17 age group was excluded from the study due to use of prohibited concomitant medication. As a result, 48 patients received one dose of study drug, and 47 patients completed the study. In addition, one patient from the 12-<17 group received a repeat of the 3 mg NG dose due insufficient delivery of glucagon the first time (which was due to device malfunction, the applicant states that the design was corrected to prevent future malfunctions). In the end, 11 patients were dosed with 2 mg IN glucagon, 18 with 3 mg IN glucagon, and 18 with IM glucagon, across a total of 84 visits (23 2mg NG Dosing Visits, 37 3mg NG Dosing Visits - 1 patient dosed twice, and 24 IM glucagon Dosing Visits).

Figure 15 Patient Disposition Study IGBB



[a]1 participant regularly taking Flonase was excluded from the study
[b]1 participant requested to withdraw prior to the second visit

Source: Figure 10.1-1 CSR

Overall 48 patients were included in the primary and exploratory analyses, with 82 dosing visits.

Table 21 Visits and Patients included in the Primary and Exploratory Analyses – Study IGBB

	Age Cohort											
	4-<8			8-<12			12-<17		Total			
Dosing group	2mg IN	3mg IN	IM	2mg IN	3mg IN	IM	3mg IN	IM	Overall	2mg IN	3mg IN	IM
Visits Included	11[‡]	12	6	11	12	6	12	12*	82	22[‡]	36*	24
Patients Dosed	5[‡]	6	6	5	6	6	6	6	48**	10[‡]	18	18

[‡] One 2mg Dosing Visit was not included in the Primary and Exploratory Analyses due to the patient blowing his nose ((b) (6)
*Patient (b) (6), who had a repeat 3mg IN dosing visit due to insufficient administration of glucagon (device malfunction – see text above), contributed the eligible 3mg IM Dosing Visit to the Primary and Exploratory Analyses
**The 2 patients with 2mg IN Dosing Visits not considered in the Primary and Exploratory Analyses (one Dosing Visit excluded due to patient blowing his nose, and one patient withdrew prior to Dosing Visit 2) each contributed a 3mg IN Dosing Visit to the Analyses.

Source: Table 11.1-2 CSR

Protocol Violations/Deviations

A total of 107 protocol deviations were reported, none of which were deemed by the applicant to have an impact on the assessment of primary and secondary objectives. A summary of protocol deviations is presented in the table below.

Table 22 Summary of Protocol Deviations – Study IGBB

Deviation group	Description	N (%)
Informed Consent	*Only one parent signature was obtained at initial consent*	4 (3.7)
	Patient signed prior ICF version	1 (0.9)
Testing Procedure	*Plasma glucose <80 mg/dL not obtained prior to glucagon administration*	3 (2.8)
	Local hematocrit not done	10 (9.3)
	Improper reference glucose monitoring during insulin administration period.	21 (19.6)
	Incorrect timing of blood sample collection	4 (3.7)
	Basal rate not increased to lower glucose level for participant on pump therapy	3 (2.8)
	Improper timing of glucagon administration	13 (12.1)
	Improper timing of vital signs assessment	3 (2.8)
	Nasal and Non-nasal Questionnaire not administered	1 (0.9)
	Incorrect timing of administration of Nasal and Non-Nasal Questionnaire	2 (1.9)
	IV insulin infusion not used to decrease glucose level for participant using MDI	3 (2.8)
	Improper timing of blood sample collection	4 (3.7)
	Basal rate on pump returned to normal prior to glucose level of 80 mg/dL	2 (1.9)
	Insulin stopped prior to target glucose level of <80 mg/dL	1 (0.9)
	Vital Signs not assessed	1 (0.9)
Lab	*Central laboratory sample not collected*	6 (5.6)
	Incomplete urinalysis results	2 (1.9)
	Improper timing of QC blood sample collection	3 (2.8)
	Samples stored in freezer with deviations from acceptable range of -70 to -85	2 (1.9)
Visit Completion	*Protocol phone call completed out of window*	2 (1.9)
	Protocol visit completed out of window	16 (15.0)
Total	-	107

* Proportion based on total number of protocol deviations reported
Source: Table 10.2-1 CSR

Demographic Characteristics

The mean (SD) age in the 4 –<8 year old cohort was 6.5 (1.2) years old. In the 8-<12 year old cohort, mean (SD) age was 11.1 (0.8) years old and in the 12-<17 year old cohort mean (SD) age was 14.6 (1.6) years old. In all age cohorts, the population was predominantly male (83.3% in the 4-<8 year old cohort; 55.6% in the 8-<12 year old cohort; 58.3% in the 12-<17 year old cohort), and ethnicity was predominantly white. In all age groups, more than 50% of patients were using an insulin pump as their main insulin delivery modality. Mean HbA1c was around 8% for all age groups, and most patients never experienced a hypoglycemic event. The demographic characteristics of the patient population is presented in Table 23 below.

Table 23 Table of Demographic Characteristics – Study IGBB

	4 to <8 years old N=18	8 to <12 years old N=18	12 to <17 years old N=12
Age (years) – *n(%)* Median (25th, 75th percentile)	6.8 (5.7, 7.5)	11.1 (10.5, 11.8)	14.5 (13.2, 15.8)
Mean ±SD	6.5 ± 1.2	11.1 ± 0.8	14.6 ± 1.6
Female – *n(%)*	3 (16.7)	8 (44.4)	5 (41.7)
Race/ethnicity – *n(%)*			
White Non-Hispanic	18 (100)	16 (88.9)	10 (83.3)
Black Non-Hispanic	0	1 (6)	1 (8)
Hispanic or Latino	0	0	1 (8)
Other Race/Ethnicity	0	1 (6)	0
Duration of diabetes (years) – *n(%)* Median (25th, 75th percentile)	2.8 (2.1, 3.8)	4.6 (3.8, 6.7)	5.9 (3.5, 8.0)
Mean ±SD	2.8 ± 1.3	4.9 ± 1.8	6.6 ± 3.9
Primary insulin modality – *n(%)*			
Insulin pump	10 (56)	16 (89)	9 (75)
Multiple daily insulin injections	8 (44)	2 (11)	3 (25)
Total daily insulin (units/kg) - median (25th, 75th percentile)	0.71 (0.55, 0.95)	0.75 (0.68, 0.84)	0.88 (0.77, 0.99)
Most recent severe hypoglycemic event[a] – *n(%)*			
≤30 days	0	0	0
31 to 90 days	2 (11)	0	0
91 to 180 days	1 (6)	2 (11)	0
181 to 365 days	1 (6)	0	1 (8)
>365 days	2 (11)	0	4 (33)
Never	12 (67)	16 (89)	7 (58)
HbA1c[b] – *n(%)*			
Mean ±SD	8.1 ± 0.8	7.9 ± 0.9	8.2 ± 1.5

* Includes only eligible participants with type 1 diabetes who completed the enrollment visit
[a]Severe hypoglycemic event defined as an episode that required third party assistance for treatment
[b]HbA1c performed locally

Source: Excerpted from Table 11.2-1 CSR

Of the 48 patients enrolled in the study, 23 (47.9%) reported a total of 43 concomitant medical conditions. None of these conditions was reported in more than 10% of patients. Of the more relevant concomitant conditions, allergic rhinitis was reported by 1 patient, and asthma by 5 patients, drug hypersensitivity by 3 patients, allergies by 6 patients.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The treatment was administered in clinical research center settings, therefore compliance is not thought to be an issue.

Efficacy Results - Primary Endpoint

The primary analysis of the study was to evaluate the PK and PD parameters of glucagon administered intranasally in comparison with commercially-available IM glucagon. Time to achieving an increase in blood glucose of ≥20mg/dL above nadir was investigated in an exploratory post-hoc analysis, to align the evaluation of efficacy in pediatrics with the efficacy outcome used in adult studies IGBI and IGBC (the increase to glucose ≥70 mg/dL is not applicable here as the target starting BG was 80 mg/dL).

In general, the maximum plasma glucagon (Cmax) was higher with the intramuscular product compared to NG, except in the patients 8 to <12 years of age, where the Cmax was highest for the 3 mg NG. The summary of pharmacokinetic parameters of glucagon are presented below. The Tmax was similar between the treatment groups. The summary of pharmacokinetic parameters by treatment and age group are presented in Table 24 below.

Table 24 Summary of Pharmacokinetic Parameters of Glucagon – Study IGBB

	4 to <8 years old			8 to <12 years old			12 to <17 years old	
PK Parameter	IM Mean (CV%)	2mg[i] Mean (CV%)	3mg Mean (CV%)	IM Mean (CV%)	2mg[i,j] Mean (CV%)	3mg Mean (CV%)	IM Mean (CV%)	3mg Mean (CV%)
N	6	11	12	6	11	12	12	12
$AUC_{0-1.5}$ (hr.pg/mL)	4158.18 (49.33)	1844.86 (53.78)	2583.90 (55.20)	3747.02 (54.76)	1767.92 (38.65)	3191.44 (35.70)	3267.09 (86.98)	2123.19 (62.12)
$AUC_{0-\infty}$ (hr.pg/mL)[b]	4446.48 (50.46)	1912.57 (54.02)	3177.21 (53.07)	4470.05 (49.46)	2065.96 (49.25)	3554.49 (38.54)	4134.62 (82.95)	2418.67 (58.16)
C_{max} (pg/mL)	6343.33 (31.99)	3530.55 (49.90)	4032.92 (60.38)	4817.17 (64.06)	2951.73 (34.68)	5832.42 (36.11)	4381.83 (86.06)	3185.58 (72.00)
T_{max} (hr)[a]	0.29 (0.08,0.50)	0.25 (0.17,0.33)	0.29 (0.17,1.00)	0.29 (0.08,0.50)	0.25 (0.17,0.33)	0.25 (0.17,0.50)	0.29 (0.08,0.50)	0.33 (0.25,0.50)
λ_z(1/hr)	2.18 (18.29)	2.48 (18.26)	1.60 (43.27)	1.36 (39.32)	1.79 (31.28)	2.00 (29.31)	1.24 (47.76)	1.73 (34.43)
CL(L/hr)[b]	0.0002 (67.76)	0.0020 (152.33)	0.0017 (108.81)	0.0003 (58.81)	0.0011 (35.10)	0.0010 (53.67)	0.0003 (40.08)	0.0019 (76.50)
$t_{1/2}$(hr)[ab]	0.33 (0.24,0.38)	0.27 (0.23,0.47)	0.51 (0.25,1.31)	0.55 (0.33,0.95)	0.36 (0.25,0.86)	0.35 (0.21,0.59)	0.63 (0.23,0.96)	0.40 (0.22,0.70)

[i]Participant (b) (6) (4-<8 years old) for practical reasons did not receive the full dose and was therefore excluded from the analysis of this period.
(b) (6) (8-<12 years old) withdrew from study after the 3mg treatment.
[a]Median (Min, Max); [b]Not computable for patient (b) (6) age group 12-<17 at 3mg treatment
Source: Table 11-4-1 CSR

The trend in Cmax for glucose was similar to what was observed with the PK parameters. Overall, peak baseline-adjusted plasma glucose levels were reached within a median 0.67-1.5 hours. The PD parameters are summarized below.

Table 25 Summary of Pharmacodynamic Parameters (Glucose) – Study IGBB

	4 to <8 years old			8 to <12 years old			12 to <17 years old	
PD Parameter	IM Mean (CV%)	2mg† Mean (CV%)	3mg Mean (CV%)	IM Mean (CV%)	2mg†† Mean (CV%)	3mg Mean (CV%)	IM Mean (CV%)	3mg Mean (CV%)
N	6	11	12	6	11	12	12	12
$AUEC_{0\text{-}1.5}$ (hr.mg/dL)	254.07 (12.89)	223.45 (31.07)	246.51 (22.07)	244.46 (11.25)	243.06 (14.15)	247.50 (15.91)	232.86 (17.02)	215.02 (13.62)
C_{max} (mg/dL)	210.33 (13.35)	188.3 6 (27.37)	207.00 (20.90)	205.33 (11.86)	201.27 (13.88)	205.83 (15.54)	193.83 (17.19)	178.17 (15.30)
T_{max} (hr)[a]	1.00 (0.67,1.50)	0.67 (0.33,1.00)	1.00 (0.50,1.50)	1.50 (1.00,1.50)	1.00 (0.67,1.50)	1.00 (0.50,1.50)	1.00 (0.67,1.50)	1.00 (0.50,1.50)
$AUEC_{Above}$	96.19 (33.90)	74.03 (75.83)	92.24 (54.75)	88.68 (27.79)	86.08 (38.13)	90.92 (42.15)	78.19 (46.17)	59.88 (46.31)
$AUEC_{Below}$	103.91 (2.28)	103.70 (2.66)	104.03 (1.62)	104.59 (0.97)	104.98 (0.05)	104.37 (1.59)	104.59 (0.64)	104.76 (0.77)
$AUEC_{Within}$	52.62 (3.00)	45.69 (32.04)	49.56 (9.87)	51.20 (5.52)	51.98 (3.80)	51.56 (3.61)	50.10 (8.07)	50.40 (4.67)
T_{Above}	0.17 (20.83)	0.20 (30.74)	0.23 (30.32)	0.25 (28.82)	0.21 (23.12)	0.22 (24.90)	0.27 (33.73)	0.28 (24.16)
T_{Below}[b]	NC	NC	NC	NC	NC	NC	NC	NC
T_{Within}	0.02 (180.45)	0.06 (166.20)	0.05 (121.82)	0.04 (244.95)	0.02 (222.62)	0.04 (115.36)	0.06 (113.02)	0.03 (250.06)
$Duration_{Above}$	1.31 (3.80)	1.08 (44.72)	1.19 (17.96)	1.25 (5.90)	1.27 (6.25)	1.27 (4.21)	1.19 (17.62)	1.17 (11.79)
$Duration_{Below}$	0.02 (180.45)	0.14 (188.05)	0.06 (125.45)	0.04 (244.95)	0.02 (222.62)	0.04 (104.74)	0.06 (113.02)	0.02 (272.81)
$Duration_{Within}$	0.17 (27.91)	0.27 (81.52)	0.25 (71.42)	0.22 (21.24)	0.21 (25.87)	0.18 (21.55)	0.25 (68.34)	0.31 (44.78)

†Participant (b) (6) (4-<8 years old) for practical reasons did not receive the full dose and was therefore excluded from the analysis of this period.
(b) (6) (8-<12 years old) withdrew from study after the 3mg treatment.
[a]Median (Min, Max); [b]Not Computable
Source: Table 11.4-3 CSR

Data Quality and Integrity - Reviewers' Assessment

I did not identify any issues with data quality.

Efficacy Results - Secondary and other relevant endpoints

<u>Participants achieving >20 mg/dL rise in blood glucose above nadir</u>

This was a post-hoc exploratory endpoint for study IGBB. All patients across all treatment and age groups achieved a rise in blood glucose of ≥ 20 mg by 20 minutes post-glucagon dosing. The timing of achieving the increase is shown below.

Table 26 Percentage of Patients with Increase ≥20 mg/dL from Nadir over Time – Study IGBB

	4 to <8 years old			8 to <12 years old			12 to <17 years old	
	IM N=6	2mg IN[a] N=11	3mg IN N=12	IM N=6	2mg IN N=11	3mg IN N=12	IM N=12	IN N=12
5 min post glucagon admin % with increase ≥20 from nadir	0	9.1%	0	0	0	0	0	0
10 min post glucagon admin % with increase ≥20 from nadir	100%	72.7%	83.3%	50.0%	54.5%	75.0%	50.0%	25.0%
15 min post glucagon admin % with increase ≥20 from nadir	100%	100%	100%	100%	100%	100%	100%	91.7%
20 min post glucagon admin[a] % with increase ≥20 from nadir	100%	100%	100%	100%	100%	100%	100%	100%

Source: Excerpted from Table 14.2-19 CSR

Dose/Dose Response

The 4 to <8 years, and 8 to <12 years groups were exposed to two doses of the study drug, 2 mg NG and 3 mg NG. As expected, the patients dosed with 3 mg dose achieved a higher maximum blood glucose level than patients dosed with 2 mg NG. For both NG doses, the time to increase in BG ≥20 mg/dL was achieved by 15 minutes.

Durability of Response

Not applicable.

Persistence of Effect

Not applicable.

Additional Analyses Conducted on the Individual Trial

While the applicant performed a multitude of analyses, none contribute to the clinical review of efficacy.

6.4. B001

6.4.1. Study Design

Study Title: A multiple center, open-label, prospective, observational study to evaluate the effectiveness and ease-of-use of LY900018 (AMG504-1) administered in the home or school environments for treating hypoglycemia in children and adolescents with type 1 diabetes.

Overview and Objective

The primary objective of the study was to evaluate the effectiveness of NG administered under clinical use (in home or school) in treating episodes of severe or moderate hypoglycemia in children and adolescents with T1DM.

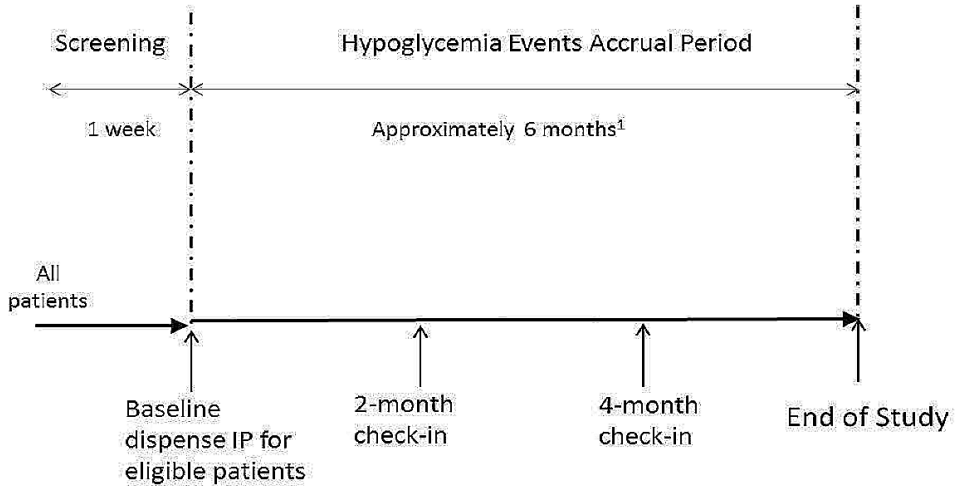
The secondary objective was to assess the ease-of-use of NG in the hands of caregivers of children and adolescents who may be called upon to treat episodes of severe or moderate hypoglycemia (evaluated via a questionnaire).

The tertiary objective was to assess the change in glucose level from NG administration to 15, 30, and 45 minutes after administration of the studied drug (based on caregiver-reported BG).

Trial Design

The study was a multicenter, single-arm, prospective, open-label study. The study design is presented in **Figure 16** below.

Figure 16 Study Design – Study B001



Abbreviation: IP = investigational product.
[1]Each patient continued in the study until he/she experienced one or more hypoglycemic events or until the study was complete, whichever came first. As some patients might have experienced 4 events in a short limited timeframe, no additional drug was distributed to this patient in order to diversify the events among other patients.

Source: Figure B001.5.1 CSR

Eligible patients and their principal caregivers (i.e., parents, family member, roommate, teacher, coach, etc.) were trained in the use of intranasal glucagon. Four doses of NG were dispensed to each patient at enrollment. Patients and their caregivers were encouraged to keep one dose with them at all times (and one blank set of questionnaires) and the other doses in a convenient location. During the study active period (approximately 6 months), each patient could be treated as many times as he or she experienced a moderate or severe hypoglycemic event. The patients returned to clinic with their caregiver at 2, 4, and 6 months after the study start.

Severe hypoglycemia was defined as an event associated with severe neuroglycopenia usually resulting in coma or seizure and requiring parenteral therapy (glucagon or intravenous glucose).

Moderate hypoglycemia was defined as an episode wherein the child/adolescent with diabetes has symptoms and/or signs of neuroglycopenia and has a blood glucose (BG) level of ≤70 mg/dL.

Study Procedures

<u>Procedures for administering glucagon</u>

- For cases of severe hypoglycemia, the NG was to be administered with the patient in fully reclined lateral position on the opposite side of the nostril being administered.
- For moderate hypoglycemia, the NG may have been administered with the patient seated or in lateral recumbency.

Treatments

- Investigational product: NG 3 mg glucagon in (b) (4) mg drug product – administered via a device that propels powder into the nostril

Study Endpoints

The primary outcome measure was the proportion of patients with severe and moderate hypoglycemia awaking or returning to a normal status within 30 minutes following study drug administration.

The secondary objective was to assess the ease-of-use of intranasally administered glucagon in the hands of caregivers of children and adolescents who may be called upon to treat episodes of severe or moderate hypoglycemia. This was evaluated with a simple questionnaire filled out by caregivers assessing the degree of difficulty using the NG kit, the time required to administer the drug, the caregiver degree of satisfaction, and the overall experience with use of the studied drug.

The tertiary objective was to assess the change in glucose level from NG administration to 15, 30, and 45 minutes after administration of the studied drug (based on caregiver-reported BG).

Inclusion/Exclusion Criteria

Motivated children/adolescents with T1DM for more than 1 year, age 4 to <18, otherwise in good general health, and motivated caregiver were considered for inclusion.

Exclusion criteria included:

- Females who are pregnant according to a positive urine pregnancy test, actively attempting to get pregnant, or lactating.

- Presence of cardiovascular, gastrointestinal, liver or kidney disease, or any other conditions which in the judgment of the investigator could interfere with the absorption, distribution, metabolism or excretion of drugs or could potentiate or predispose to undesired effects.

- Presence or history of pheochromocytoma (i.e. adrenal gland tumor) or insulinoma.

- Use of daily systemic beta-blockers, indomethacin, warfarin or anticholinergic drugs.

- Regular consumption of 3 or more units of alcoholic beverages per day.

Please see study protocol for full inclusion and exclusion criteria.

Statistical Analysis Plan

All analyses were descriptive.

Analysis populations were defined as the following:

- Enrolled: all patients who were assigned study drug.

- Efficacy Analysis Population (EAP): enrolled patients who received at least 1 dose of the study drug under study with evaluable information on treatment response. Hypoglycemic events for which patients required external professional medical assistance (i.e., paramedic/ambulance staff, admission to hospital) or used injected glucagon or oral carbohydrates within 30 minutes and before responding were considered as non-evaluable events since information on time to treatment response was not available. Patients from the good clinical practice (GCP) non-compliant site were also excluded from this population.

- Main Safety Analysis Population (MSAP): eligible enrolled patients who experienced at least 1 hypoglycemic event and received at least 1 dose of the study drug. Patients from the GCP non-compliant site were excluded from this population.

- Sensitivity Safety Analysis Population (SSAP): enrolled patients who received at least 1 dose of the study drug. Patients from the GCP non-compliant site were included in this population.

For the primary objective, the proportion of patients and events that met the response criteria was summarized for the EAP. For patients who had multiple events, the following two different scenarios were considered: (1) patients would be counted as a responder if all the events met the response definition and (2) patients would be counted as a responder if at least 1 event met the response definition. The actual and change in glucose levels following NG administration at approximately 15, 30, and 45 minutes after administration of the study drug were summarized for the EAP.

Protocol Amendments

No protocol amendments were reported, however, after the database lock, the following changes were made to the prespecified analysis plan:

- Added the summary of baseline information (including demographic, diabetes history, medical history, vital signs, physical examination, laboratory test, and Clarke

Hypoglycemia Awareness Questionnaire) for all enrolled patients
- Added the summary of the proportion of patients with impaired hypoglycemia awareness based on the Clarke Hypoglycemia Awareness Questionnaire
- Added the summary of other AEs collected in the Hypoglycemia Episode Questionnaire for SSAP

6.4.2. Study Results

Compliance with Good Clinical Practices

The applicant states that the study was compliant with Good Clinical Practices (GCP). One of the study sites (001) has been found to be non-compliant, the site was terminated, and the patients have been excluded from the analyses.

Reviewer Comment: Considering the GCP non-compliance for one site with a significant proportion of patients (11/26), the applicant assertion of GCP compliance is questionable.

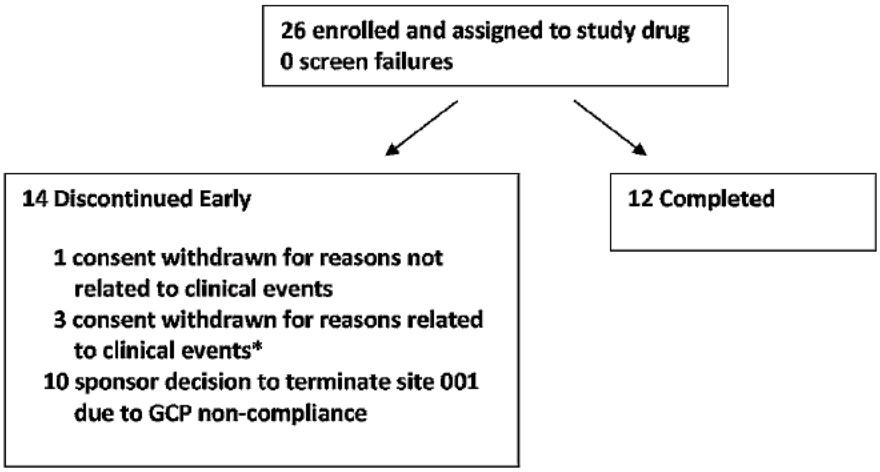
Financial Disclosure

See section 13.2 for details.

Patient Disposition

Twenty-six patients were screened and there were no screen failures. Of the 26 patients enrolled, 22 received at least one dose of the study drug. Twelve patients completed the study, and 14 discontinued early (11 patients from the non-GCP compliant site 001 – one withdrew consent related to clinical events, and 10 discontinued by the applicant due to site non-compliance).

Figure 17 Patient Disposition – Study B001



Abbreviation: GCP = good clinical practice
*See Section 8.2.2.
Source: Figure B001.6.1 CSR

As a result of the one site with GCP non-compliance, only 15 patients were eligible for the main efficacy and safety analyses. One of the 15 patients did not have a hypoglycemic episode, resulting in only 14 patients being included in the EAP.

Protocol Violations/Deviations

A summary of major protocol deviations is presented in Table 27 below. The majority of the protocol deviations were reported from site 001, which was terminated for GCP non-compliance. Additionally, there were three minor protocol deviations reported from site 002. The applicant considered unlikely that the additional protocol deviations affected the results or conclusions of the study.

Table 27 Major Protocol Deviations Study B001

Site Number	Patient ID	Description of Deviation
001	N/A	On 27/Apr/2015, the Principal Investigator inadvertently sent the applicant and CRO an electronic copy of the Master Patient Identification List. CRO/Applicant destroyed/deleted all material related to this communication.
001	N/A	The Principal Investigator sent an invitation letter for the AMG109 study to potential patients. The letter was not approved by the applicant or by the IRB.

001	N/A	The Principal Investigator and Study Coordinator did not provide evidence of GCP training prior to or during the study.
001	N/A	For most Subjects Enrolled, the laboratory reports had not been commented for clinical significance, initialed and dated. This was done retroactively during the CRA's monitoring visits.
001	N/A	For most Subjects Enrolled, the PI did not perform some of the assessments required by the protocol for the Pre- Trial Evaluation and Enrollment visit (e.g. physical exam, vital signs, weight, height, substance use habit). On many occasions, the PI used data from previous subject visits to complete the CRFs for these assessments.
001	All subjects	There was no source document for many items. The site entered the data directly in the CRF for the following items: Ethnicity, Gynecologic history, contraceptive method, Most recent hypoglycemic event, Fasting status, Training of Subject/Caregivers in the use of IN glucagon, injected glucagon, Dispensing of questionnaires and 4 doses of AMG504-1 to Subject/Caregivers.
001	All Subjects	For all Subjects Enrolled, the ICF process was incomplete and some of the signatures required on the document were not obtained at the time of consent (e.g. second parent's signature, Primary Caregiver's signature, Protected Health Information Authorization). The missing signatures were obtained later, but the signatures were back-dated of the time of consent rather than the dates they were appended.
001	N/A	For most subjects, there was no documentation of the consenting process. The principal investigator did some documentation in each patient's chart after the ICF signature, during the monitoring visit of 06 May 2015, but he wrote the date of the respective enrollment visit dates.
(b) (6)		The Witness signed the Informed Consent Form a few days after consent was obtained and never assisted during the consent process.
		Caregiver to patient #(b) (6) continued to use the study medication to treat hypoglycemia events experienced on (b) (6) and (b) (6). These events occurred after 22/May/2015, when the applicant sent an email to the Investigator to instruct his patients to immediately stop using the study medication. IRB Approval was also revoked on 29-May- 2015.
		The Witness signed the Informed Consent Form a few days after consent was obtained and never assisted during the consent process.
		Caregiver to patient #(b) (6) continued to use the study medication to treat hypoglycemia events experienced on (b) (6) and (b) (6). These events occurred after 22/May/2015, when the applicant sent an email to the Investigator to instruct his patients to immediately stop using the study medication. IRB Approval was also revoked on 29-May- 2015.
		Caregiver to patient #(b) (6) continued to use the study medication to treat a hypoglycemia event experienced on (b) (6). This event occurred after 22/May/2015, when the applicant sent an email to the Investigator to instruct his patients to immediately stop using the study medication. IRB Approval was also revoked on 29-May- 2015.
		Caregiver to patient #(b) (6) continued to use the study medication to treat a hypoglycemia event experienced on (b) (6). This event occurred after 22/May/2015, when the applicant sent an email to the Investigator to instruct his patients to immediately stop using the study medication. IRB Approval was also revoked on 29-May- 2015.

(b) (6)	The PI and the Witness signed the Informed Consent Form on (b) (6), 2 days after consent was obtained. The Witness never assisted during the consent process.
	Caregiver to patient # (b) (6) continued to use the study medication to treat hypoglycemia events experienced on (b) (6) and (b) (6). These events occurred after 22/May/2015, when the applicant sent an email to the Investigator to instruct his patients to immediately stop using the study medication. IRB Approval was also revoked on 29-May- 2015.
	The Witness signed the Informed Consent Form on (b) (6), 2 days after consent was obtained. The Witness never assisted during the consent process
	The Witness signed the Informed Consent Form on (b) (6), 1 day after consent was obtained.
	Laboratory tests were sent for analysis at (b) (4) Lab certifications, normal ranges and CV of the lab director were not provided for this laboratory.
	The ICF could not be found at the site. According to the PI and a short note in the source documents, the father and the 16 years old subject signed the ICF on (b) (6) and the father then left home with the ICF to have the mother sign. The ICF was not returned.

Source: Excerpted from Table B001 11.11 CSR

Reviewer Comment: The study had an unusual number of protocol violations, and data from almost half the patients enrolled could not be used for the main efficacy analysis. This raises general concerns regarding the study conduct.

Baseline Characteristics

The mean age of patients in the EAP was 10.2 years, 64.3% of patients were male, mean weight was 43 kg, and all patients were white. The mean duration of diabetes was 6.3 years, 71.4% of patients were using an insulin pump as a primary insulin delivery modality, the mean total daily insulin dose was 42.3 units. These characteristics are summarized for all the defined study populations in

Table **28** below.

Table 28 Table of Demographic Characteristics Study B001

Variable	Enrolled (N=26)	SSAP (N=22)	MSAP/EAP (N=14)
Age (years) Mean (SD)	11.7 (3.73)	11.3 (3.74)	10.2 (3.58)

Gender Female Male	15 (57.7%) 11 (42.3%)	11 (50.0%) 11 (50.0%)	5 (35.7%) 9 (64.3%)
Race ….Black Caucasian	1 (3.8%) 25 (96.2%)	1 (4.5%) 21 (95.5%)	0 (0.0%) 14 (100%)
Weight (kg) Mean (SD)	50.2 (23.90)	49.1 (25.50)	43.1 (25.32)

Abbreviations: NA=not applicable

Source: Excerpted from Table B001.6.1 CSR

Overall most patients (71.4%) had normal hypoglycemia awareness, and 21.4% had reduced awareness as assessed by the Clarke Hypoglycemia Unawareness Survey. One patient (7.1%) had intermediate awareness at baseline. The relevant diabetes history is summarized below.

Table 29 Diabetes History at Baseline Study B001

Variable	**Enrolled (N=26)**	**SSAP (N=22)**	**MSAP/EAP (N=14)**
Duration of diabetes (years) Mean (SD)	7.0 (4.54)	6.6 (4.40)	6.3 (3.48)
Primary Insulin Modality Pump n (%) Injection n (%)	20 (76.9%) 6 (23.1%)	16 (72.7%) 6 (27.3%)	10 (71.4%) 4 (28.6%)
Average number of daily injections of insulin Mean (SD)	5.6 (1.52)	5.6 (1.52)	5.8 (1.71)
Average total daily insulin dose (units) Mean (SD)	47.3 (28.49)	47.7 (30.91)	42.3 (31.16)
Time Since Most Recent Severe Hypoglycemic Event 0-30 days n (%) 31-90 days n (%) 181-365 days n (%) >365 days n (%) Never n (%)	 5 (19.2%) 2 (7.7%) 1 (3.8%) 7 (26.9%) 11 (42.3%)	 5 (22.7%) 2 (9.1%) 0 (0.0%) 7 (31.8%) 8 (36.4%)	 2 (14.3%) 1 (7.1%) 0 (0.0%) 5 (35.7%) 6 (42.9%)

Source: Excerpted from table B001.6.2 CSR

All patients enrolled had normal nasal examination at baseline. While more than 50% of patients reported additional medical conditions, none were relevant in the context of this study.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Per study protocol, the events included in the efficacy analysis (evaluable events), are the events where the caregiver reported administering the study drug correctly.

Efficacy Results – Primary Endpoint

Fourteen (100%) patients in the EAP experienced at least 1 hypoglycemic event (an average [SD] of 2.4 [1.22] events per patient). 33 moderate hypoglycemia events were reported, all these patients had neuroglycopenic symptoms with a BG≤70 mg/dL (range 42-70 mg/dL). The two most common neuroglycopenic symptoms were hunger (46%) and feeling tired (39%). There were no severe hypoglycemia events reported.

The primary efficacy analysis was defined as the percentage of events where the patients were awake or returned to normal status (absence of hypoglycemia symptoms) 30 minutes after NG administration. All the 33 hypoglycemic events returned to normal status at 30 minutes after NG administration. None of the patients in the EAP used injectable glucagon, or used oral carbohydrates after the administration of NG.

Data Quality and Integrity

I do not have any reasons to question the integrity of the data submitted by the applicant. Due to the closure of one site for GCP non-compliance, and the nature of the study, the data from almost half the patients could not be used for the efficacy analysis, and it is also not fully available for a post-hoc evaluation of efficacy (see below for details).

Efficacy Results – Secondary and other relevant endpoints

Notably, 9 patients from the site closed for GCP non-compliance received NG for a total of 23 hypoglycemic episodes, all had an increase in BG over baseline and above 70 mg/dL, and all but 4 reported resolution of symptoms by 30 minutes (2 did not have the outcome listed, and 2 had non-applicable listed under time to return to normal status). It is not clear whether injectable glucagon or carbohydrates were administered.

Time to treatment success

The time to treatment success is presented in the table below. Only 7 (21%) of patients had success in less than 5 minutes, and more than half of patients reported success in 15 minutes or less.

Table 30 Time to Return to Normal Status

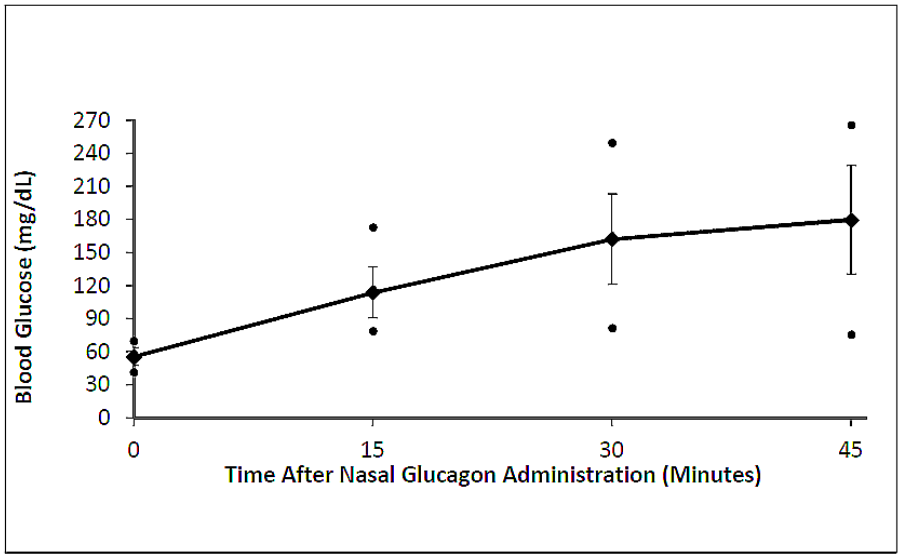
Variable	Level	Statistic	Total Number of Hypoglycemic Events (N=33)
Time to return to normal status from moderate event	<5 minutes	n (%)	7 (21.2%)
	5-<10 minutes	n (%)	11 (33.3%)
	10-<15 minutes	n (%)	4 (12.1%)
	15-<20 minutes	n (%)	5 (15.2%)
	20-<25 minutes	n (%)	5 (15.2%)
	25-<30 minutes	n (%)	1 (3.0%)

Abbreviations: NA=not applicable

Source: Excerpted from Table B001.7.1 CSR

The change in BG increased progressively over time relative to baseline (mean 55.5 mg/dL [range 42-70 mg/dL]). By 15 minutes post-dosing, all patients' BG levels increased to >70 mg/dL. The absolute mean change [SD] (mg/dL) in BG relative to baseline was 58.2 [21.16] at 15 minutes, 106.8 [39.57] at 30 minutes, and 124.1 [49.09] at 45 minutes. post-NG administration.

Figure 18 Blood Glucose Values after NG Administration



Notes: Mean ± standard deviation; (·) = minimum/maximum value.

Source: Figure B001.7.1 CSR

Although there was no severe hypoglycemia, 5 patients reported 8 applicant-defined major hypoglycemic events with neuroglycopenic symptoms and BG<50 mg/dL. In all these events, patients had neuroglycopenic symptoms and a BG range of 42-48 mg/dL at the time of NG

administration. Within 15 minutes of NG dosing, all patients' BG levels returned to above 70 mg/dL.

Caregiver satisfaction

The degree of difficulty for various tasks was captured on a scale ranging from 1 (very difficult) to 7 (very easy). For 66.7% of hypoglycemic events, caregivers reported that understanding the instruction for NG administration was very easy, while only 60.6% reported that the actual NG administration was very easy. Regardless, none of the providers reported that any of these tasks was difficult (1,2, or 3 on the scale). For the 60.6% of hypoglycemic events, caregivers were able to administer NG within 30 seconds from the time the caregiver began to open the canister, and only for 4 events (12%), the administration was delayed at between 1-2 minutes.

Dose/Dose Response

Not applicable as only one dose of intranasal glucagon was studied.

Durability of Response

Not applicable

Persistence of Effect

Not applicable.

Additional Analyses Conducted on the Individual Trial

No additional analyses are relevant for the efficacy evaluation of the NG product.

6.5. B002

6.5.1. Study Design

Study Title: Multiple Center, Open Label, Prospective, Observational Study To Evaluate The Effectiveness And Ease-Of-Use Of LY900018 (AMG504-1) Administered In The Home Or Work Environments For Treating Episodes Of Severe Or Moderate Hypoglycemia In Patients With Type 1 Diabetes

Overview and Objective

The primary objective was to evaluate the effectiveness of NG administered outside of the hospital/clinic in treating episodes of severe or moderate hypoglycemia in persons with T1D.

The secondary objectives were to:

- Assess the ease-of-use of NG in the hands of caregivers of patients who may be called upon to treat episodes of severe or moderate hypoglycemia (evaluated with a simple questionnaire filled out by caregivers assessing the degree of difficulty using the intranasal glucagon kit, the time required to administer the drug, the caregiver's degree of satisfaction, and the overall experience with use of the study drug).

- Evaluate safety data on local tolerability from the patient's perspective (evaluated through the observations recorded by the caregiver on a simple questionnaire up to 5 hours post-glucagon administration and with a Nasal Score Questionnaire which was filled out by the patient within 2 hours of full recovery after a dosing event).

The tertiary objectives were to:

- Assess the change in glucose level from NG administration to 15, 30, and 45 minutes after the studied drug administration (based on caregiver reported BG).

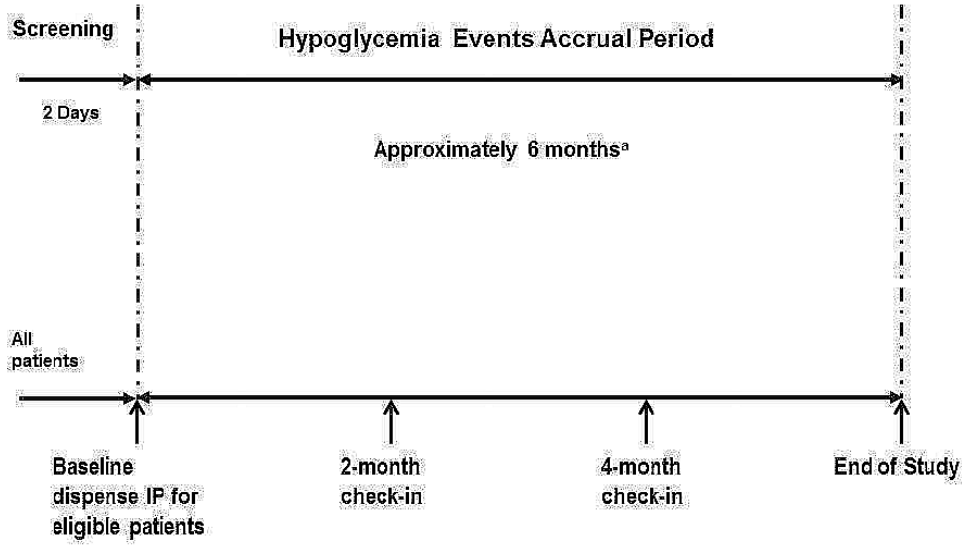
- Evaluate the immunogenicity of glucagon following NG administration (only some of the sites were equipped to process and store samples for assessment of anti-drug antibodies (ADA). Per an agreement between Food and Drug Administration (FDA) and Locemia, ADA samples were collected from patients enrolled at those sites which were equipped to process and store ADA samples: blood samples were obtained from all subjects from these sites at baseline and, for any subject from that site that receives 1 or more doses of NG during the study, a second sample was obtained at the end of the study).

Trial Design

Study B002 was a multi-center, single arm, prospective, open-label study. The target of the study was to obtain treatment response and user experience data on approximately 129 evaluable episodes of severe or moderate symptomatic hypoglycemia. Eligible patients and their principal caregiver were trained in the use of NG, and 4 doses of NG were dispensed to each patient at enrollment.

Patients returned to the clinic with their caregiver(s) at 2 and 4 months (±1week) after starting the study to verify test article inventory, to review the questionnaires that may have been filled out for each event, and receive answers to any questions they may have had. Additional doses of NG and questionnaires were dispensed to the participant/caregiver(s) as per the clinical judgment of the Principal Investigator or designee. Each patient continued in the study until he/she experienced one or more hypoglycemic events or until the study was complete (a cumulative number of approximately 129 evaluable events had occurred [approximately 6 months]), whichever came first. All patients were asked to return to the clinic for an End of Study Visit (approximately 6 months).

Figure 19 Study Design



Abbreviation: IP = investigational product.
[a]Each patient continued in the study until he/she experienced one or more hypoglycemic events or until the study was complete, whichever came first.

Source: Figure B002.5.1 CSR

Hypoglycemia definitions:

- Severe hypoglycemia was defined as an episode where the person with diabetes is clinically incapacitated (that is, unconscious, convulsions, severe mental disorientation) to the point where the person requires third-party assistance to treat the hypoglycemia.

- Moderate hypoglycemia was defined as an episode wherein the person with diabetes was showing signs of neuroglycopenia (weakness, difficulty speaking, double vision, drowsiness, inability to concentrate, blurred vision, anxiety, hunger, tiredness or confusion) and had a glucometer reading of 60 mg/dL or less based on a blood sample taken at or near the time of treatment.

Study Procedures

Procedures for administering glucagon

The patient and their principal caregiver(s) (spouse, family member, roommate, coworker, etc.) were trained on the use of NG. It was highlighted that, for cases of severe hypoglycemia, the dose of NG should have been administered with the patient lying in a fully reclined lateral position on the opposite side of the nostril being administered. For cases of moderate

hypoglycemia, NG may have been administered with the patient in the seated position or in lateral recumbency.

Treatments

- Investigational product: NG 3 mg glucagon– administered via a device that propels powder into the nostril

Notably, between May 14, 2014, and June 20, 2014, the batch of product used was found to produce partial obstruction of the delivery device resulting in sub-target dosing. At that time the sites were asked to stop recruiting and terminate all patients already recruited. The study was reactivated on November 25, 2014 with a different product batch.

Study Endpoints

The primary outcome measure was the proportion of patients who were awake or returning to a normal status within 30 minutes following study drug administration.

Inclusion/Exclusion Criteria

Eligible patients were otherwise healthy and did not have medical conditions which could interfere with the absorption, distribution, metabolism, or excretion of the study drug per the judgment of the investigator.

See study protocol for full inclusion and exclusion criteria.

Statistical Analysis Plan

Analysis populations were defined as the following:

- Enrolled: all patients who were assigned to study drug.

- Efficacy Analysis Population (EAP): enrolled patients who received at least 1 dose of the study drug with evaluable information on treatment response. Non-evaluable events included hypoglycemia events for which patients required external professional medical assistance (that is, paramedic/ambulance staff, admission to hospital) or used injected glucagon or oral carbohydrates within 30 minutes and before responding since information on time to treatment response was not available. Patients from a non-Good Clinical Practice (GCP) compliant site were also excluded from this population.

- Main Safety Analysis Population (MSAP): eligible enrolled patients who experienced at least 1 hypoglycemic event and received at least 1 dose of study drug. Patients from the non-GCP compliant site and patients who were under-dosed due to the issue of powder

aggregation before the study pause were considered ineligible thus excluded from this population.

- Sensitivity Safety Analysis Population (SSAP): enrolled patients who received at least 1 dose of study drug. Patients from the non-GCP compliant site and those who were under-dosed due to the issue of powder aggregation before the study pause were included in this population.

The sample size calculation was based on the primary effectiveness endpoint, assuming a 75% response rate. The calculation resulted in the need for 129 evaluable events.

Notably, an interim analysis was performed, and the applicant did not consider it to have impacted the study results as this is an open-label study.

Protocol Amendments

There was one protocol amendment, following FDA advice, which introduced immunogenicity assessments at baseline, 2, 4 months, and end of study.

6.5.2. Study Results

Compliance with Good Clinical Practices

The applicant states that this study was performed in compliance with the principles of GCP. One of the study sites was found to be non-GCP compliant, and the patients from that site were excluded from the main analyses.

Financial Disclosure

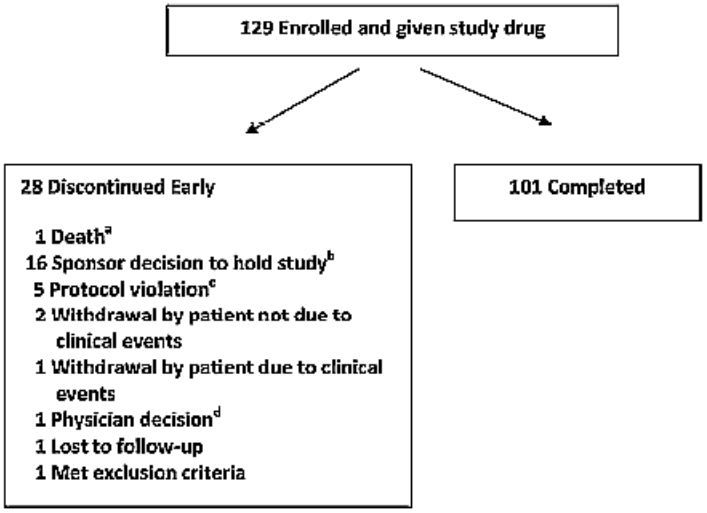
See section 13.2 for details.

Patient Disposition

The study screened 129 patients, and there were no screen failures. Of the 129 patients who entered the study, 87 received at least one dose of study drug.

The figure below shows the disposition of the 129 enrolled patients, with 28 patients discontinuing the study. One patient died of Klebsiella Pneumoniae infection, deemed unrelated to the study drug.

Figure 20 Patient Disposition Study B002



a Death not related to study drug
b Study placed on hold due to treatment with IP that was underdosed
c Site 009 was terminated due to GCP non-compliance
d Patent withdrawn due to safety reasons

Source:
Program Location: statsclstr\lillyce\prd\ly900018\i18r_mc_b002\programs
Dataset Location: statsclstr\lillyce\prd\ly900018\i18r_mc_b002\final output\shared
JSS Medical Research: Listing 16.2.1

Source: Figure B002.6.1 CSR

Protocol Violations/Deviations

Of the 32 major protocol deviations reported, the majority occurred in Site 009 (5 patients) which was terminated due to serious non-GCP compliance with a total of 18 major protocol deviations. All patients from site 009 have been excluded from the EAP and MSAP. Patients from this site who received at least 1 dose of study drug were included in the SSAP.

Three major protocol deviations were related to unauthorized use of study drug in individuals who were not enrolled in this clinical trial. During the study active period, the caregiver of patient (b) (6) administered the study medication to an individual who was not enrolled in this study but was experiencing a hypoglycemia event. Patient (b) (6) administered study drug twice (on 2 separate occasions) to an individual who was not enrolled in the study but was experiencing a severe hypoglycemic event. Data from these 2 individuals who were not enrolled in this study have been excluded from all analyses, but narratives were submitted by the applicant.

Seven major protocol deviations were related to 6 patients who consumed oral carbohydrates within 30 minutes of study drug administration. As a result, these 7 events became unevaluable, and were excluded from the EAP analysis.

Another major protocol violation was in patient (b) (6), who was enrolled in the study in error and was discontinued by the investigator for safety reasons. Since this patient was enrolled in error but received study drug, he/she was included only in the SSAP and was excluded from the MSAP and EAP.

Table 31 Major Protocol Deviations – Study B002

Site Number	Patient ID	Description of Deviation
	(b) (6)	PI oversight not observed: During a monitoring visit held on June 5, 2014 an absence of note from the PI confirming patient's eligibility to the study at Visit 1 was observed; safety labs and screening ECG tracings were not reviewed by the PI. CRF pages 15 and 16 requiring PI's signature to the Inclusion and Exclusion criteria were not signed by her either. Also it was confirmed by the PI that she did not see any of the four patients and caregivers enrolled into the study. The site was trained on this aspect during the study pause, ready to enroll
		During a monitoring visit held on 5 June 5, 2014, it was noted by the CRA that significant amount of GCP (Good Clinical Practice) and GDP (Good Documentation Practice) errors were noted in the CRF and documentation in general. It was noted that the Study Coordinator had extensive experience in academic-driven research, but this was her first trial with a pharmaceutical industry. Study staff completed GCP and ICH training during the study pause, prior to the study reactivation in November 2014.
		Subject experienced a hypoglycemia event on (b) (6), but had eaten candies as soon as she realized she was experiencing a hypoglycemia event.
		While traveling in Mexico, the caregiver administered the study medication to an individual experiencing a hypoglycemia event. This individual had not given consent to participate in the study.
		On the Hypoglycemia Questionnaire (for episode that occurred on (b) (6)) the patient reported having eaten a chicken wing in error approximately 15 minutes after using the study medication.
		As reported on the Hypoglycemia Questionnaire (for episode that occurred on (b) (6)) – after no decrease in symptoms and no injectable glucagon available, the patient was given maple syrup approximately 15 minutes after using the study medication.
		Subject was enrolled into the study in error and was discontinued for not meeting exclusion criteria #3 and #5. The patient was on a kidney transplant list for kidney failure disease and was being prescribed a prohibited medication (25 mg of Metoprolol BID for prophylaxis).

(b) (6)	
	The patient used the study medication to treat a moderate hypoglycemia event on (b) (6). In a state of panic, the caregiver mentioned that she gave the patient a box of juice as well as an apple 5 minutes prior to administering the study medication.
	The patient administered the study medication to an individual that had NOT consented to participate in the study
	For a second time, the patient administered the study medication to the same individual that had NOT consented to participate in the study
	Patient # (b) (6) signed the ICF on (b) (6) and had all procedures performed for the Pre-Trial Evaluation and Enrollment Visit on that day, except for the safety labs since she was not fasting. She returned the next day to complete the visit. The site dispensed the study drug to the patient on (b) (6), but they should have waited to dispense it on the last day when all procedures were performed. The patient experienced a severe hypoglycemia event on the first night following the visit of (b) (6) (i.e. night of (b) (6)) and used a dose of study drug. The patient started using the study drug before the safety lab samples were drawn for the first study visit.
	The patient used the study medication to treat a hypoglycemia event on (b) (6), but ingested some carbohydrates after the blood glucose reading taken 15 minutes following study drug administration because she was in the middle of doing exercises and she was not finished yet.
	The patient experienced a moderate hypoglycemia event on (b) (6). The patient indicated on the questionnaire that she had initially treated the event by eating carbohydrates (31g). After seeing no improvement in her blood glucose (approximately 15 minutes after), she decided to administer the study medication.
	The patient experienced a hypoglycemia event on (b) (6) and indicated on the questionnaire having eaten an apple. It was not confirmed with the patient whether the apple was eaten before or after the 15 minute reading.
	The patient experienced three hypoglycemia events on (b) (6) and (b) (6) and used 3 study medication devices. These events occurred after (b) (6) when the Applicant had given the Principal Investigator directives to instruct his patients to stop using the study medication. IRB Approval was also revoked on (b) (6).
	Patient was enrolled into the study without a caregiver as required per protocol.
	The patient experienced three hypoglycemia events on (b) (6) and (b) (6) and used 3 study medication devices. These events occurred after May 22, 2015 when the Applicant had given the Principal Investigator directives to instruct his patients to stop using the study medication. IRB Approval was also revoked on May 29, 2015.
	Patient was enrolled into the study without a caregiver as required per protocol.

(b) (6)		The patient experienced two hypoglycemia events on (b) (6) and (b) (6) and used 2 study medication devices. These events occurred after 22-May-2015 when the Applicant had given the Principal Investigator directives to instruct his patients to stop using the study medication. IRB Approval was also revoked on May 29, 2015.
		The witness signed the Informed Consent Form on (b) (6), 2 days after the subject and Principal Investigator had signed.
		Patient was enrolled into the study without a caregiver as required per protocol.
		The laboratory assessments were performed on (b) (6), 8 days after the Pre-Trial Evaluation & Enrollment visit and after the subject had already used 2 doses of the study medication.
		The witness signed the Informed Consent Form on (b) (6), 1 day after the subject and Principal Investigator had signed.
		The patient experienced a hypoglycemia event on (b) (6) and used the study medication. This event occurred after May 22, 2015 when the Applicant had given the Principal Investigator directives to instruct his patients to stop using the study medication. IRB Approval was also revoked on May 29, 2015.
009	N/A	The Principal Investigator distributed a non-IRB approved letter to all potential subjects inviting them to participate in the AMG108 study.
009	N/A	On April 27, 2015, the Principal Investigator inadvertently sent the applicant and CRO an electronic copy of the Master Patient Identification List. CRO/Applicant destroyed/deleted all material related to this communication.
009	N/A	The Principal Investigator and Study Coordinator did not provide any proof of GCP training prior to or during the study.
009	N/A	For most subjects, there was no documentation of the consenting process. The principal investigator did some documentation in each patient's chart much after the ICF signature, during the monitoring visit of May 7, 2015, but he wrote the date of the respective enrollment visit dates.
009	N/A	For most subjects enrolled, the laboratory reports had not been commented for clinical significance, initialed and dated. This was done retroactively during the CRA's monitoring visits.
009	N/A	For most subjects enrolled, the PI did not perform some of the assessments required by the protocol for the Pre-Trial Evaluation and Enrollment visit (e.g. physical exam, vital signs, weight, height, substance use habit). On many occasions, the PI used data from previous subject visits to complete the CRFs for these assessments.

009	All subjects	There was no source document for many items. The site entered the data directly in the CRF for the following items: Ethnicity, Gynecologic history, contraceptive method, Most recent hypoglycemic event, Fasting status, Training of Subject/Caregivers in the use of IN glucagon, injected glucagon, Dispensing of questionnaires and 4 doses of AMG504-1 to Subject/Caregivers.

Abbreviations: ALT = alanine transaminase; BID = twice daily; BUN = blood urea nitrogen; C02 = carbon dioxide; CRF = case report form; CRA = clinical research associate; ECG = electrocardiogram; HbA1c = hemoglobin A1c; ICF = informed consent form; ICH = International Conference on Harmonisation; IRB = Investigational Review Board; GFR = glomerular filtration rate; ID = identification; MPV =mean corpuscular volume ; NA = not available; PI = principle investigator; RDW = red cell distribution width; Sub-I = subinvestigator; V = visit.
Source: Table B002.11.14 CSR

Baseline Demographic Characteristics

The mean age of the participants was 46 years, men and women were well balanced, and over 95% of patients were white. The patient's demographic characteristics are presented in Table 32 below.

Table 32 Table of Demographic Characteristics – Study B002

Variable	Level	Statistic	Enrolled (N=129)	SSAP (N=87)	MSAP (N=74)
Age (years)	NA	Valid n	129	87	74
		Mean (SD)	46.6 (14.43)	46.0 (14.64)	46.2 (15.00)
		Median	49.0	47.0	46.5
Gender	Female	n (%)	56 (43.4%)	46 (52.9%)	39 (52.7%)
	Male	n (%)	73 (56.6%)	41 (47.1%)	35 (47.3%)
Race	American Indian or Alaska Native	n (%)	1 (0.8%)	1 (1.1%)	1 (1.4%)
	Black	n (%)	5 (3.9%)	3 (3.4%)	2 (2.7%)
	White	n (%)	123 (95.3%)	83 (95.4%)	71 (95.9%)
Body Mass Index (kg/m^2)	NA	Valid n	129	87	74
		Mean (SD)	27.1 (4.10)	26.6 (4.24)	26.6 (4.39)
Country	Canada	n (%)	81 (62.8%)	58 (66.7%)	55 (74.3%)
	United States	n (%)	48 (37.2%)	29 (33.3%)	19 (25.7%)

Abbreviations: CI = confidence interval; MSAP = Main Safety Analysis Population; N = number of patients; NA = not available; SD = standard deviation; SSAP = Sensitivity Safety Analysis Population.

Source: Excerpted from Table B002.6.2 CSR

The mean diabetes duration was over 25 years, and over 50% of patients were using an insulin pump as the primary insulin delivery modality.

Table 33 Diabetes History – Study B002

Variable	Level	Statistic	Enrolled (N=129)	SSAP (N=87)	MSAP (N=74)
Duration of diabetes (years)	NA	Valid n	129	87	74
		Mean (SD)	27.2 (13.61)	26.8 (13.44)	26.3 (13.56)
		Median	27.9	27.3	25.9
Primary insulin modality	Pump	n (%)	72 (55.8%)	48 (55.2%)	39 (52.7%)
	Injection	n (%)	57 (44.2%)	39 (44.8%)	35 (47.3%)
Average number of daily injections of insulin	NA	Valid n	57	39	35
		Mean (SD)	4.4 (1.11)	4.3 (1.11)	4.2 (0.87)
		Median	4.0	4.0	4.0
Average total daily insulin dose (units)	NA	Valid n	129	87	74
		Mean (SD)	52.9 (25.63)	48.6 (21.72)	49.5 (21.68)
		Median	49.0	48.0	48.0
Time since most recent severe hypoglycemic event	0-30 days	n (%)	27 (20.9%)	20 (23.0%)	16 (21.6%)
	31-90 days	n (%)	24 (18.6%)	14 (16.1%)	13 (17.6%)
	91-180 days	n (%)	18 (14.0%)	11 (12.6%)	9 (12.2%)
	181-365 days	n (%)	12 (9.3%)	6 (6.9%)	5 (6.8%)
	>365 days	n (%)	37 (28.7%)	29 (33.3%)	24 (32.4%)
	Never	n (%)	11 (8.5%)	7 (8.0%)	7 (9.5%)

Abbreviations: CI = confidence interval; MSAP = Main Safety Analysis Population; N = number of patients; NA = not applicable; SD = standard deviation; SSAP = Sensitivity Safety Analysis Population.

Source: Excerpted from Table B002.6.3 CSR

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The applicant reports that non-study glucagon was not used for any of the events, and that emergency services were not required for any of the patients.

Seven patients reported ingesting carbohydrates within 15 minutes of study drug administration, and their characteristics are presented below.

Table 34 Hypoglycemic Events in which the Patient Ingested Oral Carbohydrates Study B002

Patient ID	Event Description
(b) (6)	The patient ate candy as soon as she realized she was experiencing a hypoglycemic episode, just before using the device to administer NG
	The patient reported eating a chicken wing in error 15 minutes post BG administration
	The patient received maple syrup 15 minutes after NG administration because the symptoms of hypoglycemia did not resolve
	The caregiver panicked and gave the patient a juice box and an apple 5 minutes prior to NG administration

(b) (6)	
	The patient ingested carbohydrates 15 minutes post NG administration because she wanted to continue to exercise
	The patient initially treated the event with carbohydrates, and when the BG did not rise, she administered the study medication
	The patient/caregiver indicated on the questionnaire that they ate an apple but the timing is unclear

Source: Table B002.6.1 CSR

Efficacy Results – Primary Endpoint

The primary efficacy endpoint, as defined in the Study B002 protocol, was the percentage of patients awake or returning to a normal status within 30 minutes following NG administration. However, the primary efficacy analyses in the SAP, was stated as the percentage of events where patients awaken or return to normal status within 30 minutes after NG administration. Both analyses are presented below.

Of the 69 patients included in the EAP, 66 (95.7%) awakened or achieved normality within 30 minutes in at least one evaluable event during the study period, while 64 (92.8%) patients achieved normality in all evaluable events.

The 69 patients in the EAP reported 157 hypoglycemic events in total (an average [SD] of 2.3 [1.77] events per patient). During these hypoglycemic episodes, patients reported experiencing neuroglycopenic symptoms with a patient reported fingerstick glucose range of 21.6 to 73.9 mg/dL at the time of glucagon administration. Of the 157 evaluable hypoglycemic events, 151 (96.2%) events were resolved within 30 minutes following NG administration and 6 (3.8%) events were not resolved within 30 minutes. Of the 6 events, 5 events were reported as resolved between 30 to 45 minutes. One event was not reported as resolved because the patient reported persistent headache. A total of 12 severe hypoglycemia events have been included in the EAP – this analysis is presented under Secondary and other relevant endpoints.

179 hypoglycemic events were reported for the MSAP, and 207 events for the SSAP. For the MSAP, the 22 extra events were as follows: 7 reported carbohydrate intake within 15 minutes of study drug administration, and 15 were missing information on the response. The additional 28 events in SSAP were as follows: 16 events from the discontinued site, and 9 events where the patients were under-dosed due to the issue of powder aggregation.

Reviewer comment: While the efficacy numbers for the EAP appear reasonable, I am concerned that there is a lot of missing data in this study, and we do not know what happened to the patients who were excluded from the efficacy analyses. This study also had other conduct issues such as site closure for GCP non-compliance, drug delivery issues, etc, and the data is not very robust. This may be acceptable as this was a real use and not a pivotal study, and efficacy has been demonstrated in the pivotal study.

Data Quality and Integrity

This is a real use study and the data is not as rigorous as a randomized clinical trial. Additionally, a large number of major and minor protocol deviations lead to multiple unevaluable events. I did not identify any data quality issues with the data that was included in the primary analysis.

Reviewer comment: As for study B001, the data quality is less than ideal, leading to many unevaluable events. This study is being reviewed for both efficacy and safety as supportive evidence, however, it is not rigorous enough for inclusion in the product label.

Efficacy Results – Secondary and other relevant endpoints

Severe Hypoglycemia

A total of 19 episodes of severe hypoglycemia were reported by 12 patients. Only 12 severe hypoglycemia events have been included in the EAP. The seven excluded events were as follows: one patient received a dose before the study pause, 2 consumed oral carbohydrates, 2 were reported with user error (plunger not completely depressed), and 2 were from a GCP non-compliant site.

The 12 events included in the EAP were reported by 7 patients. In all these events, patients had neuroglycopenic symptoms and a BG range of 28.8-59.5 mg/dL at the time of NG administration. Patients/caregivers reported the occurrence of the following symptoms during severe hypoglycemic events: unconsciousness 3 (25%), convulsions 7 (58.3%), severe mental disorientation 7 (58.3%) or other 1 (8.3%) events. The 12 episodes were reported by the applicant as resolved by 15 minutes. However, only 11 had BG over 70 mg/dL at 30 minutes (the 12th patient still had an increase of 20 mg/dL over baseline at 20 minutes).

Reviewer comment: Excluding some of the 7 events presented above is incongruous with the purpose of this study, which is to test real-life use of the NG drug product. While it may be adequate to not include the patients who received oral carbohydrates, and the one who received the NG drug product before changes were made to improve delivery, the two patients who did not depress the plunger enough to appropriately deliver the NG are relevant to the analysis, as this is a situation that can happen in real life use, and it is concerning particularly for a product meant for emergency rescue.

Moderate Hypoglycemia

One hundred forty-five moderate hypoglycemia events were included in the EAP. The most common sign/symptoms were weakness (62.8%) and inability to concentrate (42.8%). Within

15 minutes following NG administration, 71% of the moderate hypoglycemic events were reported as resolved and within 30 minutes 95.9% resolved.

Five patients reported 6 moderate hypoglycemic events that did not return to normal status within 30 minutes after the administration of NG. In 4 of these events, BG was reported >70 mg/dL at 30 minutes. For the other 2 events, BG was reported >70 mg/dL between 30 and 45 minutes. One of these patients reported persistent headache even after BG normalization.

Dose/Dose Response

Not applicable as only one dose of intranasal glucagon was studied.

Durability of Response

Not applicable

Persistence of Effect

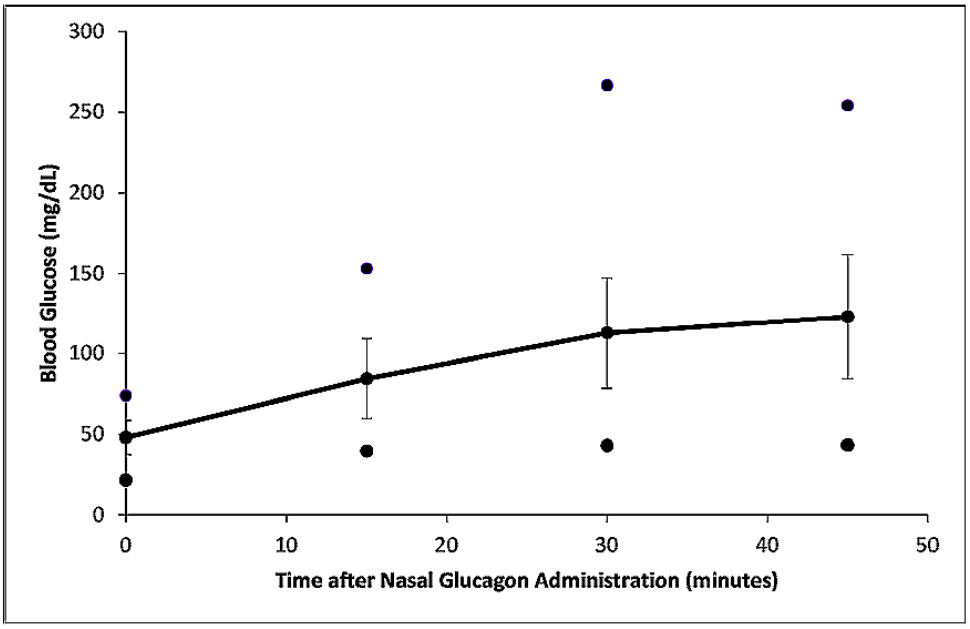
Not applicable.

Additional Analyses Conducted on the Individual Trial

BG response over time

The mean BG at baseline was 47.9 mg/dL, and it increased to 84.4 mg/dL by 15 minutes post dose, and continued to rise thereafter. The change in BG is summarized for 15, 30, and 45 minutes after the NG administration.

Figure 21 Mean Blood Glucose After NG Administration



Abbreviations: SD = standard deviation.
Note: Data points are mean ± SD; (·) = min/max value

Source: Figure B002.7.1 CSR

User Satisfaction

Caregivers filled out a user friendliness questionnaire after the NG administration. Caregivers reported that the administration of NG was very easy in 55.9% of events. For 70.4% of the events, caregivers were able to administer the NG within 30 seconds after beginning to open the cannister. 92.8% of the caregivers opined that intranasal delivery of glucagon would be preferable over needle-based delivery for treatment of severe hypoglycemia.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

There were 5 studies that were considered relevant for evaluation of efficacy. The "bridging study" – study IGBI – was considered the pivotal study for the purpose of the FDA review, as it was performed with one of the to-be-marketed product batches, and with the to-be-marketed device, in adults with T1DM. IGBC was performed in adults with T1 and T2DM, and was similar to IGBI in design and primary efficacy endpoint, and was performed in clinic/research facility setting in the context of insulin-induced hypoglycemia. For studies IGBC and IGBI, hypoglycemia

was induced by an intravenous infusion of regular insulin, with goal of reducing the glucose to <50 mg/dL (infusion stopped when glucose reached <60 mg/dL, glucagon administered 5 minutes later). The design of study IGBC was agreed upon with the FDA via a SPA, including the adequacy of the primary endpoint, and the noninferiority margin. The non-inferiority margin agreed with FDA was 10% between NG and IMG, and it was chosen on the basis of the data for glucagon injection in a simulated emergency study where 10% of participants (parents of children and adolescents with T1D) failed entirely to administer the injectable glucagon product[1].

The applicant also submitted the pediatric study IGBB, which was conducted in pediatric patients with T1DM, in a clinical research setting where insulin was used to lower BG to <80 mg/dL, followed by glucagon administration. Studies IGBI, IGBB, and IGBC used currently marketed intramuscular glucagon as comparator.

The applicant also submitted two real use studies: B001, which was conducted with pediatric patients, and B002, which was conducted with adult patients. In both studies, the NG product was administered by a caretaker at home, and the interpretability of the studies is marred by issues of study conduct that lead to a study site closure and many non-evaluable events.

While several doses of the NG product were evaluated during development, only one dose – 3 mg – was evaluated in the controlled phase 3 studies in adults, and the real use study in pediatrics. In study IGBB, 2 doses were evaluated, 2 mg, and 3 mg. Only the 3 mg dose is proposed for marketing.

7.1.1. Primary Endpoints

The primary endpoint was different for the real use studies compared to the pivotal studies, however, all the endpoints converge around resolution of hypoglycemia at 30 minutes. The endpoints used to assess efficacy in the relevant clinical trials are outlined in the table below.

Table 35 Endpoints Used to Assess Efficacy by Trial

Endpoint	Study(ies)
Proportion of patients who achieved either an increase in glucose to ≥70 mg/dL or an increase of ≥20 mg/dL from nadir within 30 min after receiving study glucagon.	IGBI, IGBC
Proportion of patients who achieved an increase in glucose of ≥20 mg/dL (1.1 mmol/L) from nadir within 30 min after receiving study glucagon.	IGBB
Proportion of patients who awakened or returned to normal status within 30 min after receiving study glucagon.	B001, B002

[1] Harris et al, 2001

In both IGBI, and IGBC, NG 3 mg demonstrated non-inferiority to CG based on the proportion of patients achieving the primary endpoint. The percentage of patients that achieved treatment success with NG was 100% in IGBI, and 98.7% in IGBC. CG had 100% success rate in both studies. Study IGBC also has a very small subpopulation of patients with T2DM, not included in the primary analysis. All the 5 evaluable patients with T2DM achieved treatment success at 30 minutes.

In the pediatric study IGBB, NG achieved 100% treatment success across all age groups.

In the adult actual use study (B002), where NG was administered by caregivers to treat naturally occurring moderate and severe hypoglycemic episodes, NG 3 mg resolved 96.2% of the hypoglycemic events within 30 minutes. In most remaining cases, the patients reached normoglycemia, and the neuroglycopenic symptoms resolved by 30 minutes, but they had other persistent symptoms which prevented them from being marked as achieving the primary endpoint of returning to normal status. All the patients from the EAP with severe hypoglycemia awoke, stopped convulsing, or returned to normal status within 30 minutes following NG administration. However, 7 patients with severe hypoglycemia were excluded from the EAP analysis, 2 of which reported errors in depressing the plunger. Notably the device and powder used for the B002 are not the same as the to be marketed product, and the relevance of the delivery issues cannot be assessed.

In the pediatric actual use study (B001), 100% of hypoglycemia events were resolved within 30 minutes of NG administration. Notably, all events were moderate, there was no event of severe hypoglycemia reported in this study.

While all these studies are supportive of the efficacy of the 3 mg NG, only study IGBI is supportive of the efficacy of the to-be-marketed drug product, as this is the only study where the to be marketed drug product was used.

In order to link the commercial drug product to the efficacy from what the applicant considers the pivotal study, IGBC, the applicant looked at the between study comparison to demonstrate non-inferiority of the to-be-marketed drug product (used in IGBI) compared to the NG drug product used in study IGBC. In this analysis, the risk difference observed in study IGBC, and the risk difference observed in IGBI, were compared. The results of this analysis are presented below, and the applicant concluded that the commercial product is non-inferior compared to the drug product used in study IGBC.

Table 36 Indirect Comparison of Treatment Success of Nasal Glucagon Used in Study IGBC and Study IGBI

	Primary Efficacy Analysis IGBC (T1D) N=75[a]		Primary Efficacy Analysis IGBI (T1D) N=66[a]	
	NG 3 mg	IMG 1 mg	NG 3 mg	IMG 1 mg
Treatment Success – n (%)	74 (98.7)	75 (100)	66 (100)	66 (100)
Treatment Difference (Confidence Interval)[b]	1.3% (4.0%)[c]		0% (1.5%)[d]	
Indirect Comparison (Confidence Interval)	-1.3% (2.7%)[d,e]			

Abbreviations: CI = confidence interval; CSR = clinical study report; IMG = intramuscular glucagon; n = number of patients in the specified group; N = number of patients in the analysis population; NG = nasal glucagon; NIM = non-inferiority margin; T1D = type 1 diabetes mellitus.

a The Efficacy Analysis Population consisted of all patients who received both doses of the Study Drug with evaluable primary outcome.

b Difference calculated as (percentage with success in IMG) – (percentage with success in NG); NIM = 10%.

c 1-sided 97.5% CI from a 1-sample mean of the paired differences in occurrence of outcome.

d Upper limit of the 2-sided 95% CI from Wald method with continuity correction.

e Difference calculated as (treatment difference in IGBI) – (treatment difference in IGBC); NIM = 10%.

Source: Table 2.7.3.12 Clinical Efficacy Summary

Reviewer comment: In general, NG met the efficacy endpoint in all phase 3 trials. The variability in the drug product throughout the development program does not appear to impact the efficacy evaluation of nasal glucagon.

7.1.2. Secondary and Other Endpoints

Time to treatment success

CG appears to lead to faster hypoglycemia resolution compared to the BG. Only two of the studies were designed to specifically look at time to treatment success as it compared to the currently marketed glucagon, IGBI, and IGBC. The difference in time to treatment success between NG and CG (NG minus CG) was 1.5 minutes for Study IGBI, which was shorter than what was observed in Study IGBC (4 minutes).

7.1.3. Subpopulations

T2DM

The majority of the patients enrolled in these studies had T1DM. Six adults with T2DM were enrolled in study IGBC, and 5 were included in the efficacy analysis. All 5 (100%) patients receiving 3 mg NG achieved treatment success as defined in the study protocol. NG was

delayed by about 1 minute compared to CG in patients with T2DM, as expected from the analyses for patients with T1DM.

Additionally, pharmacodynamic data was collected from the 6 patients with T2DM in study IGBC, and from 9 patients with T2DM in study IGBG and the response appeared similar to the one observed for patients with T1DM.

The applicant concludes that no difference is expected between patients with T1DM, and T2DM, for response to 3 mg NG.

Reviewer comment: There is no pathophysiological reason why the hypoglycemia response to glucagon would be different in patients with T2DM compared to patients with T1DM. While the population with T2DM studied in the NG development program is insufficient to draw conclusions based on data in patients with T2DM alone, I believe that the findings for T1DM can be extended to patients with T2DM.

Pediatric Subpopulation

The development program included patients between ages 4-<18 with T1DM. There were 2 studies performed in pediatric patients, study IGBB, which was a research center-based study, and B001, which was a real use study.

In study IGBB, insulin was used to lower BG to about 80 mg/dL. NG 3 mg was similar in efficacy (increasing BG by >20 mg/dL at 30 minutes compared to nadir) to CG. In study B001, NG was used successfully by caregivers of pediatric patients with T1DM, and was found to be effective in treating moderate hypoglycemia.

Notably, none of these studies used the to-be-marketed drug product. The commercial product was not used in any pediatric patients. **Dose and Dose-Response**

Efficacy for doses other than 3 mg

Since the commercial drug product as proposed by the applicant (b) (4) would allow for a dose as low as 2 mg to be delivered, the efficacy for the 2 mg dose is discussed here. The applicant argues that (b) (4) the dose of 2 mg of NG has been confirmed to produce a clinical response. The applicant was asked to submit the efficacy and clinical pharmacology data for the patients exposed to 2 mg NG in the development program.

The applicant provided a response on November 24, 2018, stating that the glycemic response to the 2 mg NG dose was evaluated in 3 clinical studies, IGBA, IGBB, and IGBD. The drug product used in these studies was not the to-be-marketed drug product, but rather various

earlier iterations of the NG product. The to-be-marketed drug product has not been studied at doses other than 3 mg.

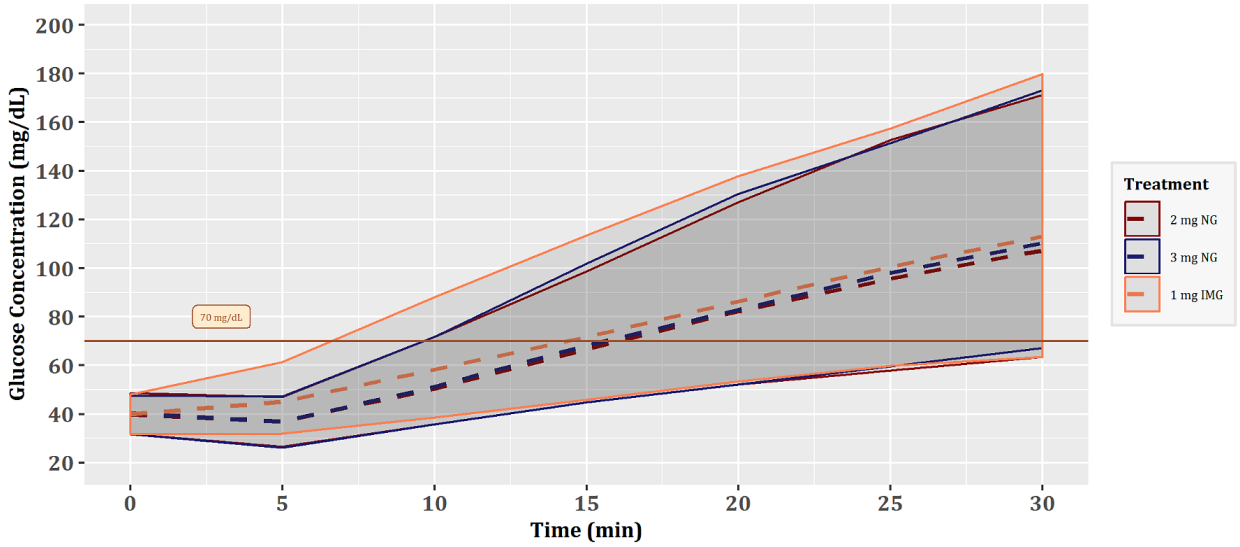
Study IGBD was the first clinical study in the NG development program, and was conducted in healthy volunteers. This study will not be discussed as treatment success was not defined for study IGBD. Applicant-defined "treatment success" was evaluated for studies IGBA and IGBB which enrolled adult and pediatric patients with T1DM. Since study-defined treatment success was different between the two studies, the applicant used the definition agreed upon with the FDA under a SPA for study IGBC to analyze the results of the efficacy of the 2 mg dose post-hoc. The post-hoc definition for treatment success was an increase in BG from nadir to at least 70 mg/dL or an absolute increase in BG of at least 20 mg/dL from nadir within 30 minutes of glucagon treatment. Because the protocol for Study IGBB did not require the glucose level to be decreased below 70 mg/dL prior to glucagon administration, only the second part of the treatment success definition was used to assess the treatment success in study IGBB.

In study IGBA, using the post-hoc treatment success definition, 16/18 (88.9%) patients exposed to 2 mg NG were considered responders. However, no substantial glucagon levels detected for 4/18 patients exposed to 2 mg NG, making the interpretation of the efficacy results questionable. Two of these 4 patients were non-responders, and 2 were responders. It is not clear why 2/16 responders did not have detectable glucagon levels. The applicant stated that one possible reason is the glucagon assay used in this study, which was less sensitive than the one used later in the development program. In the same study, 100% of patients exposed to CG, or to 3 mg NG achieved treatment success.

In the pediatric study IGBB, there were 22 exposures to 2 mg NG: 11 exposures in the 4-8 years group, and 11 in the 8-12 group. All these patients achieved an increase in glucose by $\geq$20 mg/dL at 30 minutes. Notably, by study design and in accordance to pediatric ethics concerns, these patients were not hypoglycemic at the time of the NG administration.

Additionally, the applicant performed an exposure-response analysis with 2 mg nasal glucagon and it appears to have similar exposure as the 1 mg IMG around 15 minutes post-dosing (Figure 22). It also appears that saturation of the response is seen above 2 mg with the nasal glucagon. Please see Clinical Pharmacology Review by Dr Sury Sista for details regarding the interpretation of the clinical pharmacology simulations.

Figure 22 Predicted Glucose Response Over Time (up to 30 Minutes) with NG 2, and 3 mg, and 1 mg IMG



Source: Dr Sury Sista, Clinical Pharmacology Reviewer

Reviewer comment: While clinical data regarding the clinical effect of the 2mg NG dose exists, it is limited. Additionally, all these studies were performed with drug products that were not the to-be-marketed product, and they differ in the size of particles for the glucagon powder, and delivery device. Also some clinical pharmacology parameters were different between the to-be-marketed product and product used during the development program, and it is not clear how this impacts the potential efficacy of the 2 mg NG dose. In this context, the clinical program alone is not supportive of efficacy for the 2 mg dose. However, it appears that the clinical pharmacology data and simulations are supportive of similarity between the 2 mg NG and the 1 mg injectable glucagon products. The totality of clinical and clinical pharmacology information is supportive of the 2 mg dose for the NG drug product as the lowest possible dose to be delivered for the 3 mg drug product.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

Not applicable.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

In the postmarket setting, the NG product will be used as emergency rescue product for hypoglycemia in patients with diabetes mellitus. The drug products already approved for this indication are injectable, and require reconstitution, which delays, and limits their use as caregivers may not be comfortable administering an injectable product. The efficacy of the NG product is delayed by 1-4 minutes compared to the currently marketed injectable glucagon. While time is very important in the context of a rescue product administration, the applicant of

NG is making the argument that this delay in efficacy matches a delay in administration of the injectable product due to the need for reconstitution. This argument seems reasonable, and the efficacy of the NG product is supported by the development program.

7.2.2. Other Relevant Benefits

The NG drug product offers an alternative to the injectable glucagon rescue products. It is not clear whether the lack of need to reconstitute, and different route of administration, will have a positive impact on the use of emergency glucagon by the caregivers of patients with diabetes, but it is plausible that it may. The real use studies with NG collected user friendliness data via questionnaire and it appears that, in general, the NG product was well received.

7.3. Integrated Assessment of Effectiveness

The clinical program generally supports the efficacy of the 3 mg NG drug product. This conclusion is mainly based on the efficacy observed in study IGBI in adult patients with T1DM and insulin-induced hypoglycemia, where the commercial drug product was used. The other phase 3 clinical studies in the development program were performed using various versions of the glucagon powder, and delivery device, and their results were supportive of the efficacy observed in study IGBI. All studies met their primary, or post-hoc efficacy endpoint and demonstrated efficacy of the 3 mg NG drug product. The NG appears to be delayed by a few minutes when compared to the currently marketed IMG, however, this difference may not be clinically meaningful since the drug product appears easier to use and does not need to be reconstituted. The efficacy of the NG drug product has been demonstrated both in adults, and in pediatric patients age 4 and above.

8. Review of Safety

8.1. Safety Review Approach

The primary safety analysis in this review is based on study IGBI, the only study performed with the to-be-marketed drug product.

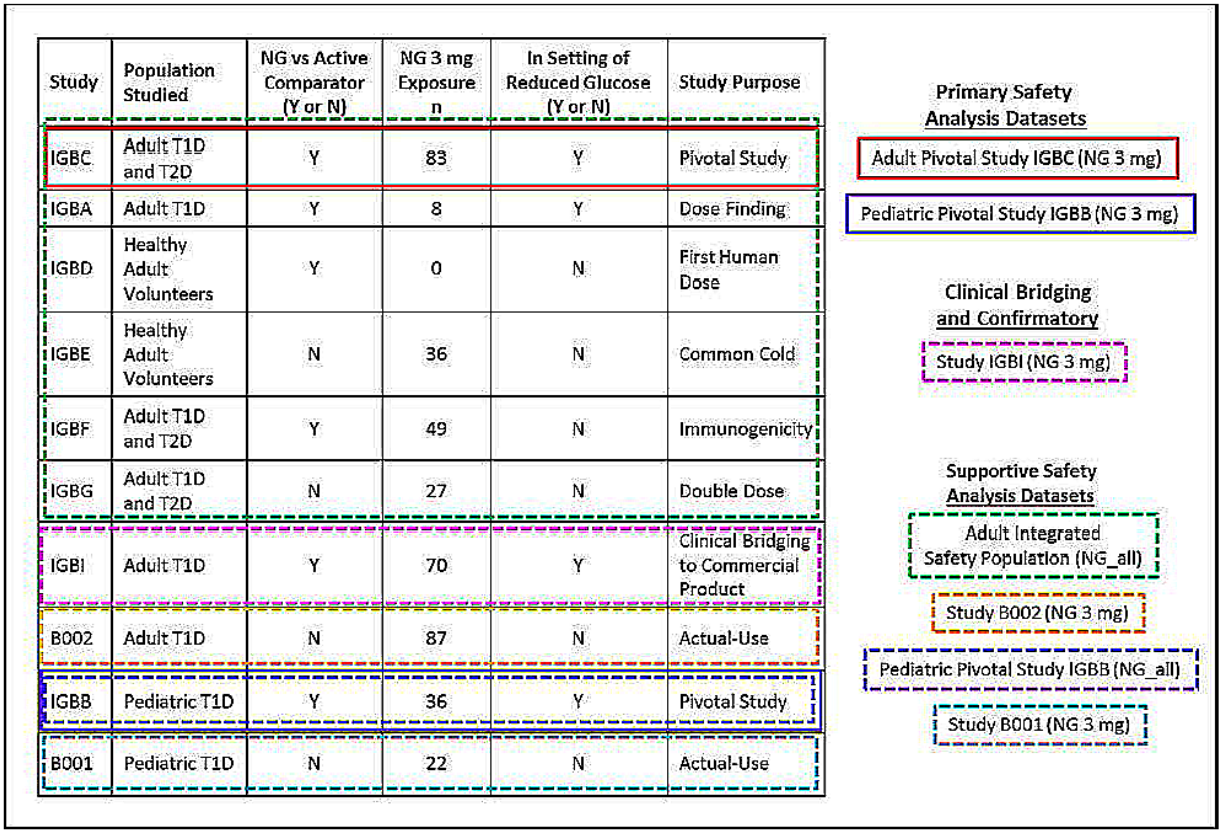
Additional safety was evaluated in studies IGBC (adults) and IGBB (pediatrics), considered as pivotal studies by the applicant, and proposed for inclusion in the product label. The applicant refers to this as the Primary Safety Analysis dataset.

Additional supportive safety analyses for NG were performed using the Adult Integrated Safety Population (all NG doses from all studies), all NG doses from the pediatric study IGBB, and the actual use studies B001, and B002 (although the safety information from the actual use studies was not collected in a rigorous manner, and it is not informative).

The safety datasets as submitted by the applicant are presented in the table below.

Table 37 Safety Groupings

Study	Population Studied	NG vs Active Comparator (Y or N)	NG 3 mg Exposure n	In Setting of Reduced Glucose (Y or N)	Study Purpose
IGBC	Adult T1D and T2D	Y	83	Y	Pivotal Study
IGBA	Adult T1D	Y	8	Y	Dose Finding
IGBD	Healthy Adult Volunteers	Y	0	N	First Human Dose
IGBE	Healthy Adult Volunteers	N	36	N	Common Cold
IGBF	Adult T1D and T2D	Y	49	N	Immunogenicity
IGBG	Adult T1D and T2D	N	27	N	Double Dose
IGBI	Adult T1D	Y	70	Y	Clinical Bridging to Commercial Product
B002	Adult T1D	N	87	N	Actual-Use
IGBB	Pediatric T1D	Y	36	Y	Pivotal Study
B001	Pediatric T1D	N	22	N	Actual-Use



Abbreviations: n = number of patients; N = no; NG = nasal glucagon; T1D = type 1 diabetes mellitus; T2D = type 2 diabetes mellitus; Y = yes.
Note: Study IGBH was terminated early and is not included in this figure. Three patients received NG 3 mg. The safety data from this study are presented in the IGBH clinical study report. Study IGBH was repeated under a new trial alias, Study IGBG, and data from Study IGBG are included in the Adult Integrated Safety Population.

Source: Figure 2.7.4.1 Clinical Safety Summary

The safety analyses will be presented separately for adult and pediatric patients.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

A total of 461 patients receiving NG during the development program, and 421 patients receiving the 3 mg dose proposed for use. Of the 461 NG treated patients, 365 had T1DM, 44

had T2DM, and 52 were adult healthy volunteers.
58 of the 461 patients were age 4-<18. Exposure to both NG and CG is presented in Table 38 below.

Table 38 Summary of Exposure

Population	Total (N)	CG[a] (Total) (N)	NG (Total) (N)	NG 3 mg (N)	NG (T1D) (N)	NG (T2D) (N)	NG (HV) (N)
Adult patients[b]	429	210	403	363	307	44	52
Pediatric patients[b]	70	24	58	58	58	--	--
Total[b]	**499**	**234**	**461**	**421**	**365**	**44**	**52**

Abbreviations: CG = control glucagon; CSR = clinical study report; HV = adults without diabetes; N = total number of patients; NG = nasal glucagon; T1D = type 1 diabetes mellitus; T2D = type 2 diabetes mellitus.
a Included 1 mg intramuscular injection of glucagon or 1 mg subcutaneous injection of glucagon in adult studies, and 0.5 or 1 mg intramuscular injection of glucagon in the pediatric study.
b Number of total patients is not the sum of NG- and CG-treated patients because a patient may have received both NG and CG in a crossover study and is counted in each respective treatment group, but is only counted once in the total.
Source: Table 2.7.4.2 Clinical Safety Summary

The summary of exposure for pediatric patients is presented below.

Table 39 Exposure for Pediatric Patients with T1DM

	CG (N=24)	NG_all (N=58)	
	IMG 0.5 or 1 mg n (%)	NG 2 mg n (%)	NG 3 mg n (%)
Total number of patients	24 (100)	23 (39.7)	58 (100)
Total number of doses	24	23	89

Abbreviations: CG = control glucagon; CSR = clinical study report; NG = nasal glucagon; IMG = intramuscular glucagon; N = total number of patients; n = number of patients in the specified category.
Note: The number of patients in NG_all group is not the sum of each NG dose because a patient may have received different NG doses, but is only counted once in the NG_all group.
Sources: CLUWE: //statsclstr//lillyce/prd/ly900018/idb/output/shared/smexp112.rtf; B001 CSR, Table B001.8.1.
Source: Table 2.7.4.4 Clinical Safety Summary

Patient Disposition

The disposition for adult patients is presented in the table below. A larger proportion of the NG treated patients (40/403 – 9.9%) discontinued the study prematurely, compared to 1% (2/210) CG treated patients.

One of the discontinued NG patients died of an unrelated reason (See 8.4.1 for further details), and 7 patients discontinued from the study due to an AE (4/7 occurred in studies without

comparator arm).

Other reasons for study discontinuation of NG-treated patients were withdrawal by patient (6 [1.5%]), physician decision (2 [0.5%]), applicant's decision (19 [4.7%]), and protocol violation (5 [1.2%]). Thirty of the 32 discontinuations for other reasons occurred in NG studies without a CG comparator.

The 2 patients who discontinued CG are reported as discontinuation due to AE.

Table 40 Discontinuations by Treatment Group

	CG (N=210) n (%)	NG_all (N=403) n (%)
Study Disposition		
Completed	208 (99.0)	363 (90.1)
Discontinued	2 (1.0)	40 (9.9)
Reasons for Discontinuation		
Adverse Event	2 (1.0)	7 (1.7)
Death	0	1 (0.2)
Protocol Violation[a]	0	5 (1.2)
Withdrawal by Patient	0	6 (1.5)
Physician Decision	0	2 (0.5)
Sponsor Decision[b]	0	19 (4.7)

Abbreviations: CG = control glucagon; CSR = clinical study report; N = total number of patients; n = number of patients in the specified category; NG = nasal glucagon.

[a] Sponsor terminated a site in Study B002 due to good clinical practice (GCP) noncompliance.

[b] Study IGBH terminated and Study B002 temporarily placed on hold due to potential subtarget dosing (IGBH CSR; B002 CSR, Sections 5.4 and 6.1; Section 3.2.P.2.3).

Note: Control glucagon included 1 mg intramuscular injection of glucagon and 1 mg subcutaneous injection of glucagon.

Source: Table 2.7.4.5 Clinical Safety Summary

In pediatric patients, 12/58 (20.7%) NG-treated patients and no CG-treated patients discontinued from Study IGBB or B001 prematurely. There were 4 study discontinuations due to AEs, 3/4 reported from study B001 (no control arm). The remaining 8 patients who discontinued prematurely were from the non-GCP compliant site from study B001. One patient was reported to have discontinued due to AE in study IGBB.

8.2.2. Adequacy of the safety database:

In general, the safety database appears adequate for evaluation of safety. However, only one of the studies in the clinical program used the to-be-marketed drug product. The powder batch, including particle size, as well as the delivery devices, varied in the clinical development

program. Whether these differences may have impacted the safety of the NG drug product is unknown.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

I have not identified any issues with data integrity.

8.3.2. Categorization of Adverse Events

Adverse events (AEs) were collected and assessed in two ways: as spontaneously reported AEs, and as symptoms solicited through questionnaires (Nasal and Non-Nasal Score Questionnaire, Nasal Score Questionnaire, and Hypoglycemia Episode Questionnaire).

8.3.3. Routine Clinical Tests

Based on the intended use as a rescue medication, and clinical experience with glucagon therapy, comprehensive laboratory assessments were not considered necessary. Laboratory measurements were either collected at baseline or not collected at all in IGBB, IGBC, IGBI, B001, and B002.

Collection of vital signs (BP, pulse rate, and body temperature) was recorded at screening, and again approximately 0.5 to 1 hour prior to, and approximately 0.75 hours after each glucagon administration in the NG development program. Baseline was defined as the pre-dose value at each visit. Treatment-emergent high or low vital sign values were summarized separately by treatment group for pivotal Study IGBC (primary safety dataset), the Adult Integrated Safety Population (supportive safety dataset), and pediatric pivotal Study IGBB (primary safety dataset, supportive dataset).

8.4. Safety Results

8.4.1. Deaths

There was one death reported during the NG clinical program. Patient (b) (6) from study B002 was a 66 year old male with T1DM who enrolled in the study on (b) (6) During the trial, the patient experienced 2 moderate hypoglycemic episodes on (b) (6), and (b) (6), with BG 41 mg/dL and 36 mg/dL respectively (clinical manifestation was weakness), both recovered to normal clinical status between 5 and 15 minutes after NG administration. The patient was diagnosed with pneumonia due to Klebsiella pneumoniae, developed acidosis, sepsis, and multiple organ failure on (b) (6), and died on (b) (6). The death recorded was not related to the study drug as evaluated by the investigator.

Reviewer comment: I do not see any evidence that this death was related to the trial drug product, and I agree with the assessment of the study investigator.

No death was reported in pediatric patients.

8.4.2. Serious Adverse Events

Adult Patients

One SAE was reported in the 9 completed clinical studies in adults: patient (b) (6) with T2DM, enrolled in study IGBG on (b) (6). Upon arrival at the study site on (b) (6), BG was 173 mg/dL. After eating breakfast, BG was 88 mg/dL prior to glucagon administration. He received 6 mg NG, and subsequent BGs at 6, 12, and 30 minutes were 83, 92, and 115 mg/dL, respectively. The patient reported mild increase in lacrimation in the left eye after dosing. Blood pressure was reported to be elevated at 45 minutes after dosing but not clinically significant, the actual blood pressure measurement was not reported in the patient narrative. On (b) (6), the patient's fasting BG was 130 mg/dL, and dropped to 70 mg/dL after eating breakfast, 30 minutes prior to administration of the study drug. At 6 and 30 minutes following NG 6 mg administration, BGs were 77 and 115 mg/dL. The patient again reported increased lacrimation, and blood pressure was found to be elevated, but considered not clinically significant. On (b) (6), fasting BG was 216 mg/dL, and 234 mg/dL prior to study drug administration. At 6 and 20 minutes after NG 6 mg administration, the BGs were 150 mg/dL, and 180 mg/dL, respectively. The signs and symptoms reported after NG administration were similar to the previous visits. On the same day, the patient experienced increasing pain in his right leg, with muscle spasms, noted a red plaque, and was unable to walk. It is not clear whether the symptoms were present at the time of the study visit. On (b) (6), he presented to the Emergency Room, and was diagnosed with cellulitis, for which he was treated with parenteral antibiotics. The patient withdrew consent to participate in the study on (b) (6). The episode of cellulitis was reported as resolved on (b) (6). The investigator considered this event as unrelated to the study drug.

Reviewer comment: While glucagon can elevate blood glucose temporarily, there is no evidence that it has contributed to the event of cellulitis. From review of the narrative, it appears that the patient's fasting blood glucose was uncharacteristically high the morning of the last study visit, immediately preceding the diagnosis of cellulitis, which may suggest either a cause, or a symptom of the infection. I agree with the investigator that this is unlikely to be related to the study drug.

Pediatric patients

One pediatric patient was reported with an SAE during the development program. Patient

(b) (6) from study IGBB was reported with an SAE of severe hypoglycemia. The patient was a 7 year old white male with T1DM managed with insulin pump, who was randomized into the study on (b) (6), and received 1 mg IM glucagon. The patient had a history of a severe hypoglycemic episode over a year prior to enrollment. During the study, the patient had a baseline glucose of 88 mg/dL, and glucose levels at 5, 10, 15, 20, 30, and 45 minutes after glucagon administration were 84, 117, 144, 157, 199, and 215 mg/dL, respectively. Glucose was 230 mg/dL at 1 hour, and 217 mg/dL at 1.5 hours. After completing the study procedures, he was offered a meal, and received bolus insulin to cover the carbohydrates. He exhibited symptoms of severe hypoglycemia, became nauseated and vomited several times after lunch. The patient became difficult to arouse, was disoriented, and uncooperative with oral carbohydrate intake. While the patient was resting after vomiting, a random blood glucose (BG) check revealed a blood glucose of 55 mg/dL, which later dropped to 32 mg/dL. His insulin pump was suspended at 3:32pm and resumed at 4:19 pm. The patient was given 90 grams of carbohydrates, and made a full recovery from the severe hypoglycemic event before leaving the clinic.

Reviewer comment: This episode appears to be related to the study procedures rather than the study treatment (which was intramuscular glucagon), however, it is possible that the nausea and vomiting were related to the use of glucagon as they are common adverse reactions, and may have contributed to hypoglycemia.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Adult patients

A total of 9 patients discontinued due to an AE from 9 completed adult studies, 7 in the NG group (1.7%) vs 2 in the CG group (1%). Four of the 7 discontinuations with NG occurred in studies without a CG comparator. One out of 9 patients listed as discontinuing the study is the patient presented under section 8.4.1 Deaths. Details about the remaining 8 patients are presented below.

- Patient (b) (6) was a 34 year old white female with T1DM enrolled in study IGBC on (b) (6). On the same day, the patient had an insulin infusion per study procedures, which was stopped when BG was 58 mg/dL, and she received 3 mg NG in her left nostril. BGs at 5, 10, 15, 20, 25, and 30 minutes post glucagon administration were 55, 67, 80, 87, 92, and 99 mg/dL, respectively. Subsequent BG values continued to increase at 40, 50, 60, and 90 minutes post-dosing, to 118, 127, 130, and 129 mg/dL, respectively. Nasal examination was reported normal 90 minutes after the NG administration. The patient had nausea and vomiting 90 minutes after NG administration, and elevated BG 2 hours after dosing. The narrative states that the event was resolved by 9PM the day of the test (unclear how long after NG administration). The patient withdrew consent the same day, and did not return for the

second study visit. She was not included in the primary efficacy analysis.

- Patient (b) (6) was a 24 year old white female enrolled in study IGBI, who received 3 mg NG for insulin-induced hypoglycemia on (b) (6). She developed nausea and vomiting following NG administration and declined to return for the second study visit. No additional details were provided for this patient.

- Patient (b) (6) was a 40 year old healthy male enrolled in study IGBD on (b) (6). On (b) (6), he was administered 2 mg NG in his left nostril. The patient reported nasal adverse events, including congestion for over 1 hour, itching for 5 hours, and a runny nose for 3 hours. Additionally, the patient reported ocular adverse events, including watering for over 1 hour, redness in his left eye for less than 30 minutes, itchy eyes, which lasted 30 minutes, and for 2 hours in his left eye, and a swollen left lower eyelid after NG administration. He also felt restless for 3 hours after NG was given, with a headache that lasted for 11 hours. On (b) (6), the patient received a subcutaneous injection of 1 mg glucagon in his right abdominal wall. The patient reported itchy eyes at 3 hours post dosing, burning in the left eye for 2 hours, abdominal pain for 4 hours, and nausea for 2 hours. After completing 2 glucagon treatments, the patient withdrew consent to participate in the study on (b) (6), for reasons related to clinical events.

- Patient (b) (6) was a 21 year old white female with T1DM enrolled in the study IGBF on (b) (6). The patient received 1 mg intramuscular glucagon in her left thigh. The reported pre-dose BGs were 193, and 159 mg/dL, taken 20 minutes apart, 30 minutes before dosing. BGs at 15, 30, 60, and 120 minutes post dose were 220, 231, 286, and 195 mg/dL, respectively. The patient fainted 2 hours after dosing, BG at the time was 263 mg/dL. She recovered after being placed in a reclined position with a cold compress. Nausea and vomiting were also reported starting 2.5 hours after dosing. The patient withdrew consent on (b) (6), for reasons related to clinical events.

Reviewer comment: There are some discrepancies in the reported BG at 2 hours (195 vs 263 mg/dL, however they are likely irrelevant, as the BG during the fainting episode was not suggestive of hypoglycemia.

- Patient (b) (6) was a 25 year old white female with T1DM, enrolled in study IGBF on (b) (6). On (b) (6), she received a dose of 3 mg NG in her left nostril. Her BG 30 minutes pre-dose was 115 mg/dL, and increased to 142, 193, 261, and 250 mg/dL at 15, 30, 60, and 120 minutes post dosing, respectively. The patient reported musculoskeletal pressure at the nape of the neck which lasted for 2 hours post-dosing, for which she received 1000 mg acetaminophen. She reported several other adverse events, which were all mild in severity, including watery eyes, eye

redness, runny nose, nasal congestion, and a headache. All eye and nasal symptoms resolved within 2 hours after dosing, except for eye redness and headache, which resolved after 4 and 6 hours, respectively. One hour after NG dosing, the patient reported mild nausea, and vomited 400 mL of yellow liquid with food particles. She vomited 150 mL of clear liquid an hour later. She also felt dizzy at 90 minutes post-NG dosing, and vital signs were assessed for safety (blood pressure 112/68 mm Hg, pulse 68 beats/minute). She recovered from dizziness within 4 hours after NG dosing. On (b) (6), the patient received 3 mg NG again. The pre and post-dose BGs were similar to the first visit.

- Patient (b) (6) was a 33 year old white male with T1DM who entered study IGBG on (b) (6). The patient did not have a history of hypertension, but reported taking medications for an upper respiratory infection including pseudoephedrine. On the same day, prior to NG dosing, the patient's blood pressure was 138/94 mmHg and 140/90 mm/Hg, and pulse rate was 104, and 102 bpm. He received 6 mg NG (3 mg in each nostril per study protocol). BG was 61 mg/dL 20 minutes prior to dosing, 49 mg/dL 5 minutes after the second dosing, and increased to 97, 133, 160, and 173 mg/dL at 20, 30, 45, and 60 minutes post dosing, respectively. The patient reported mild nasal symptoms after dosing, and BP was 137/81 mmHg, pulse rate was 94 bpm. On (b) (6), the patient returned for a study visit. Baseline BP was 143/102 mmHg and pulse rate 116 bpm, confirmed by subsequent measurements. The patient was not given NG due to elevated BP. On (b) (6) and (b) (6), the patient returned, BP and HR were elevated similar to the previous visit, and NG was not administered. The investigator decided to withdraw this patient due to high blood pressure, and pulse rate.

- Patient (b) (6) was a 43 year old white male with T1DM, enrolled in study IGBG on (b) (6). He received NG 6 mg on (b) (6) and (b) (6). He also received NG 3 mg on (b) (6). The patient experienced mild local symptoms after the administration of NG. Unrelated to the study, on (b) (6), the patient was hit in the left eye with a ball while playing sports, and reported being unconscious for about 30 seconds. He reported blood in his left eyeball, along with vision alterations (described as a white film over his vision), pain, swelling and bruising, and a moderate headache. All symptoms, except for the bruising, lasted for about 6 hours after the accident. He was accompanied to the ER immediately after the incident, and was released. He visited an ophthalmologist the next day, and was treated with topical (ophthalmic) homatropine hydrobromide and travopost/timolol for trauma to the left eye. The patient withdrew consent to participate in the study on (b) (6) for reasons related to clinical events.

- Patient (b) (6) was a 67 year old white female with T1DM enrolled in study B002 on

(b) (6). On (b) (6), she felt light-headed due to a moderate hypoglycemic event, with BG 43 mg/dL. NG 3 mg was administered, with subsequent BG values of 81, 90, and 141 mg/dL at 15, 30, and 45 minutes post NG, respectively. The caregiver reported that the patient returned to normal clinical status within 5 minutes after the NG was given. The caregiver reported that the patient had a headache, nasal irritation, and a burning sensation in the face, eyes, and nose, which were all severe and lasted over 1 hour after NG administration. The patient withdrew consent to participate in the study on (b) (6) for reasons related to clinical events.

Pediatric Patients

There were 4 pediatric patients who discontinued participation in the study due to an AE, all received NG (6.9%). Three out of the 4 occurred in study B001, where there was no comparator arm. Details for the 4 patients are presented below.

- Patient (b) (6) was an 11 year old black male with T1DM for 7 years, randomized into study IGBB on (b) (6) Following administration of 3 mg NG on the same date, the patient experienced nausea and headache (unclear timing), and, on nasal examination, the left turbinate was found to be inflamed and erythematous. The patient requested withdrawal from the study indicating that the visit was too painful. The patient's BG was 64 mg/dL at baseline, and 67, 86, 106, 124, 139, and 160 mg/dL at 5, 10, 15, 20, 30, and 45 minutes post dosing.

- Patient (b) (6) was a 5 year old white female with T1DM enrolled in study B001 on (b) (6) The patient had 3 moderate hypoglycemic episodes during the trial, and although all resolved with administration of NG, the patient experienced nasal discomfort, nausea, vomiting, headache, watery eyes on all 3 occasions following the administration of the drug product. On (b) (6) the patient discontinued the study for reasons related to the clinical events.

- Patient (b) (6) was a 12 year old white male with T1DM enrolled in study B001 on (b) (6) The patient experienced 2 moderate hypoglycemic episodes during the study, both returned to normal status with NG. Both times, following NG administration, the patient experienced nausea and vomiting, watery eyes, headache, nasal discomfort, and runny nose. The patient withdrew consent and discontinued the study on (b) (6) for reasons related to clinical events.

- Patient (b) (6) was a 17 year old white male with T1DM enrolled in study B001 on (b) (6) The patient experienced 2 episodes of moderate hypoglycemia during the study, both returned to normal status following NG administration. On both occasions, following NG administration, the patient experienced headache, nausea, vomiting,

watery eyes, and nasal discomfort. The patient discontinued the study on (b) (6) after withdrawing consent for reasons related to clinical events.

8.4.4. Significant Adverse Events

Clinical events were graded by the investigator as mild, moderate, or severe according to the following definitions:

- Mild: Causing no limitation of usual activities; the patient may have experienced slight discomfort
- Moderate: Causing some limitation of usual activities; the patient may have experienced annoying discomfort.
- Severe: Causing inability to carry out usual activities; the patient may have experienced intolerable discomfort or pain.

Generally, few events in all studies were categorized as severe. In study IGBC, 2 patients on CG, and 9 patients on NG were reported with events that were severe, although not SAEs. The preferred terms for the actual AEs reported as severe are listed in the table below. No events were reported as severe from study IGBI, however, the nasal and ocular AEs were not reported in the AE datasets, but rather in questionnaire form.

Table 41 Adverse Events Graded by the Investigator as Severe in Study IGBC

Preferred term	NG (N=83) #events	CG (N=82) #events
Eye pruritus	1	0
Fatigue	2	0
Headache	2	0
Hyperhidrosis	1	1
Hypoglycemia	1	0
Lacrimation increased	2	0
Nasal congestion	1	0
Nasal discomfort	2	0
Ocular hyperemia	1	0
Pruritus	1	0
Rhinorrhea	1	0
Vomiting	2	1
Total Patients with Events	**9**	**2**

Source: Reviewer generated using JReview and Adverse Events and Demographics datasets for study IGBC

In study IGBB, 3 AEs were reported as severe, 2 with NG (headache, and nasal congestion), and one with CG (hypoglycemia, this was the SAE presented in section 8.4.2).

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

This section will focus on the studies IGBI and IGBC for the adult population. Additionally, the Adult Integrated Safety Population, which includes study IGBC, will be used as supportive safety. The pediatric study IGBB will be discussed separately. Specific TEAEs will be discussed in more detail.

Adult Patients

Study IGBI

Unlike study IGBC and the adult integrated safety population which will be discussed next in this review, the nasal and ocular adverse events were not to be reported in the AE dataset unless they were SAEs, but rather documented through the use of Nasal and Non-Nasal Score Questionnaire. Because of this, the TEAEs in the AE datasets for this study do not allow for a full evaluation of the safety of the study drug, particularly since the nasal and ocular AEs make up a significant proportion of TEAEs for the NG drug product.

As reported in the AE datasets, TEAEs were relatively balanced in study IGBI between NG and CG treated patients (44.3% of patients in the NG group, and 46.4% of patients in the CG group). The most frequently reported TEAEs for both NG and CG were nausea and vomiting, which is consistent with current prescribing information for approved glucagon products. Nausea and vomiting were reported more frequently in the CG group. Headache was reported more frequently with NG compared to CG. An overview of selected TEAEs that occurred in >2% of patients (by SOC and preferred term) is presented in the table below.

Table 42 TEAEs reported in >2% of patients – Study IGBI

System Organ Class Preferred Term	NG N=70 N(%)	CG N=69 N(%)
Patients with ≥1 TEAE	31 (44.3)	32 (46.4)
Gastrointestinal disorders	23 (32.9)	30 (43.5)
Nausea	22 (31.4)	29 (42.0)
Vomiting	10 (14.3)	12 (17.4)
Nervous system disorders	11 (15.7)	7 (10.1)
Headache	11 (15.7)	7 (10.1)
Infections and infestations	4 (5.7)	3 (4.3)
Nasopharyngitis	4 (5.7)	2 (2.9)
Respiratory, thoracic and mediastinal disorders	3 (4.3)	1 (1.4)

Source: Table APP 2.7.4.8 Clinical Safety Summary

Study IGBC

At least one TEAE was reported by 55.4% of NG-treated patients and 45.1% of CG-treated patients. Frequently reported TEAEs (≥10% of patients) in the NG group were nausea, headache, and vomiting. Nausea and vomiting were reported with similar incidences in the NG and CG groups. Headache was reported more commonly with NG (20.5%) compared to CG (8.5%). In addition, a subset of TEAEs that the applicant selected as nasal/respiratory/anosmia TEAEs were commonly reported (≥10% of patients) in the NG group, as anticipated for this route of administration. The severity of the symptoms related to the route of administration is summarized in the Nasal and Non-Nasal Questionnaire analysis under Section 8.4.4 Significant Adverse Events.

Table 43 Summary of Treatment-Emergent Adverse Events in At Least 2% of Patients in Either Treatment Group by System Organ Class, Preferred Term and Treatment Group - Study IGBC

System Organ Class Preferred Term	CG (N=82) n (%)	NG 3 mg (N=83) n (%)
Patients reporting ≥1 TEAE	37 (45.1)	46 (55.4)
Gastrointestinal disorders	30 (36.6)	29 (34.9)
Nausea	22 (26.8)	18 (21.7)
Vomiting	9 (11.0)	13 (15.7)
Nervous system disorders	8 (9.8)	18 (21.7)
Headache	7 (8.5)	17 (20.5)
Head discomfort	0	2 (2.4)
Somnolence	0	2 (2.4)
Respiratory, thoracic, and mediastinal disorders	1 (1.2)	16 (19.3)
Nasal discomfort	0	8 (9.6)
Nasal congestion	1 (1.2)	7 (8.4)
Rhinorrhea	1 (1.2)	2 (2.4)
Eye disorders	1 (1.2)	8 (9.6)
Lacrimation increased	1 (1.2)	7 (8.4)
Eye pruritus	1 (1.2)	2 (2.4)
General disorders and administration site conditions	7 (8.5)	8 (9.6)
Fatigue	7 (8.5)	7 (8.4)
Facial pain	0	2 (2.4)
Skin and subcutaneous tissue disorders	2 (2.4)	4 (4.8)
Pruritus	1 (1.2)	3 (3.6)
Musculoskeletal and connective tissue disorders	0	3 (3.6)
Muscular weakness	0	2 (2.4)
Ear and labyrinth disorders	1 (1.2)	2 (2.4)
Ear pain	1 (1.2)	2 (2.4)

Abbreviations: CG = control glucagon (intramuscular glucagon); N = total number of patients; n = number of patients in the specified category; NG = nasal glucagon; TEAE = treatment-emergent adverse event.

Source: Table 2.7.4.7 Clinical Safety Summary

Adult Integrated Safety Population

The safety findings in this population are supportive of the findings in IGBC, which is not surprising considering that IGBC is a large part of this applicant-defined patient population. Nausea and vomiting were reported in a similar proportion of patients regardless of the treatment group, while headache, nasal and ocular symptoms were more commonly reported with NG.

Table 44 TEAEs by SOC and PT Occurring in ≥5% of Patients in the NG group, Adult Integrated Safety Population

System Organ Class **Preferred Term**	**NG** **N=234** **N(%)**	**CG** **N=141** **N(%)**
Patients with ≥1 TEAE	192 (82.5)	83 (58.9)
Respiratory, thoracic and mediastinal disorders	142 (60.7)	4 (2.8)
Rhinorrhea	68 (29.1)	2 (1.4)
Nasal discomfort	64 (27.4)	0
Nasal congestion	53 (22.6)	2 (1.4)
Nasal Pruritus	53 (22.6)	0
Sneezing	28 (12.0)	1 (0.7)
Cough	17 (7.3)	0
Throat Irritation	14 (6.0)	0
Eye disorders	132 (56.4)	4 (2.8)
Lacrimation increased	122 (52.1)	2 (1.4)
Ocular hyperemia	52 (22.2)	2 (1.4)
Eye pruritus	34 (14.5)	3 (2.1)
Nervous system disorders	126 (53.8)	27 (19.1)
Headache	86 (36.8)	14 (9.9)
Somnolence	30 (12.8)	7 (5.0)
Dizziness	28 (12.0)	5 (3.5)
Dysgeusia	18 (7.7)	0
Parosmia	15 (6.4)	0
Gastrointestinal disorders	83 (35.5)	48 (34.0)
Nausea	64 (27.4)	38 (27.0)
Vomiting	39 (16.7)	19 (13.5)
General disorders and administration site conditions	49 (20.9)	36 (25.5)
Fatigue		
Asthenia	17 (7.3)	11 (7.8)
Injection site pain	16 (6.8)	4 (2.8)
	0	8 (5.7)
Vascular disorders	18 (7.7)	9 (6.4)
Hot flush	13 (5.6)	6 (4.3)

Source: Table APP 2.7.4.9 Summary of Clinical Safety

Reviewer comment: In general, the safety profile of the NG drug product in adults is well

represented by the safety of study IGBC and the adult integrated safety population. Study IGBI did not adequately capture the nasal and ocular AEs in the AE datasets, and therefore it may look like the to-be-marketed product which was studied in study IGBI may have better local tolerability. This is unlikely though, because the analyses of the Nasal and Non-Nasal Questionnaire did not reveal any improvement in local symptoms in study IGBI compared to study IGBC. As a result, the nasal and ocular TEAEs from study IGBI as reported in the datasets (b) (4) *I believe that the nasal and non-nasal safety collected in the Nasal and Non-Nasal Questionnaire for study IGBI accurately reflects nasal and ocular safety for the NG drug product, and propose presenting the percentage of patients experiencing each of the symptoms captured in the questionnaire in the product label in Section 6.*

Pediatric Patients – Study IGBB

The NG 3 mg dose in pediatric pivotal Study IGBB is the primary dataset used for determining the AE profile of NG. The combined NG 2 mg and NG 3 mg doses is used as a supportive dataset when a population-wide perspective is more informative.

In the pediatric controlled study IGBB, 55.6% of NG 3 mg-treated patients and 75.0% of CG-treated patients reported at least 1 TEAE. Very commonly reported TEAEs (≥10% of patients) in the NG 3 mg group at the preferred term level were vomiting, headache, and nausea. In the CG group, nausea, vomiting, headache, and injection site discomfort were very commonly reported TEAEs, with similar incidences of nausea and vomiting as reported in the NG 3 mg group. In addition, nasal/respiratory/anosmia TEAEs were very commonly reported (≥10% of patients) in the NG 3 mg group.

Table 45 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Treatment Group - Study IGBB

System Organ Class Preferred Term	CG (N=24) n (%)	NG 3 mg (N=36) n (%)
Patients with ≥1 TEAE	18 (75.0)	20 (55.6)
Gastrointestinal disorders	16 (66.7)	17 (47.2)
Vomiting	9 (37.5)	11 (30.6)
Nausea	8 (33.3)	6 (16.7)
Abdominal pain upper	1 (4.2)	1 (2.8)
Diarrhoea	1 (4.2)	0
Nervous system disorders	3 (12.5)	9 (25.0)
Headache	3 (12.5)	9 (25.0)
Dizziness	1 (4.2)	0
Respiratory, thoracic, and mediastinal disorders	0	6 (16.7)
Nasal discomfort	0	3 (8.3)
Nasal congestion	0	2 (5.6)
Sneezing	0	1 (2.8)
Eye disorders	0	2 (5.6)
Eye irritation	0	1 (2.8)
Ocular discomfort	0	1 (2.8)
General disorders and administration site conditions	5 (20.8)	0
Catheter site pain	1 (4.2)	0
Injection site discomfort	5 (20.8)	0
Metabolism and nutrition disorders	1 (4.2)	0
Hypoglycaemia	1 (4.2)	0

Abbreviations: CG = control glucagon (intramuscular glucagon); N = total number of patients; n = number of patients in the specified category; NG = nasal glucagon; TEAE = treatment-emergent adverse event.
Note: CG refers to a 0.5 mg or 1 mg intramuscular injection of glucagon.
Source: Table 2.7.4.9 Clinical Safety Summary

The safety profile did not appear to be significantly different for any age subgroup, or for the dose of NG used (2mg vs 3 mg). TEAEs by treatment arm and age group are presented in the table below.

Table 46 TEAEs by Age Group and Treatment Arm – Study IGBB

Adverse Event Group	4 to <8 years old			8 to <12 years old			12 to <17 years old	
	IM N=6	2mg IN N=12	3mg IN N=12	IM N=6	2mg IN N=11	3mg IN N=12	IM N=12	IN N=13
Total patients with ≥1 event	**5(83.3)**	**6(50.0)**	**5(41.7)**	**6(100.0)**	**5(45.5)**	**6(50.0)**	**6(50.0)**	**7(53.8)**
GI								
Abdominal pain (upper)	1(16.7)	1(8.3)	0	0	0	1(8.3)	0	0
Diarrhea	0	0	0	1(16.7)	0	0	0	0
Nausea	4(66.7)	4(33.3)	2(16.7)	3(50.0)	1(9.1)	1(8.3)	1(8.3)	3(23.1)
Vomiting	1(16.7)	1(8.3)	3(25.0)	3(50.0)	3(27.3)	4(33.3)	5(41.7)	4(30.8)
Total (≥1 GI events)[a]	5(83.3)	5(41.7)	5(41.7)	5(83.3)	4(36.4)	6(50.0)	6(50.0)	6(46.2)
Head pain								
Headache	0	2(16.7)	1(8.3)	2(33.3)	2(18.2)	4(33.3)	0	3(23.1)
Nasal								
Nasal congestion	0	0	0	0	0	0	0	1(7.7)
Nasal discomfort	0	0	2(16.7)	0	0	0	0	1(8%)
Sneezing	0	0	0	0	0	1(8.3)	0	0
Rhinalgia	0	1(8.3)	0	0	0	0	0	0
Total (≥1 nasal events)[a]	0	1(8.3)	2(16.7)	0	0	1(8.3)	0	2(15.4)
Ocular								
Eye irritation	0	0	0	0	0	0	0	1(7.7)
Lacrimation increased	0	0	0	0	1(9.1)	0	0	0
Ocular discomfort	0	0	0	0	0	0	0	1(7.7)
Total (≥1 ocular events)[a]	0	0	0	0	1(9.1)	0	0	2(15.4)
Sensory/Pain								
Catheter site pain	0	0	0	0	0	0	0	0
Injection site discomfort	2(33.3)	0	0	3(50.0)	0	0	0	0
Total (≥1 sensory/pain events)[a]	2(33.3)	0	0	3(50.0)	0	0	0	0
Hypoglycemia								
Hypoglycemia	0	0	0	0	0	0	0	0
Cardiovascular								
Tachycardia	0	1(8.3)	0	0	0	0	0	0
Neurological								
Dizziness	0	0	0	1(16.7)	0	0	0	0

*1 Dosing Visit was included in the safety analysis and was not included in the efficacy analysis: 1 participant in the 12-<17 years old cohort had a repeat 3 mg IN Dosing Visit due to insufficient administration of glucagon (device malfunction)
[a] Total number (%) of participants with at least 1 occurrence of the adverse event group

Source: Table 12.2.4 IGBB CSR

TEAEs of special interest

For adults, these TEAEs will be discussed first in the Adult Integrated Safety population (which includes studies IGBA, IGBC, IGBD, IGBE, IGBF, IGBG), for a more global view of the NG drug product safety profile. Additionally, results from study IGBI will be discussed for AEs other than

nasal or ocular, as they were mostly reported in the questionnaire for this study. In pediatrics, results from study IGBB will be reported.

1. **Nasal/Respiratory/Anosmia TEAEs**

The applicant created a customized AE search "upper respiratory tract irritation" to pool the nasal/respiratory/anosmia TEAEs. The preferred terms included in this grouping are presented in the table below.

Table 47 Preferred Terms Included in the Upper Respiratory Tract Irritation Grouping

Administration site reaction	Nasal septum disorder
Administration related reaction	Nasal septum haematoma
Allergic sinusitis	Nasal septum perforation
Anosmia	Nasal septum ulceration
Chronic eosinophilic rhinosinusitis	Nasal turbinate abnormality
Chronic hyperplastic eosinophilic sinusitis	Nasal turbinate hypertrophy
Congenital perforated nasal septum	Nasal ulcer
Cough	Nasal varices
Dry throat	Oroantral fistula
Empty nose syndrome	Oropharyngeal pain
Eosinophilic rhinitis	Paranasal cyst
Epistaxis	Paranasal sinus aplasia
Hiccups	Paranasal sinus discomfort
Hyposmia	Paranasal sinus haematoma
Increased upper airway secretion	Paranasal sinus hypersecretion
Intranasal hypoaesthesia	Paranasal sinus mucosal hypertrophy
Intranasal paraesthesia	Paranasal sinus necrosis
Maxillary sinus pseudocyst	Parosmia
Nasal adhesions	Rhinalgia
Nasal cavity mass	Rhinitis allergic
Nasal cavity toxicity	Rhinitis atrophic
Nasal congestion	Rhinitis hypertrophic
Nasal crusting	Rhinitis perennial
Nasal cyst	Rhinitis ulcerative
Nasal discomfort	Rhinolithiasis
Nasal disorder	Rhinorrhoea
Nasal dryness	Seasonal allergy
Nasal inflammation	Silent sinus syndrome
Nasal mucosa atrophy	Sinus barotrauma
Nasal mucosal discolouration	Sinus congestion
Nasal mucosal disorder	Sinus disorder
Nasal mucosal erosion	Sinus headache
Nasal mucosal hypertrophy	Sinus perforation
Nasal mucosal ulcer	Sinus polyp
Nasal necrosis	Sinus polyp degeneration
Nasal odour	Sinusitis noninfective
Nasal oedema	Sneezing
Nasal polyps	Throat irritation
Nasal pruritus	Upper-airway cough syndrome
Nasal septum deviation	Vasomotor rhinitis

Source: Table APP.2.7.4.13 Appendix to Clinical Safety Summary

Adults

In the Adult Integrated Safety Population, 143/234 (61.1%) patients receiving NG reported at least one TEAE that fit in this category, vs only 4/141 (2.8%) of patients receiving CG. Of the 143 patients, only 8 patients experienced 10 events that were categorized as severe (5 severe events of rhinorrhea, 2 severe events of nasal discomfort, 2 severe events of nasal congestion

and 1 severe event of sinus headache). All these severe events occurred in patients receiving 3 mg NG, except the event of sinus headache which occurred in a patient who received 2 mg NG. None of the events reported as severe was an SAE. All patients with severe nasal/respiratory/anosmia events reported resolution in ≤1 day, except patients in study IGBE (3 patients reported 4 severe events lasting from 4.94 to 21.94 days). The mean time to resolution of TEAEs of nasal/respiratory/anosmia AEs in NG treated patients was 15 hours, with a median time of 1 hour. 75% of events resolved within 3 hours. Study IGBE required patients to have common cold symptoms at baseline, and this may have affected the duration of the reported symptoms.

None of the events reported in the CG was categorized as severe.

Table 48 Time to Resolution of Nasal/Respiratory/Anosmia TEAEs – Adult Integrated Safety Population

Characteristics	CG (N=141)	NG_all (N=234)	NG 0.5 mg (N=15)	NG 1 mg (N=26)	NG 2 mg (N=34)	NG 3 mg (N=203)	NG 6 mg (N=32)
Patients with nasal TEAE[a]	4	143	2	8	20	109	27
Number of nasal TEAEs[a]	6	515	2	17	32	369	95
Number of nasal TEAEs[a] resolved	6	508	2	17	32	363	94
Time to resolution (days)[b]							
Mean (SD)	0.36 (0.500)	0.62 (2.446)	0.03 (0.015)	1.55 (2.979)	0.51 (1.989)	0.61 (2.519)	0.53 (2.211)
(Min, Median, Max)	(0.01, 0.04, 1.00)	(0.00, 0.04, 28.67)	(0.02, 0.03, 0.04)	(0.01, 0.07, 8.99)	(0.00, 0.04, 10.91)	(0.00, 0.04, 28.67)	(0.00, 0.01, 13.97)
(Q1, Q3)	(0.03, 1.00)	(0.01, 0.12)	(0.02, 0.04)	(0.02, 0.44)	(0.02, 0.13)	(0.01, 0.12)	(0.00, 0.06)

Abbreviations: CG = control glucagon; Max = maximum; Min = minimum; N = total number of patients; NG = nasal glucagon; Q1 = 25 percentile; Q3 = 75 percentile; SD = standard deviation; TEAE = treatment-emergent adverse event.

[a] Nasal TEAE = treatment emergent nasal/respiratory/anosmia adverse events.

[b] Time to resolution is based on number of nasal TEAEs resolved.

Note: The number of patients in the NG_all group is not the sum of each NG dose because a patient may have received different doses but is only counted once in NG_all. CG included 1 mg intramuscular injection of glucagon and 1 mg subcutaneous injection of glucagon.

Source: Table Summary of Clinical Safety

Pediatrics

In study IGBB, Of the 7 NG-treated patients with nasal/respiratory/anosmia TEAEs, 6 reported nasal/respiratory/anosmia TEAEs events with a maximum severity of mild or moderate. One patient (NG 3 mg) rated an event of nasal congestion as severe. The event resolved on the same day it started. The mean time to resolution of 7 nasal/respiratory/anosmia TEAEs in the 7 NG-treated patients reporting such events was 1 day.

2. Parosmia

Adults

In the Adult Integrated Safety Population, 18 events of parosmia was reported by 15 (6.4%) of NG treated patients. 10/18 were reported a "vinegar smell", and 17/18 resolved within 1 hour (the remaining event was resolved by 3 hours).

Pediatrics

No events of parosmia were reported in pediatric patients.

3. Epistaxis

Adults

Epistaxis was reported in 8 (3.4%) of NG treated patients in the Adult Integrated Safety Population, all events were categorized as mild. Two events were prolonged, both from study IGBG, where the study participants reported seeing blood on tissue after blowing their nose for 3 and 9 days, respectively, after NG administration. Most events began within 5 hours of the NG administration, and resolved in less than 10 minutes.

In study IGBI, such AEs were reported only as part of the Nasal and Non-Nasal Questionnaire per protocol. One event epistaxis was reported in the NG group.

Pediatrics
No events of epistaxis were reported in pediatric patients.

4. Eye Disorders

Adults
In the adult integrated Safety Population, increased lacrimation was reported by 122 (52.1%) of NG-treated patients, and only 2 (1.4%) of CG -treated patients. Four events in NG treated patients were categorized as severe, none were SAEs. Most events (90%) resolved within one hour, and all resolved within 1 day. Ocular hyperemia was reported by 52 patients (22.2%) treated with NG, and 2 patients (1.4%) treated with CG. One event in an NG treated patient was reported as severe, but not an SAE. Most events were resolved within 1 day. Eye pruritus was reported in 34 NG-treated patients (14.5% and 3 (2.1%) CG treated patients. Two events in the NG group were characterized as severe, none was an SAE. All events resolved within 1 day.

In study IGBI, one event of eye pain was reported in the NG group.

Pediatrics
No events of eye disorders were reported in pediatric patients

5. Headache

Adults
In the adult Integrates Safety Population, 86 (36.8%) NG-treated patients reported 114 TEAEs of headache, and 14 (9.9%) CG-treated patients reported 16 events. Two events (NG) were severe, but none of the events were considered serious. Three events (NG, 1; CG, 2) did not

have a documented resolution during the study. More than 90% of events resolved within a day.

In study IGBI, headache was reported in 11 patients on NG (13 events), and 7 patients on CG (7 events). In the NG group, 9 events occurred within 1 hour of dosing, and 4 events had an onset over 1 hour postdose (1 hour 12 minutes to more than2 days). Six of 13 events lasted less than 3 hours, and 7/13 more than 3 hours (up to 15 hours and 45 minutes). In the CG group, 2/7 events occurred in the first hour post administration, and 5/7 occurred between 1 hour and >2 days. Three of 7 events resolved within 3 hours, and all resolved within 5 hours.

Pediatrics
Twelve (33.3%) NG-treated patients reported 13 TEAEs of headache, and 3 (12.5%) CG-treated patients reported 3 events. The verbatim term for each event was 'headache.' One severe (NG) event was reported, but was not considered serious. Of the 16 total events, 14 (88%) events resolved within 1 day and 2 events (NG, 1; CG, 1) resolved in 1-2 days.

6. Dizziness and Syncope

Adults
In the Adult Integrated Safety Population, 28 (12.0%) NG-treated patients and 5 (3.5%) CG-treated patients reported dizziness. All events were mild or moderate in severity. One event (CG exposure) did not have a documented resolution during the study. Approximately 98% of events resolved within 1 day. Changes in BP did not appear to be a contributing factor to the reported events per applicant report. One (0.4%) NG-treated patient and 1 (0.7%) CG-treated patient each reported 1 TEAE of syncope. The verbatim term reported by the NG-treated patient was 'feels faint,' and the term used by the CG-treated patient was 'fainted.' The event in the NG-treated patient was of moderate severity and resolved in 4 minutes. The event in the CG-treated patient was severe and resolved in 2 minutes. Neither event was serious. No vital signs were collected at the time of these events.

No events of dizziness or syncope were reported from study IGBI.

Pediatrics
One (4.2%) CG-treated patient reported 1 TEAE of dizziness. The event was mild in severity and resolved within 1 day. Changes in BP did not appear to be a contributing factor to the reported event. No events of dizziness were reported in NG-treated patients.

7. Dysgeusia

Adults
In the adult Integrated Safety Population, 18 (7.7%) NG-treated patients reported dysgeusia.

Verbatim terms used in approximately 60% of events included 'vinegar taste' or 'bitter taste.' All events were mild in severity and resolved within 3 hours. No CG-treated patients reported dysgeusia.

No event of dysgeusia was reported in study IGBI.

Pediatrics
No events of dysgeusia were reported in study IGBB.

8. Nausea and Vomiting

Adults
Nausea was reported in a similar proportion of NG-treated and CG-treated patients (64 [27.4%] and 38 [27.0%] patients, respectively) in the Adult Integrated Safety Population. Four events (NG, 3; CG, 1) were severe, but none were considered serious. In studies that captured AE resolution in actual time, approximately 80% of all events resolved within 3 hours. In all studies, approximately 98% of events resolved within 1 day. Thirty-nine (16.7%) NG-treated patients and a similar proportion of CG-treated patients (19 [13.5%] patients) reported vomiting. Three TEAEs (NG, 2; CG, 1) of severe vomiting were reported by 2 patients; none of the events were considered serious. In studies that captured AE resolution in actual time, all events in both NG- and CG-treated patients resolved within 4 minutes. In all studies, approximately 97% of events resolved within 1 day.

In study IGBI, 22 events of nausea were reported in 22 patients exposed to NG, and 29 events (29 patients in patients exposed to CG. All events on NG except one occurred in the 3 hours post-dosing (the remaining event occurred 3 hours and 17 minutes post dosing), and lasted between <1 hour to 9 hours and 40 minutes. Twenty-seven out of 29 events on CG occurred in the first 3 hours, the remaining 2 events occurred at 3 hours and 31 minutes, and 4 hours and 10 minutes, and lasted between <1 hour to >2 days. For both treatments, the majority of the events resolved within 3 hours. Vomiting was reported in 10 patients (10 events) on NG, and 12 patients (12 events on CG. The duration and resolution of the nausea events were similar between the treatment arms, with events in both groups resolved within 4 hours.

Pediatrics
Similar proportions of NG-treated patients (11 patients – 30.6%) and CG-treated patients (8 patients – 33.3%) reported TEAEs of nausea. All events were mild or moderate in severity, and 84% resolved within 1 day.

Similar proportions of NG-treated patients and CG-treated patients reported TEAEs of vomiting (14 [38.9%] patients and 9 [37.5%] patients, respectively). All events were mild or moderate in severity. All but 1 event in NG-treated patients resolved within a day, and that event resolved

in 1-2 days; the only prolonged event lasting more than 2 days occurred in a CG-treated patient.

9. Hypersensitivity reactions

The applicant identified hypersensitivity reactions using the following preferred terms: urticaria, rash, pruritus, eyelid edema, eye swelling, chest discomfort, and erythema. Events reported as cough, sneezing, nasal edema, ocular hyperemia, and eye pruritus are analyzed under nasal and ocular symptoms.

Adults
A larger proportion of NG-treated patients (10 patients, 4.3%) reported events of hypersensitivity, compared to CG-treated patients (2 patients, 1.4%) in the Adult Integrated Safety Population. The only preferred term that was reported in more than one patient in either treatment group was pruritus, reported in 4/10 patients on NG, and one patient on CG. It is hard to know whether the pruritus was part of a systemic reaction as the verbatim term was itching for most of the events.

No events of hypersensitivity were reported in study IGBI.

Pediatrics
Only one event was reported in study IGBB, sneezing, in a patient following NG exposure. Because this event is more likely to be related to the nasal route of administration, the applicant did not considered it as a hypersensitivity event, and this is reasonable in the context.

Reviewer comment: Generally, the TEAEs with NG were not significantly different between adults and children, and no notable differences were seen in the pediatric age subgroups. Nausea and vomiting were similar with what was seen with the control glucagon in all patient populations, however, headache was more commonly observed with NG, and nasal/ocular symptoms were almost exclusively seen with NG.

8.4.6. Laboratory Findings

Comprehensive laboratory evaluation was not considered necessary based on the on experience with glucagon and intermittent use as rescue medication. Studies IGBB, IGBC, IGBI, B001, and B002 only collected baseline laboratories, or no laboratories at all, not contributing at any relevant clinical laboratory data. The applicant submitted laboratory changes (as maximum post-baseline result) for hematologic parameters for the Adult Integrated Safety Population. For each individual parameter, over 90% of post-treatment laboratory values were missing for both NG and CG. No relevant information can be gleaned from evaluation of clinical laboratory data for NG.

Regardless, given the long experience with glucagon products, and the fact that this is not a chronically administered product, I do not think that laboratory information is needed for evaluation of safety of NG.

8.4.7. Vital Signs

Collection of vital signs (BP, pulse rate, and body temperature) was limited, recorded at screening, approximately 0.5 to 1 hour prior to, and approximately 0.75 hours after each glucagon administration in NG studies. Baseline was defined as the pre-dose value at each visit. Treatment-emergent high or low vital sign values were summarized separately by treatment group for the adult studies IGBC and IGBI, the Adult Integrated Safety Population, and pediatric study IGBB (primary safety dataset, supportive dataset).

Abnormal values for vital signs were defined per the table below.

Table 49 Reference Limits for Treatment-Emergent Blood Pressure and Pulse Measurements for Adult and Pediatric Patients

Age (years)	Abnormality	Systolic BP, mm Hg	Diastolic BP, mm Hg	Pulse/HR bpm
2-4	Low	≤75 and decrease ≥20	≤40 and decrease ≥10	<60 and decrease ≥15
	High	≥116 and increase ≥20	≥76 and increase ≥10	>160 and increase ≥15
5-9	Low	≤80 and decrease ≥20	≤45 and decrease ≥10	<60 and decrease ≥15
	High	≥122 and increase ≥20	≥78 and increase ≥10	>150 and increase ≥15
10-11	Low	≤85 and decrease ≥20	≤50 and decrease ≥10	<60 and decrease ≥15
	High	≥126 and increase ≥20	≥82 and increase ≥10	>140 and increase ≥15
12-14	Low	≤90 and decrease ≥20	≤50 and decrease ≥10	<50 and decrease ≥15
	High	≥136 and increase ≥20	≥86 and increase ≥10	>120 and increase ≥15
≥15	Low	≤90 and decrease ≥20	≤50 and decrease ≥10	<50 and decrease ≥15
	High	≥140 and increase ≥20	≥90 and increase ≥10	>100 and increase ≥15

Abbreviations: BP = blood pressure; bpm = beats per minute; HR = heart rate.

Source: Table 2.7.4.17. Clinical Safety Summary

Study IGBC

Vital signs were collected prior to the start of the procedure to induce hypoglycemia, and approximately 0.75 hours after glucagon administration.

Treatment-emergent high systolic blood pressure (SBP) was observed in 4 (5.6%) NG-treated patients (maximum SBP of 176 mmHg), and 1 (1.3%) CG-treated patient (maximum SBP of 142 mmHg). Treatment-emergent high diastolic blood pressure (DBP) was observed in 5 (6.2%) NG-treated patients (maximum DBP of 100 mmHg) and no CG-treated patients. Treatment-emergent high pulse rate was not observed in NG-treated patients, but was observed in one (1.3%) CG-treated patient (maximum pulse rate of 116 beats per minute).

Other findings in adult patients

One adult patient discontinued from the NG clinical development program (Study IGBG) due to elevated BP and heart rate. The narrative for this patient is summarized under Section 8.4.3. The increase in pulse and blood pressure for this patient preceded any administration of glucagon.

Study IGBI

Vital signs were collected prior to the start of the procedure to induce hypoglycemia, and approximately 45 minutes after glucagon administration.

In Study IGBI, treatment-emergent high SBP was observed in 5 (8.8%) NG-treated patients (maximum SBP of 164 mmHg), and 2 (3.3%) CG-treated patients (maximum SBP of 158 mmHg). Similar percentages of patients in both treatment groups reported treatment-emergent high DBP: 6 NG (10.0%) (maximum DBP of 102 mmHg) and 6 CG (9.5%) (maximum DBP of 102 mmHg); no patients reported treatment-emergent high pulse rate. No changes in vital signs from baseline were assessed as clinically significant by the study investigators.

Table 50 Treatment-Emergent High or Low Vital Signs in Studies IGBC and IGBI

			Study IGBC		Study IGBI	
Parameter	Abnormality	Treatment	N	n (%)	N	n (%)
SBP	Low	CG	80	0	69	0
		NG 3 mg	82	0	70	0
	High	CG	75	1 (1.3)	60	2 (3.3)
		NG 3 mg	72	4 (5.6)	57	5 (8.8)
DBP	Low	CG	81	1 (1.2)	69	0
		NG 3 mg	81	0	69	0
	High	CG	75	0	63	6 (9.5)
		NG 3 mg	81	5 (6.2)	60	6 (10.0)
Pulse	Low	CG	80	2 (2.5)	68	0
		NG 3 mg	81	1 (1.2)	68	0
	High	CG	80	1 (1.3)	69	0
		NG 3 mg	79	0	70	0

Abbreviations: CG = control glucagon (intramuscular glucagon); DBP = diastolic blood pressure; N = number of patients with a normal (that is, not low at baseline if calculating 'low' and not high at baseline if calculating 'high) baseline and at least 1 postbaseline result; n = number of patients in the specified category; NG = nasal glucagon; SBP = systolic blood pressure.
Source: Table 2.7.4.18 Clinical Safety Summary

Pre and post dose vital signs for adult studies IGBC and IGBI are summarized in the table below. Overall there were no significant changes to the mean blood pressure or pulse rate at baseline vs after glucagon administration.

Table 51 Summary of Vital Signs Pre- and Post-dose in Studies IGBC and IGBI

	Study IGBC		Study IGBI	
Parameter Time Point	CG (N=81)	NG 3 mg (N=82)	CG (N=69)	NG 3 mg (N=70)
SBP (mm Hg), mean ± SD				
Predose	121.9 ± 12.4	121.2 ± 15.7	129.5 ± 9.9	129.7 ± 13.6
45 min Postdose	115.5 ± 12.6	122.0 ± 15.4	126.5 ±13.3	133.4 ± 13.6
DBP (mm Hg), mean ± SD				
Predose	73.9 ± 9.2	73.5 ± 9.3	78.2 ± 7.8	78.0 ± 9.2
45 min Postdose	67.4 ± 8.6	72.9 ± 9.4	76.0 ± 10.2	81.0 ± 10.6
Pulse (bpm), mean ± SD				
Predose	74.3 ± 12.8	73.5 ± 13.9	67.4 ± 11.3	67.7 ± 10.0
45 min Postdose	69.3 ± 11.1	70.1 ± 11.0	65.5 ± 11.2	65.8 ± 10.7

Abbreviations: bpm = beats per minute; CG = control glucagon (intramuscular glucagon); CSR = clinical study report; DBP = diastolic blood pressure; min = minutes; N = total number of patients; NG = nasal glucagon; SBP = systolic blood pressure; SD = standard deviation.

Source: Table 2.7.4.19 Clinical Safety Summary

Study IGBB

Treatment-emergent high SBP was not observed in NG 3 mg-treated patients and treatment emergent high DBP was observed in 1 (2.9%) NG 3 mg-treated patient (maximum DBP of 95 mmHg); no NG-treated patients had a treatment-emergent high pulse rate. No CG-treated patients had treatment-emergent high SBP, DBP or pulse rate.

One patient reported a TEAE of tachycardia after administration of NG 2 mg. This 7-year-old patient became tachycardic with a pulse rate of 151 bpm (upper reference limit for this age is 150 bpm) approximately 2.5 hours after NG dosing. He was placed in a supine position and his pulse rate decreased. The patient had a baseline pulse rate of 79 bpm and a 45-minute post-dose pulse rate of 81 bpm. He was released with normal vital signs. The event was considered related to study treatment and procedures by the investigator.

8.4.8. Electrocardiograms (ECGs)

Electrocardiograms, when obtained, were locally read and interpreted qualitatively as normal or normal variant, thus precluding any analysis of quantitative ECG parameters. Studies IGBB, IGBC, IGBI, and the actual-use studies did not collect ECGs. The applicant stated that, in studies where ECGs were collected, the patients who shifted from normal baseline to abnormal post

treatment actually shifted to normal variant, not clinically significant, although details are not provided.

8.4.9. QT

No QT study was performed.

8.4.10. Immunogenicity

Consistent with the immunogenic properties of protein and peptide therapeutics, individuals exposed to NG could develop an immune response, including formation of antidrug antibodies (ADA). Data from 3 studies of the NG development program (IGBF, IGBG, and B002) demonstrated minimal incidence (2%) of treatment-emergent antidrug antibodies (TE ADA) for NG. None of the patients with TE ADA experienced a hypersensitivity AE, and no patient developed neutralizing antibodies. The applicant concluded that these results suggest there is a very low probability of immunogenic reaction following NG administration.

The occurrence of events that could be related to hypersensitivity was low and occurred only in adult patients (NG, 4.3% [n=10]; injectable glucagon, 1.4% [n=2]). The most predominantly reported event was pruritus, which occurred in 0% to 3.6% of patients in Studies IGBI and IGBC. Reported hypersensitivity events were typically mild or moderate in severity, and none were serious. No patients discontinued due to a hypersensitivity event. These data do not indicate an increased risk of systemic hypersensitivity events with NG treatment beyond the currently marketed injectable glucagon therapies.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Nasal and Ocular Symptoms

Nasal and Ocular symptoms were evaluated via Nasal and Non-Nasal Questionnaire in studies IGBI, IGBC, and IGBB. For the real use studies B001, and B002, the Hypoglycemia Episode Questionnaire and Nasal Score Questionnaire were used to elicit symptoms related to the delivery location.

Nasal and Non-Nasal Questionnaire

The Nasal and Non-Nasal Score Questionnaire (Simons et al. 2003; Kim et al. 2006) was used to solicit the occurrence and severity of 4 nasal symptoms (rhinorrhea, nasal stuffiness/congestion, nasal itching, and sneezing) and 5 non-nasal symptoms (itching/burning eyes, tearing/watering eyes, redness of eyes, itching of ears, or itching of throat) to supplement information collected from spontaneously reported AEs in studies IGBA, IGBB, IGBC, IGBD, IGBE, IGBF, and IGBI. Each symptom was individually rated by the patient using a 4-point scale and

was collected prior to glucagon administration and at approximately 15, 30, 60 minutes, and 1.5 to 4 hours (1.5 hours in studies IGBB, IGBC, and IGBI; 2 hours in study IGBF; 3 hours in studies IGBA and IGBE; 4 hours in study IGBD) after glucagon administration.

The following scoring system was used during the studies in order to quantify symptoms:

0 = I am not experiencing this (no symptoms at all).
1 = I am only experiencing a mild case of this and it is easily tolerated.
2 = I am experiencing a moderate level of this symptom. It is bothersome, but tolerable.
3 = I am experiencing a severe level of this symptom. It is hard to tolerate and interferes with my activities.

The total symptom score was calculated as the sum of the scores for all 9 symptoms, for a minimum score of 0 and a maximum score of 27. Descriptive statistics were used to summarize the total score at baseline (defined as the symptom score measured prior to glucagon administration at each study visit) and various post-dose time points (15, 30, and 60 minutes, and >1 hour) by treatment group. In addition, the number and proportion of patients shifting from baseline to maximum post-dose severity category and last post-dose severity category were summarized by treatment group.

Adult Patients

Study IGBI

Notably, per the study protocol, the nasal and ocular symptoms were to be preferentially reported in the questionnaire rather than as spontaneous AEs. The Nasal and Non-Nasal Questionnaire was administered 30 minutes before the induction of hypoglycemia and at 15, 30, 45, 60, and 90 minutes post-dose.

The frequency of patients with increased nasal and non-nasal symptoms, as well as shifts to severe symptoms for the NG exposures, are presented in the table below. Notably 10% of patients reported severe watery eyes at some point after NG administration. All other severe symptoms were reported by fewer patients. The symptom severity peaked at 15 minutes, and, at the 90 minutes timepoint, none of the symptoms with NG were reported as severe. Only minimal symptoms were reported with CG.

Table 52 Summary of Shifts in Nasal and Non-Nasal Symptom Severity from Baseline to Maximum Post-Dose Severity – Study IGBI

	Nasal Glucagon N=70	
	Any increase in symptom severity	Shifting to severe at any time
Runny Nose	26 (37.1%)	1 (1.4%)

Nasal congestion	27 (38.6%)	3 (4.3%)
Nasal Itching	34 (48.6%)	3 (4.3%)
Sneezing	17 (24.3%)	1 (1.4%)
Watery eyes	44 (62.9%)	7 (10%)
Itchy eyes	14 (20%)	2 (2.9%)
Redness of eyes	15 (21.4%)	1 (1.4%)
Itching of ears	2 (2.9%)	0
Itching of throat	9 (12.9%)	0

Source: Modified from Tables IGBI.8.3 and IGBI.8.4 CSR

Study IGBC

The results for study IGBC were similar to what was observed in IGBI.

The summary of shifts in questionnaire scores for NG exposures in study IGBC is presented below.

Table 53 Summary of Shifts in Nasal and Non-Nasal Symptom Severity from Baseline to Maximum Post-Dose Severity – Study IGBC

	Nasal Glucagon N=83	
	Any increase in symptom severity	Shifting to severe at any time
Runny Nose	27 (32.5%)	1 (1.2%)
Nasal congestion	40 (48.2%)	6 (7.2%)
Nasal Itching	26 (31.2%)	2 (2.4%)
Sneezing	13 (15.7%)	0
Watery eyes	46 (55.4%)	7 (8.4%)
Itchy eyes	19 (22.9%)	2 (2.4%)
Redness of eyes	23 (27.7%)	1 (1.2%)
Itching of ears	3 (3.6%)	0
Itching of throat	10 (12%)	0

Source: Modified from table APP.2.7.4.27 Clinical Safety Summary

Again, the most common symptom reported as severe at any timepoint was watery eyes (8.4% of patients), followed by nasal congestion reported as severe in 7.2% of patients. None of the severe symptoms was still reported as severe at the 90 minutes timepoint.

Pediatric patients – Study IGBB

Similar to the adult studies, symptoms were reported in the Nasal and Non-Nasal

Questionnaire, peaking at 15 minutes, and trending down by 30 minutes.

A summary of shifts from baseline to maximum severity and shifts to severe at any timepoint is presented in the table below. A significant proportion of patients experienced any increase in symptom severity compared to baseline, but very few were severe. The only questionnaire category where more than one patient shifted to severe was "watery eyes" – 3 patients (8.3%). Additionally, one patient reported severe nasal congestion, nasal itching, sneezing, and itchy eyes post-baseline.

Table 54 Summary of Shifts in Nasal and Non-Nasal Symptom Severity from Baseline to Maximum Post-Dose Severity – Study IGBB

	NG_all (N = 36) n (%)	
Symptom	**Any Increase in Symptom Severity**	**Shifting to Severe at Any Time**
Runny Nose	12 (33.3)	0
Nasal Congestion	18 (50.0)	1 (2.8)
Nasal Itching	11 (30.6)	1 (2.8)
Sneezing	8 (22.2)	1 (2.8)
Watery Eyes	19 (52.8)	3 (8.3)
Itchy Eyes	11 (30.6)	1 (2.8)
Redness of Eyes	10 (27.8)	0
Itching of Ears	4 (11.1)	0
Itching of Throat	4 (11.1)	0

Abbreviations: N = number of patients studies; n = number of patients in specified category; NG = nasal glucagon.
Source: Table 2.7.4.13 Clinical Safety Summary

At the last timepoint (90 minutes), only 3 reported severe events of nasal itching, watery eyes, and itchy eyes, which were reported by one patient.

The nasal and ocular symptoms peaked at 15 minutes, and then decreased steadily, approaching baseline at 90 minutes post dose.

Hypoglycemia Episode Questionnaire and Nasal Score Questionnaire

For the actual-use studies (Studies B001 and B002), the Hypoglycemia Episode Questionnaire (reported by caregiver) and the Nasal Score Questionnaire (reported by patient) were used after NG administration to solicit symptoms, in the absence of spontaneously reported AEs.

The Hypoglycemia Episode Questionnaire was to be answered by the caregiver as soon as possible following the hypoglycemia event. This questionnaire documented, among other factors reported in the efficacy section, symptoms experienced after dosing (nausea, vomiting, nasal discomfort, watery eyes, headache, and other). The severity (low, moderate, severe) and

duration (≤1 hour, >1 hour) of the listed symptoms was also documented.

The Nasal Score Questionnaire had the same content as the Nasal and Non-Nasal Score Questionnaire used in the other NG studies. However, in the actual-use studies, these symptoms were not collected at baseline (prior to NG administration), were self-administered, and were collected at only one time point (within 2 hours of recovery from the hypoglycemic event).

Symptoms solicited through the Hypoglycemia Episode Questionnaire in study B002 included: nausea, vomiting, nasal irritation, headache, and 'other.' Adjustments were made to the questionnaire in Study B001 to include nasal discomfort instead of nasal irritation, and to add watery eyes.

Adult Population – Study B002

A total of 87 patients received at least one dose of study drug (including patients from non-compliant sites). In patients receiving at least one dose of NG, 85.1% and 82.8% of patients reported at least one symptom solicited through the Hypoglycemia Episode Questionnaire and Nasal Score Questionnaire, respectively.

In the Hypoglycemia Episode Questionnaire, , nasal irritation was most commonly reported by 67 patients (77%), with 14 severe events, and 36 events lasting more than one hour. The next common symptom was headache, reported by 45 patients (51.7%), with 14 severe events, and 30 events lasting longer than one hour. As expected with a glucagon product, nausea and vomiting were also commonly reported.

Table 55 Summary of Adverse Events Collected in Hypoglycemia Episode Questionnaire after Dosing – Caregiver Perspective, Study B002

	N=87
	N (%)
		# episodes
		N=207
		N (%)
			# severe episodes	# events lasting more than 1 hour

Nausea	20 (23)	29 (14)	2	11
Vomiting	8 (9.2)	16 (7.7)	2	1
Nasal Irritation	67 (77)	117 (56.5)	14	36
Headache	45 (51.7)	72 (34.8)	14	30
Other	37 (42.5)	55 (26.6)	14	21

Source: Modified from Table B002.11.1 CSR

Symptoms listed as "other" were reported by 37 patients (42.5%), with 14 severe events, and 21 events lasting more than one hour. The symptoms reported as "other" are summarized in the table below, and overall the symptoms appear to be related to nasal/ocular symptoms, as

well as headache.

Table 56 Summary of 'Other' Adverse Events Collected in Hypoglycemia Episode Questionnaires after Dosing by System Organ Class (SOC) and Preferred Term (PT) - Caregiver Perspective, Study B002

System Organ Class	Preferred Term	N of Events	N of Patients	% of Patients
Patients with at least one AE across all SOC/PT	NA	53*	35*	40.2%
Ear and labyrinth disorders	Ear pain	6	5	5.7%
	Patients with at least one AE within the specific SOC	6	5	5.7%
Eye disorders	Eye inflammation	1	1	1.1%
	Eye pain	3	2	2.3%
	Hypoaesthesia eye	1	1	1.1%
	Lacrimation increased	10	8	9.2%
	Patients with at least one AE within the specific SOC	15	12	13.8%
General disorders and administration site conditions	Asthenia	1	1	1.1%
	Facial pain	1	1	1.1%
	Feeling abnormal	1	1	1.1%
	Pain	1	1	1.1%
	Product taste abnormal	3	3	3.4%
	Patients with at least one AE within the specific SOC	7	7	8.0%
Musculoskeletal and connective tissue disorders	Muscle tightness	1	1	1.1%
	Musculoskeletal pain	1	1	1.1%
	Patients with at least one AE within the specific SOC	2	2	2.3%
Nervous system disorders	Burning sensation	1	1	1.1%
	Head discomfort	1	1	1.1%
	Sinus headache	2	2	2.3%
	Somnolence	2	1	1.1%
	Patients with at least one AE within the specific SOC	6	5	5.7%
Respiratory, thoracic and mediastinal disorders	Choking	1	1	1.1%
	Cough	1	1	1.1%
	Nasal congestion	2	2	2.3%
	Nasal discomfort	5	3	3.4%
	Paranasal sinus discomfort	3	3	3.4%
	Rhinorrhoea	2	2	2.3%
	Sneezing	2	2	2.3%
	Patients with at least one AE within the specific SOC	16	12	13.8%
Skin and subcutaneous tissue disorders	Erythema	1	1	1.1%
	Patients with at least one AE within the specific SOC	1	1	1.1%

Abbreviations: AE = adverse event, N = number; NA = not available, PT = preferred term, SOC = system organ class

Source: Table B002.11.2 CSR

The Nasal Questionnaire was to be filled out by the patient following a hypoglycemic event where NG was administered. A summary of the Nasal Questionnaire symptoms is presented below. While a large proportion of patients reported events, few were reported as severe. The most commonly reported severe event was nasal itching, reported as severe by 10 patients (11.5%).

Table 57 Summary of Nasal Questionnaire Symptoms – Study B002

	Patients		Events	
	All with event	Patients with severe event	Any severity	Severe
Runny nose	55 (63.2)	4 (4.6)	96 (46.4)	4 (1.9)
Nasal congestion	33 (37.9)	1 (1.1)	63 (30.4)	1 (0.5)
Nasal itching	45 (51.7)	10 (11.5)	73 (35.3)	13 (6.3)
Sneezing	27 (31)	4 (4.6)	35 (16.9)	4 (1.9)
Watery eyes	47 (54)	4 (4.6)	71 (34.3)	4 (1.9)
Itchy eyes	23 (26.4)	4 (4.6)	28 (13.5)	4 (1.9)
Redness of eyes	19 (21.8)	1 (1.1)	22 (10.6)	1 (0.5)
Itching of ears	9 (10.3)	3 (3.4)	12 (5.8)	5 (2.4)
Itching of throat	12 (13.8)	0	17 (8.2)	0
Other	3 (3.4)	2 (2.3)	7 (3.4)	5 (2.4)

Source: Modified from Table B002.11.3 Study Report Body

Three patients reported 7 events identified as “other”. These events are summarized in the table below.

Table 58 Summary of ‘Other’ Adverse Events Collected in Nasal Score Questionnaire - Sensitivity Safety Analysis Population, Study B002

System Organ Class	Preferred Term	N of Symptoms (Adverse Events)	N of Patients	% of Patients
Number of symptoms (AEs) and patients with at least one symptom (AE) across all SOC/PT	NA	7	3	3.4%
Nervous system disorders	Headache	6	3	3.4%
	Patients with at least one AE within the specific SOC	6	3	3.4%
Respiratory, thoracic and mediastinal disorders	Paranasal sinus discomfort	1	1	1.1%
	Patients with at least one AE within the specific SOC	1	1	1.1%

Abbreviations: AE = adverse event, MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients; NA = Not Applicable; PT = preferred term, SOC = system organ class; SSAP = Sensitivity Safety Analysis Population.

Note: Symptoms (adverse events) were coded by MedDRA version 18.1. A patient may have reported more than one symptom (adverse event). Percentages based on the total number of SSAP patients (N=87).

Source: Table B002.11.5 CSR

<u>Pediatric Population – Study B001</u>

There were 22 patients that received at least one dose of NG for 52 hypoglycemic events. In patients receiving at least one dose of NG, 90.9% of patients reported at least 1 symptom solicited through each of these questionnaires.

In the Hypoglycemia Event Questionnaire, the most commonly reported event was nasal discomfort, reported by 19 patients (86.4%) with 41 events, with 7 events reported as severe. Watery eyes were reported by 18 patients (81.8%) with 37 events, 3 reported as severe. Headache was reported in 14 patients (63.6), with 26 events, 5 reported as severe. Nausea and vomiting were also reported, although none of the events were severe.
A summary of these symptoms is presented in Table 59 below. The results are somewhat similar to what was reported in the Nasal and Non-Nasal Questionnaire in the controlled studies.

Table 59 Summary of Hypoglycemia Questionnaire – Caregiver Perspective, Study B001

	N=22 N (%)	**# episodes N=52 N (%)**	**# severe episodes**	**# events lasting more than 1 hour**
Nausea	6 (27.3)	10 (19.2)	0	2 (3.8)
Vomiting	1 (4.5)	1 (1.9)	0	0
Nasal discomfort	19 (86.4)	41 (78.8)	7 (13.5)	15 (28.8)
Watery eyes	18 (81.8)	37 (71.2)	3 (5.8)	4 (7.7)
Headache	14 (63.6)	26 (50)	5 (9.6)	12 (23.1)
Other	10 (45.5)	18 (34.6)	5 (9.6)	3 (5.8)

Source: Excerpted from Table B001.11.1 CSR

Ten patients (45.5%) reported 18 events as “other”, 5 events were reported as severe. These events are summarized below.

Table 60 Summary of "Other" Adverse Events Collected in Hypoglycemia Episode Questionnaires after Dosing – Caregiver Perspective (SSAP)- Study B001

		SSAP (N=22)		
System Organ Class (SOC)	Preferred Term (PT)	N of Events	N of Patients	% of Patients
Patients with at least one AE across all SOC/PT	NA	18	10	45.5%
Gastrointestinal disorders	Abdominal pain upper	2	2	9.1%
	Patients with at least one AE within the specific SOC	2	2	9.1%
General disorders and administration site conditions	Fatigue	1	1	4.5%
	Product taste abnormal	2	1	4.5%
	Patients with at least one AE within the specific SOC	3	2	9.1%
Incomplete dose administered	Incomplete dose administered	1	1	4.5%
	Patients with at least one AE within the specific SOC	1	1	4.5%
Injury, poisoning and procedural complications	Face injury	4	1	4.5%
	Patients with at least one AE within the specific SOC	4	1	4.5%
Nervous system disorders	Dizziness	1	1	4.5%
	Somnolence	1	1	4.5%
	Tremor	1	1	4.5%
	Patients with at least one AE within the specific SOC	3	3	13.6%
Respiratory, thoracic and mediastinal disorders	Paranasal sinus hypersecretion	1	1	4.5%
	Rhinorrhoea	2	2	9.1%
	Sneezing	1	1	4.5%
	Patients with at least one AE within the specific SOC	4	2	9.1%
Skin and subcutaneous tissue disorders	Hyperhidrosis	1	1	4.5%
	Patients with at least one AE within the specific SOC	1	1	4.5%

Notes: One patient may have had more than 1 AE during the hypoglycemic event. Proportions based on the total number of patients who had available hypoglycemic events (N=22).

Source: Table B001.11.2 CSR

The Nasal Score Questionnaire results are summarized below. Overall a large proportion of patients experienced events assessed in the questionnaire, but few were reported as severe. In order of highest to lowest incidence, were watery eyes (17 of 22 [77.3%] patients; 3 severe), runny nose (15 of 22 [68.2%] patients; 1 severe), nasal congestion (12 of 22 [54.5%]; 1 severe), sneezing (11 of 22 [50.0%] patients; 0 severe), redness of eyes (8 of 22 [36.4%] patients; 3

severe), nasal itching (7 of 22 [31.8%] patients; 0 severe), and itchy eyes (4 of 22 [18.2%] patients; 1 severe)

Table 61: Summary of Nasal Score Questionnaire – Study B001

	Patients		Events	
	All with event	Patients with severe event	Any severity	Severe
Runny nose	15 (68.2)	1 (4.5)	27 (51.9)	2 (3.8)
Nasal congestion	12 (54.5)	1 (4.5)	19 (36.5)	2 (3.8)
Nasal itching	7 (31.8)	0	9 (17.3)	0
Sneezing	11 (50)	0	16 (30.8)	0
Watery eyes	1 (77.3)	3 (13.6)	39 (75)	5 (9.6)
Itchy eyes	4 (18.2)	1 (4.5)	10 (19.2)	1 (1.9)
Redness of eyes	8 (36.4)	3 (13.6)	15 (28/8)	3 (5.8)
Itching of ears	1 (4.5)	0	1 (1.9)	0
Itching of throat	2 (9.1)	0	4 (7.7)	0

Source: Table B001.11.3 CSR

8.6. 4 Month Safety Update (4MSU)

The 4MSU was submitted on October 23, 2018. At the time there was one ongoing study with NG, study IGBJ, a single-dose, 2 treatment, 2 period, cross-over study conducted in adult Japanese patients with T1 or T2DM. This study was not at database lock at the time of this safety update, and limited data was available to be reported in the 4MSU. At the time of the data cut-off for this report (September 14, 2018), 72 adults with diabetes received at least one dose of study drug in study IGBJ. No deaths have been reported from study IGBJ at the time of the reporting. Only one SAE was reported, benign positional vertigo, not related to study drug in the opinion of the investigator (no other information available). No other new safety information was reported, either for the NG product, or for other glucagon products.

8.7. Safety Analyses by Demographic Subgroups

Gender

There was no difference between NG-treated males and NG-treated females in the percentage of patients reporting at least 1 TEAE (81.7% and 83.5%, respectively). Fewer females than males reported TEAEs related to eye disorders (44.7% and 63.4%, respectively), and more females than males reported events related to gastrointestinal disorders (48.5% and 20.6%, respectively) and general disorders and administration site conditions (22.3% and 11.5%, respectively). The same trend regarding gastrointestinal disorders and general disorders and administration site conditions was observed in CG-treated patients.

Race

Most study participants were white, therefore no conclusions can be drawn for other races.

Age

The applicant analyzed safety data for patients above and below the age of 65, however, since most patients were below 65, these analyses are not meaningful. As seen in section 8.4, there were no major differences in safety between adult and pediatric patients, or within pediatric age subgroups.

Patients with T1DM

Patients with T1DM were evaluated in studies IGBC, IGBB, IGBI, and the safety from these studies is detailed in Section 8.4.

Patients with T2DM

Of the 42 patients with T2DM exposed to NG, 41 were exposed to the 3 mg dose. AEs occurring in ≥5% in the NG group is presented below for the 42 patients. No notable differences in the AE profile between patients with T1D or T2D were observed.

Table 62 Summary of Treatment Adverse Events by System Organ Class, Preferred Term, and Treatment Group Adult Integrated Safety Population-T2DM (Events occurring ≥5% in the NG group)

System Organ Class Preferred Term	NG N= 42 N(%)	CG N= 20 N(%)
Patients with ≥1 TEAE	39 (92.9)	11 (55)
Eye disorders	36 (85.7)	1 (5)
Lacrimation increased	36 (85.7)	0
Ocular hyperemia	14 (33.3)	1(0.5)
Eye pruritus	9 (21.4)	0
Eye irritation	6 (14.3)	0
Ocular discomfort	3 (7.1)	0
Respiratory, thoracic and mediastinal disorders	30 (71.4)	0
Nasal discomfort	18 (42.9)	0
Nasal congestion	14 (33.3)	0
Rhinorrhea	14 (33.3)	0
Nasal Pruritus	10 (23.8)	0
Cough	8 (19)	0
Sneezing	4 (9.5)	0
Throat Irritation	4 (9.5)	0
Dry throat	3 (7.1)	0

Rhinalgia	3 (7.1)	0
Nervous system disorders	24 (57.1)	3 (15)
Headache	16 (38.1)	1 (5)
Dysgeusia	8 (19)	0
Parosmia	5 (11.9)	0
Somnolence	5 (11.9)	1 (5)
Dizziness	3 (7.1)	2 (1)
Tremor	3 (7.1)	0
Gastrointestinal disorders	10 (23.8)	3 (15)
Nausea	7 (16.7)	1 (5)
Investigations	5 (11.9)	1 (5)
….Blood glucose decreased	3 (7.1)	0

Source: Modified from table APP.2.7.4.51 Clinical Safety Summary

8.8. Specific Safety Studies/Clinical Trials

Common cold and the use of nasal decongestants

Study IGBE evaluated the effects of common cold and concomitant administration of nasal decongestant (oxymetazoline) on the pharmacokinetics and pharmacodynamics of NG 3 mg in patients with a common cold. Safety was also assessed in this study.

When comparing the safety of NG with and without cold symptoms, the incidence of AEs was reduced by approximately 50% in patients who had returned to their normal health status (17 patients, 64 AEs) versus that observed while the patients were experiencing a common cold (18 patients, 112 AEs).

When comparing the safety of NG with and without nasal decongestant, the total number of AEs was almost the same in patients administering only NG (18 patients, 112 AEs) compared to patients also receiving nasal decongestant approximately 2 hours prior to administration of NG (18 patients, 113 AEs).

No drug-drug interaction studies were conducted with NG.

8.9. Additional Safety Explorations

8.9.1. Human Carcinogenicity or Tumor Development

Not applicable.

8.9.2. Human Reproduction and Pregnancy

No reproductive and developmental toxicity studies of NG have been conducted in animals. The novel excipient DPC was not teratogenic in rats at intravenous (IV) doses up to 5 mg/kg/day or

in rabbits at IV doses up to 1 mg/kg/day. Male and female reproduction and early embryonic development was not adversely affected in rats at IV DPC doses up to 3 mg/kg/day. Reproduction and development were not adversely impacted in the offspring of maternal rats given IV DPC doses up to 1 mg/kg/day from implantation until weaning. Reproduction studies conducted in rats and rabbits with animal-sourced glucagon have revealed no harm to the fetus due to glucagon

It is possible for emergency glucagon to be used in pregnancy. There are no adequate and well controlled studies with glucagon in pregnant women. Glucagon does not cross the human placental barrier, but it is not known whether glucagon is excreted in the human milk.

8.9.3. Pediatrics and Assessment of Effects on Growth

Not applicable, this is an emergency use drug product, and glucagon rescue products are already approved for use in pediatrics.

8.9.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Per the currently approved glucagon product labels, if overdosage of glucagon occurs, the patient may experience nausea, vomiting, inhibition of gastrointestinal tract motility, increases in BP and pulse rate, and a decrease in serum potassium.

Because glucagon has a short half-life, treatment of overdose is symptomatic, primarily for nausea, vomiting, and hypokalemia. If the patient develops a dramatic increase in BP, non-selective alpha-adrenergic blockade has been shown to be effective in lowering BP for the short time that control would be needed.

Neither NG nor the active comparators have a known profile as a drug of abuse. There were no reported instances of intended drug abuse in the NG clinical program.

8.10. Safety in the Postmarket Setting

8.10.1. Safety Concerns Identified Through Postmarket Experience

Not applicable. NG is not currently marketed in any region.

8.10.2. Expectations on Safety in the Postmarket Setting

Nasal glucagon is intended to be prescribed as an emergency treatment for severe hypoglycemia. In addition to safety concerns with the glucagon emergency products (nausea and vomiting), it appears that headache is more common with the nasal glucagon compared to the currently marketed glucagon. In addition, new TEAEs have been identified with the nasal glucagon product, in the form of nasal and ocular adverse events. Although none of these

events were SAEs, some were graded by the patients/caregivers as severe, and some lead to product discontinuation. While this new safety information can be adequately reflected in the prescribing information for the nasal glucagon drug product, it is expected to impact postmarket use of the product based on the clinical trials experience.

8.10.3. Additional Safety Issues From Other Disciplines

While multiple issues were identified during the review cycle, most were resolved by communication with the applicant. Please see CMC, CDRH, and Clinical Pharmacology reviews for details on the issues identified during the review cycle.

Because of deficiencies identified with the container labelling, the applicant was asked to revise the label and conduct a repeat human factors studies. This study was ongoing at the time of this review. Please see DMEPA consult for details.

8.11. Integrated Assessment of Safety

The NG clinical development program is comprised of 9 completed studies in adults with or without diabetes mellitus and 2 completed studies in children and adolescents with diabetes mellitus, for a total of 461 healthy subjects and diabetes patients who received nasal glucagon study drug. The majority of the patients with diabetes enrolled in the NG clinical development program were adults with T1DM.

The primary purpose of the safety analyses was to characterize the safety profile of NG relative to the safety profile of currently marketed injectable glucagon therapies. Therefore, the 3 active comparator-controlled studies (IGBI, IGBC, and IGBB) conducted in patients with T1DM or T2DM in an insulin-induced hypoglycemia setting offered the best opportunity to evaluate the safety profile of NG. Of these, only IGBI was performed with the to-be-marketed drug product. Several additional studies, including actual-use studies, were also reviewed as supportive.

Across all completed studies of the NG clinical development program, 1 death (adult treated with NG) and 2 serious adverse events (SAEs) (1 adult treated with NG, 1 pediatric patient treated with CG) were reported. None of these appeared to be related to the study treatment.

As expected for a glucagon emergency use product, nausea, vomiting and headache were common adverse events with the NG product. The rate of occurrence for nausea and vomiting was similar between the NG product and the currently marketed injectable glucagon comparator. Headache was observed more commonly with the NG product when compared to CG, in all clinical studies.

Additionally, symptoms related to the route of administration, such as nasal and ocular

symptoms, were very commonly reported with the NG product, and some were reported as severe, and leading to treatment discontinuation. None of these AEs was an SAE.
In addition to AE reporting, Nasal and Non-Nasal Questionnaire was used to assess the presence and severity of nasal and eye related symptoms, at baseline, and different timepoints after study drug administration. A significant proportion of patients exposed to NG experienced an increase in severity for each of the captured symptoms, however, less than 10% were reported as severe at any timepoint after the NG administration, and by the 90 minutes timepoint (last timepoint), none of these symptoms was reported as severe in any safety population. The Hypoglycemia and Nasal Questionnaire administered to patients and caregivers in the real-use studies yielded similar results.

Transient increases in blood pressure and heart rate have been reported for the currently marketed injectable glucagon products. In the adult and pediatric studies IGBI, IGBC and IGBB, vital signs were assessed at baseline and at 45 minutes post glucagon administration. In the NG clinical program, more NG-treated patients shifted beyond the reference range values than CG-treated patients but the incidence in both groups was small, and none of the values were considered clinically significant by the investigators or the applicant.

In conclusion, common AEs with NG were nausea and vomiting, with a frequency similar to the one observed with CG. Headache was more common with NG compared to CG, possibly due to the route of administration. Unlike the currently marketed glucagon products, other common AEs with NG were AEs related to the nasal route of administration were mostly reported as mild or moderate in intensity, and transient, however, there were patients who reported these events as severe (although not SAEs), and who discontinued due such AEs. While these findings are important, the NG drug product is not intended for chronic use, but rather for emergency use where it can be life-saving.

9. Advisory Committee Meeting and Other External Consultations

No Advisory Committee Meeting was part of this application.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Labeling is not yet finalized at the time of this review. I will discuss my opinion regarding some information from the prescribing information below.

Indication and Usage:
BAQSIMI™ is indicated for the treatment of severe hypoglycemia in adult and pediatric patients with diabetes.

Reviewer comment: I generally agree that the drug product was studied and supports an indication down to the age of 4. There are no studies in children younger than 4, and, at the time of the agreed iPSP, the applicant asked for a deferral of such studies until studies in older children were performed. The current plan is for a waiver below the age of 1, and assessment for children age 1 to <4. Details regarding this assessment, including the dose, are currently under discussion.

Dosage and Administration

BAQSIMI delivers a single 3 mg intranasal dose of glucagon in both adult and pediatric patients.

Reviewer comment: The data is supportive of the 3 mg NG dose for both adult and pediatric patients. It is not clear at this time whether this dose would be supported in patients younger than age 4.

Contraindications

BAQSIMI is contraindicated in patients with known hypersensitivity to glucagon or to any of the excipients, and is also contraindicated in patients with pheochromocytoma.

Reviewer comment: This is adequate.

Warnings and Precautions

- Pheochromocytoma In the presence of pheochromocytoma, glucagon may stimulate the release of catecholamines from the tumor. If the patient develops a dramatic increase in blood pressure, 5 to 10 mg of phentolamine mesylate, administered intravenously, has been shown to be effective in lowering blood pressure.
- Insulinoma In patients with insulinoma, administration of glucagon may produce an initial increase in blood glucose; however, glucagon administration may directly or indirectly (through an initial rise in blood glucose) stimulate exaggerated insulin release from an insulinoma and cause hypoglycemia. A patient developing symptoms of hypoglycemia after a dose of BAQSIMI should be given glucose orally or intravenously.
- Hypersensitivity and Allergic Reactions Allergic reactions, which have been reported

with glucagon, may occur and include generalized rash, and in some cases anaphylactic shock with breathing difficulties, and hypotension.
- Glycogen Stores and Hypoglycemia Glucagon is effective in treating hypoglycemia only if sufficient liver glycogen is present. Because glucagon is of little or no help in states of starvation, adrenal insufficiency, or chronic hypoglycemia, these conditions should be treated with glucose.

Reviewer comment: This is adequate.

Section 6 Adverse Reactions - Clinical trial data

The applicant is planning to present the [redacted] (b) (4) from studies IGBC and IGBI in a table format. The pediatric study IGBB is to be presented in a separate table.

Reviewer comment: The presentation of [redacted] (b) (4) *and would consider adding the data from the Nasal and Non-Nasal Questionnaire to better illustrate the AEs in question for study IGBI.*

Section 14

The applicant is proposing to present the efficacy data from studies IGBC and IGBI for adults in both text and table format [redacted] (b) (4) For pediatric patients the applicant is proposing to present data from study IGBB. [redacted] (b) (4)

Reviewer comment: The data proposed for the efficacy evaluation is generally adequate but the details will be decided at the time of the labeling negotiations.

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

No REMS was deemed necessary for nasal glucagon. Please see review by Dr.Mei-Yean Chen from Division of Risk Management for details.

12. Postmarketing Requirements and Commitments

No PMCs are recommended for this product. We are recommending the following PMR study for this product.

- An open-label pediatric study to evaluate safety, efficacy, and pharmacokinetics of BAQSIMI in pediatric patients age 1 year to less than 4 years.

The timelines for protocol submission and study completion are under discussion.

13. Appendices

13.1. References

1. Harris G et al, Pract Diab Int. 2001;18(1):22-25
2. GlucaGen HypoKit United States Prescribing Information, Novo Nordisk
3. Glucagon for Injection United States Prescribing information, Lilly

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): IGBI

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 25		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455):		

0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsorof covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 1		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): IGBC

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 75		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0		

Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 13		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): IGBB

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 56		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial	Yes ☒	No ☐ (Request details from Applicant)

interests/arrangements:		
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 2		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): B001

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 3		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): B002

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 17		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

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/s/

ANDREEA O LUNGU
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