Cross-Discipline Team Leader Review

Date	July 19, 2019
From	Mitra Rauschecker
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	NDA 210134
Applicant	Lilly
Date of Submission	June 28, 2018
PDUFA Goal Date	July 26, 2019
Proprietary Name	BAQSIMI
Established or Proper Name	Glucagon
Dosage Form(s)	Nasal Powder
Applicant Proposed Indication(s)/Population(s)	Treatment of Severe Hypoglycemia
Applicant Proposed Dosing Regimen(s)	3 mg
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of Severe Hypoglycemia
Recommended Dosing Regimen(s) (if applicable)	3 mg

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Severe hypoglycemia is a serious medical condition that is most commonly the result of insulin therapy, and occurs in patients with both type 1 (T1DM) and type 2 diabetes mellitus (T2DM). It is characterized by neurological impairment that can result in loss of consciousness, seizures, or even death. Severe hypoglycemia is more common in patients with T1DM, occurring in approximately 22% to 46% of patients with T1DM annually, and 7% to 25% of patients with T2DM who are treated with insulin. Treatment options include intravenous dextrose, which requires administration by a healthcare professional in a hospital or emergency medical setting, and injectable glucagon, which is can be administered by a caregiver outside of a hospital setting. The two currently approved glucacon products, GlucaGen and Glucagon for injection, require reconstitution prior to administration. Nasal glucagon (NG) was developed as an alternative treatment for severe hypoglycemia in both adult and pediatric patients with diabetes, and is comprised of synthetic glucagon, delivered intranasally.

The clinical development program for NG consisted of a total of eleven studies, which included 3 controlled clinical studies in adults and pediatric subjects (IGBI, IGBC, and IGBB), and two real use studies (adults and pediatrics). NG demonstrated non-inferiority to injectable glucagon (CG) in all three controlled clinical studies in increasing glucose to ≥ 70 mg/dL or increasing by ≥ 20 mg/dL from nadir within 30 minutes after treatment with glucagon.

The overall incidence of AEs in Studies IGBI, IGBC, and IGBB were similar in frequency between NG and CG, and were anticipated based on the known safety profile of injectable glucagon. There was a higher incidence of nasal and ocular AEs with NG, which is expected given the route of administration, and these nasal and ocular symptoms were non-serious and had mostly resolved by 90 minutes postbaseline. The Applicant utilized a Nasal and Non-Nasal Symptom Score Questionnaire in order to capture details related to the timing and duration of nasal and ocular adverse events, however in Study IGBI, these symptoms were not to be reported in the AE dataset. As a result, the AE datasets for Study IGBI do not fully capture nasal and ocular AEs, which made up a large proportion of TEAEs in subjects exposed to NG. For purposes of labeling, the Nasal and Non-Nasal Symptom Score Questionnaire should be used in addition to reported TEAEs to allow for a more complete and accurate representation of AEs associated with NG.

In summary, the clinical development program demonstrated NG has a favorable benefit-risk profile. While there was a 1-4 minute delay in comparison to CG in reaching blood glucose ≥ 70 mg/dL, NG was overall efficacious, and the time lag is likely mitigated by the requirement of CG for reconstitution. Additionally, although there were changes in formulation due to manufacturing changes during the development program, the clinical bridging study IGBI was performed with the to-be-marketed formulation, and studies IGBB and IGBC provided additional evidence of the safety and efficacy of NG. Furthermore, due to (b) (4) a dose as low as 2 mg of NG, rather than 3 mg evaluated in the majority of clinical studies, could be delivered. However, the clinical study data for 2 mg, in addition to clinical pharmacology modeling data, provide evidence that in a “worst case scenario”, a 2 mg dose of NG is efficacious. I recommend approval of NG for the treatment of severe hypoglycemia.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Severe hypoglycemia is a serious medical condition that is often a result of insulin treatment. • It occurs in patients with both T1DM and T2DM • It occurs in approximately 22% to 46% of patients with T1DM annually, and 7% to 25% of patients with T2DM who are treated with insulin.	Severe hypoglycemia is a serious medical condition characterized by neurologic impairment, and can lead to death.
Current Treatment Options	• Intravenous dextrose infusion can be administered in a healthcare setting only • Injectable glucagon can be administered in an outpatient setting, but currently available formulations require reconstitution.	Injectable glucagon, which requires reconstitution prior to use, is the only treatment option available outside of a healthcare setting.
Benefit	• NG demonstrated noninferiority compared to CG in achieving blood glucose of ≥70 mg/dL, or rise of blood glucose ≥20 mg/dL from nadir within 30 minutes of glucagon administration, in both adults and pediatric subjects. • NG does not require reconstitution.	NG was effective in increase blood glucose levels. The intranasal route of administration offers a potentially easier to administer glucagon product for emergency use.
Risk and Risk Management	• Safety generally consistent with injectable glucagon products, although higher incidence of non-serious nasal and ocular AEs • Some of the nasal and ocular AEs were rated as severe, but generally resolved by 90 minutes. • The time to achieve a blood glucose of ≥70 mg/dL was delayed by 1-4 minutes for NG compared to CG.	The safety of NG can be adequately communicated in labeling. Although there was a delay to reach a blood glucose of ≥70 mg/dL for NG compared to CG by 1-4 minutes, NG does not require reconstitution. It is reasonable to assume this would offset, at least in part, the delay.

2. Background

Diabetes mellitus is a serious chronic medical condition characterized by hyperglycemia, and includes two main types of diabetes; T1DM and T2DM. Patients with T1DM have impaired insulin production and secretion, and require insulin treatment for survival, while many patients with T2DM may also require insulin to achieve glycemic targets. Insulin therapy, as well as insulin secretagogues, are associated with the inherent risk of severe hypoglycemia, which is characterized by neurological impairment that can result in loss of consciousness, seizures, or even death. Severe hypoglycemia is more common in patients with T1DM, occurring in approximately 22% to 46% of patients with T1DM annually, and 7% to 25% of patients with T2DM who are treated with insulin.

There are two currently available treatment modalities for severe hypoglycemia, intravenous dextrose and injectable glucagon. Intravenous dextrose requires administration by a healthcare professional in a hospital or emergency medical setting, while glucagon is administered via injection and can be administered by a caregiver outside of a hospital setting. The two currently approved glucacon products, GlucaGen and Glucagon for injection, require reconstitution prior to administration.

Nasal glucagon (NG) was developed as a treatment for severe hypoglycemia in both adult and pediatric patients with diabetes. It was originally developed by AMG Medical, and later by Locemia Solutions ULC, prior to being acquired by Eli Lilly in 2015. The drug substance is synthetic glucagon, which is identical to human glucagon, a peptide consisting of 29 amino acids. Eli Lilly, hereafter referred to as the Applicant, has submitted a new drug application (NDA) under the 505(b)(1) pathway, seeking approval for NG, a single-use glucagon for rescue. NG would be the first nasally administered glucagon for emergency use for hypoglycemia to be marketed in the United States.

The indication for NG proposed by the Applicant is *an antihypoglycemic agent indicated for the treatment of severe hypoglycemia.* The Applicant is proposing only one dose for NG of 3 mg. The proposed trade name for NG is BAQSIMI. The drug product will be administered via a prefilled device for nasal administration.

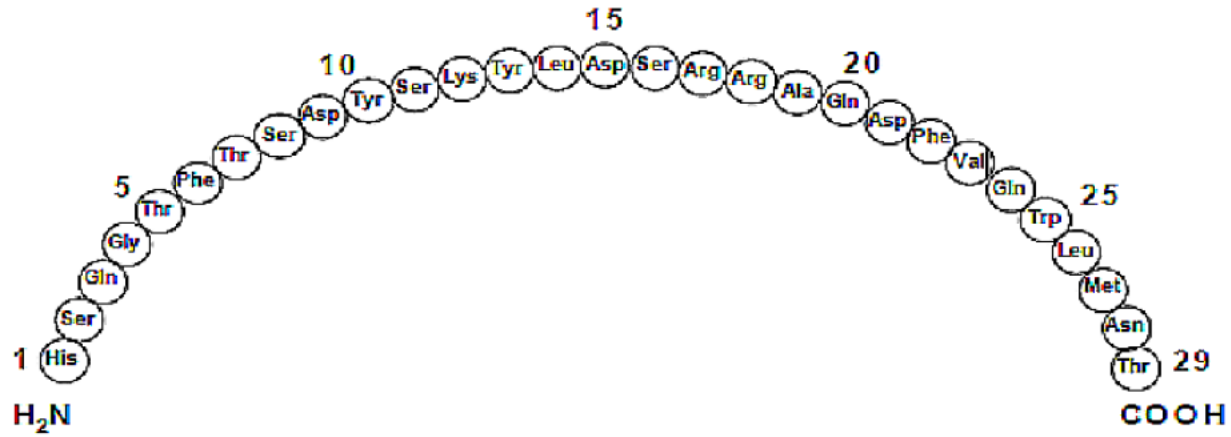
In support of this NDA, the Applicant conducted a total of 11 trials, which included 9 studies in adults, of which 7 were supportive studies including an actual-use study, and 2 studies conducted in pediatric subjects, including 1 supportive actual-use study. A Special Protocol Assessment (SPA) was agreed upon with the FDA and AMG Medical Incorporation (and later Locemia Solutions) in 2013 for Study IGBC, and in 2015, the FDA confirmed the study was performed in accordance with the SPA. However, Eli Lilly aquired the product from Locemia in 2015. Since the study drug used in Study IGBC was not produced using the intended commercial manufacturing process, FDA recommended the sponsor conduct a bridging study (Study IGBI) to bridge the commercial product with the product used in Study IGBC.

3. Product Quality

Drug Substance:

The drug substance of NG, synthetic glucagon, is a peptide hormone identical to human glucagon produced by the pancreatic alpha cells, as well as glucagon in approved glucagon for emergency kits. It is composed of 29 amino acid residues, arranged in a single-chain polypeptide, with a molecular weight of 3483. The empirical formula is $C_{153}H_{225}N_{43}O_{49}S$. The chemical structure of glucagon is shown below, in Figure 1.

Figure 1: Chemical Structure of Glucagon



Source: Figure 2.7.1.1 Biopharmacology Summary

The drug substance is manufactured using [redacted] (b) (4)

During the course of the development program, the Applicant used two different synthetic glucagon drug substance supplies, [redacted] (b) (4). This process was used in the phase 3 studies, and is the one that will be used for the commercial supply.

Drug Product

NG is a [redacted] powder that contains 3 mg of synthetic glucagon, along with the addition of [redacted] mg of dodecylphosphocholine (DPC), and [redacted] mg of beta-cyclodextrine (β-CD). DPC acts as a [redacted] while β-CD acts to [redacted] material, [redacted] The drug powder is contained in a primary container closure system within device constituent components, which delivers the drug intranasally. The components of NG drug powder are shown below, in Table 1.

Table 1: Unit Formula for Nasal Glucagon Drug Powder

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

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

[redacted]

Source: Table 2.3.P.1-1 from the Applicant's Drug Product Document

The applicant conducted testing to evaluate long-term storage conditions, which included testing at 25°C/60% RH, 30°C/65% RH, 30°C/75% RH, and at the accelerated storage condition 40°C/75% RH. Based on the provided stability data, Dr. Ramaswamy recommends an expiration period of 18 months when stored at [redacted] 30°C for the combination product packaged in shink-wrapped secondary packaging.

Although the combination product is intended to dispense 3 mg of glucagon per actuation, the dispensed dose delivered along the shelf life of the drug product is a range, and can decrease with time. It was noted by Dr. Ramaswamy in his review that at the end of shelf-life, "the mean dose dispensed from the device can be as low as [redacted] mg glucagon with an understanding 90% of the samples tested will have a potency of [redacted] mg and the potency of the remaining of the sample population may lie between [redacted] mg."

The efficacy of a 2 mg dose of NG was evaluated during the clinical development program, and the applicant provided additional clinical pharmacology data to support the efficacy of the 2 mg dose, as this is the lowest individual dose that may be dispensed from the device at the end of shelf-life. Although the intended dose of NG is 3 mg, the clinical study data, along with clinical pharmacology data, provide evidence that in a "worst case scenario", a 2 mg dose of NG is efficacious. The clinical pharmacology and efficacy considerations for the 2 mg dose of NG are discussed in Section 7.

The manufacturing process was found to be adequate. During development, changes to facilitate production of large quantities of drug product were made to the manufacturing to support commercializing. Since the earlier manufacturing process involved (b) (4)

(b) (4)

performance attributes. For detailed discussion of the drug product manufacturing process and the drug product in its primary container closure, see Dr. Haber's and Dr. Ramaswamy's reviews.

Device:

NG is designed to be delivered via a single-use delivery device, which is inserted into a nostril, and following device actuation, NG powder is delivered to the nasal mucosa. The powder is not intended to be inhaled. The device, primary container system, and tube with dessicant is displated below, in Figure 2.

Figure 2: Device, Primary Container, and Tube with Dessicant

(b) (4)

Source: Figure 2.7.1.2.2 from the Applicant's Biopharmaceutical Summary

NG is to be marketed in a device that distributes the product for intranasal administration. The proposed device and its performance characteristics were reviewed by Dr. Matthew Ondeck from the Center for Devices and Radiologic Health (CDRH). There were device changes made to the to-be-marketed device from what was used in the clinical study. Dr. Ondeck has concluded that the design changes will not change the device essential performance requirements. Essential performance requirements for a nasal spray device, which include pump delivery, spray pattern and plume geometry shape, spray content uniformity, droplet/particle size distribution, and actuation force, were reviewed by the CDRH reviewer. The applicant had initially proposed a device with an upper specification for the actuation force of (b) (4) kgF, which was determined to be too high for many users, and in comparison to other emergency use products, such as EpiPen. The applicant was adviced to decrease the actuation force, and the applicant responded with a new final actuation force acceptance criteria at room temperature of (b) (4) kgF. Literature references for palmar pinch strength of adolescents aged 10-19 years old were provided to justify the new upper actuation force. The majority of NG devices tested also had a lower actuation force during testing of approximately (b) (4) kgF, and the applicant also provided justification with their human factors validation testing. In light of the fact that there were no user complaints regarding difficulty with actuation, and the study included adolescent participants, Dr. Ondeck concluded that the applicant had adequately validated the upper specification for actuation force.

Based on the device data provided by the Applicant, the design and performance of the device was found to be acceptable and supportive of approval.

The applicant conducted a human factors validation study in order to support that intended users could understand product instructions and appropriately administer the dose. The validation study results were reviewed by the Division of Medication Error Prevention and Analysis (DMEPA), and their review determined that the human factor study results did not support that users can use the BAQSIMI device correctly due to errors performing the critical task of depressing the plunger in order to administer the dose. DMEPA recommended the applicant implement recommended changes to product labeling, finalize the proposed to-be-marketed product, and conduct a supplemental usability study after recommended changes were implemented, to confirm safe and effective use of the product. These recommendations were communicated to the applicant on January 20, 2019. The applicant submitted the results of the supplemental usability study on April 2, 2019. It was determined that this additional study represented a major study amendment, and the User Fee goal date was extended in order to allow DMEPA to completely review the study.

The results of the supplemental usability study were reviewed by DMEPA, and were found to support that users could safely use the BAQSIMI device correctly. For further details, please see the DMEPA review by Dr. Ariane Conrad.

Facilities:

The manufacturing process and control information, including microbiological control of the process, was reviewed by Dr. Ramesh Dandu and Dr. Joanne Wang. Pre-approval insections at the combination product manufacturing facility were also performed by Dr. Wang. Additional input on the combination product manufacturing was given by ORA and the CDRH compliance reviewer. The CMC reviewers concluded that information provided in process and facilities is acceptable to support the approval of this NDA.

4. Nonclinical Pharmacology/Toxicology

The nonclinical program for NG was designed to appropriately assess the effects of intranasal glucagon when administered intranasally for the intended short-term clinical usage, and to evaluate the effects of the excipients not previously qualified for intranasal administration.

The review of the submitted nonclinical data was completed by Dr. Dongyu Guo. Findings from Dr. Guo's review are summarized here. For detailed discussion, see Dr. Guo's nonclinical review.

The applicant conducted two 28-day repeat-dose toxicity studies in rats and dogs, who were administered the study drug via the nasal route. In rats, reversible ulcerations/erosions were seen in the turbinates of the nasal cavities, while in dogs, mild to moderate atrophy and degeneration of the olfactory epithelium were seen after 28-days of once daily exposure, which were reversible. The NOAEL in rats was 0.1 mg glucagon/day, based on the nasal turbinate findings, with a safety margin of 45-times the human exposure, based on AUC. The NOAEL in dogs was not established based on the histopathologic findings in the nasal cavities. There were no test article-related adverse effects on body weight and/or food consumption, ophthalmology, electrocardiography, hematology, coagulation parameters, clinical chemistry, urinalysis, or organ weights, and no macroscopic findings at necropsy in the studies.

The Applicant also conducted two 28-day repeat-dose studies in rats to evaluate the effect of β-CD and DPC excipients. No significant excipient-related toxicities were observed. Minimal local nasal irritation was noted in the vehicle control group in dogs.

While the nonclinical studies showed reversible lesions in the nasal cavity, this is unlikely to be a concern in humans as the product is only intended for single use. In summary, based on the data reviewed, Dr. Guo recommends approval.

5. Clinical Pharmacology

The clinical development program for NG included four dose selection studies, two dose confirmation studies, and one supportive study. Since there were changes in formulation during the development program, and Study IGBI, which was the bridging and dose confirmation study, was the only study conducted with the to-be-marketed product, it is the focus of the clinical pharmacology discussion. See Table 2, below.

Table 2: Clinical Studies for NG with PK/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 from Applicant's Clinical Pharmacology Summary

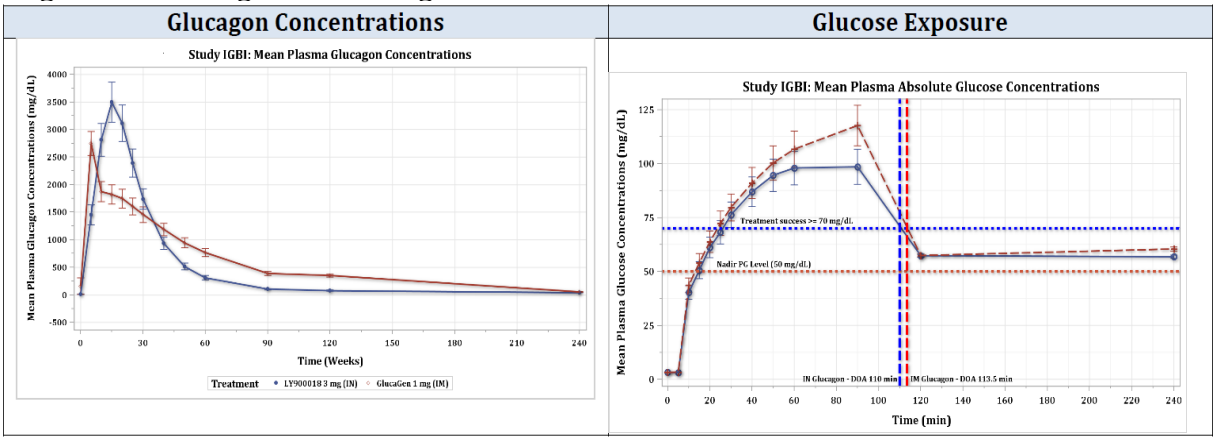
As discussed above, due to (b) (4), the final dose delivered could potentially be as low as 2 mg for NG. Clinical pharmacology and efficacy considerations for the 2 mg dose of NG are discussed in Section 7.

Glucagon acts to increase plasma glucose levels, and has been available by injection since 1998. When administered intranasally, NG achieves peak plasma levels of 6130 pg/ml at 15 minutes, and is rapidly eliminated, with a mean half-life of approximately 38 minutes.

In Study IGBI, the mean PK (glucagon) and PD (glucose) profiles for NG were compared to intramuscularly (IM) administered glucagon (CG) after a single dose of 3 mg and 1 mg, respectively. The PK and PD profiles are displayed graphically in Figure 3 and in tabular format in Table 3 below.As seen in the left panel of Figure 3 and in Table 3, compared to CG, the C_{max} of NG was higher (geometric mean of 6130 pg/mL as discussed above vs 3750 pg/mL for CG), while the $AUC_{0\text{-}tlast}$ was lower (2740 pg·hour/mL vs 3320 pg·hour/mL) for NG compared to CG. The applicant conducted statistical analyses and determined the 90% confidence intervals did not overlap for C_{max} between treatment groups. The mean glucose-time profiles, as seen in the right panel of Figure 3, show that the mean time to treatment success, which was defined as a blood glucose concentration above 70 mg/dL, was 16.2 minutes for NG, and 12.3 minutes in the CG treatment groups.

Figure 3: Mean Plasma Glucagon Concentration and Glucose Exposure- Study IGBI

Single dose of 3 mg NG and 1 mg CG



Source: Figure 3 from Clinical Pharmacology review

The BG_{max} change from baseline was statistically different between treatment groups, with CG having a higher BG_{max} of 160.3 mg/dL, and 131.2 mg/dL for NG (Table 3). However, this difference in BG_{max} is not clinically relevant, and in fact, the pharmacodynamic response of NG may be preferable for T1DM patients, in whom avoidance of hyperglycemia is desirable.

Table 3: PK and PD parameters for NG and CG

	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
Note the T_{max} is displayed in Table 3 by median (range), while Figure 3 displays mean T_{max} values

Overall, the clinical pharmacology data demonstrates the glucose response curves for both NG and CG were similar, which support the dose selection of 3 mg for NG. Although the C_{max} was higher for NG than CG, this did not appear to impact the safety of NG (see section 8 of this memo). While the time to reach BG > 70 mg/dL was slower for NG by several minutes, this difference is not clinically meaningful, as NG appears to offer greater ease of use in comparison to CG.

Based on the reviewed clinical pharmacology data, which support the pharmacodynamic response of NG, Dr. Sista and Dr. Khurana support approval of NG for treatment of severe hypoglycemia. The Office of Study Integrity and Surveillance (OSIS) performed an inspection of the analytical portion of studies conducted at (b) (4). The OSIS reviewer concluded that the data submitted are reliable for Agency review.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The efficacy discussion will focus on Studies IGBI, IGBC, and IGBB, with a primary focus on the 3mg dose, as listed in Table 4, below. The efficacy of the 2 mg dose will be noted, where applicable, given the potential for dose degradation, as discussed in Section 3 of this review. The actual use studies are not further discussed in this CDTL review, due to concerns regarding study conduct and interpretability of data. For a complete listing of clinical studies conducted by the Applicant, see Appendix 1.

The non-inferiority of NG to CG in the proportion of subjects achieving treatment success, as defined by either an increase in 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 glucose level, was reviewed by Dr. Roberto Crackel. The efficacy findings are summarized in this review. For a more detailed discussion, please see Dr. Crackel's review.

Table 4: Clinical Studies Conducted with NG in Support of Efficacy

Study ID	**Population**	**Design Comparator; Route of Administration**	**Number of Patients Receiving Study Drug**	**Key Endpoints**
Pivotal Studies				
I8R-MC-IGBC	Adult patients, 18 to 65 years, with T1D or T2D	Multicenter, randomized, open-label, 2-period, crossover; insulin-induced hypoglycemia (insulin infusion was stopped when glucose was <60 mg/dL 1 mg GlucaGen HypoKit; IM	NG 3 mg: 83 IMG 1 mg: 82 Enrolled/ Completed: 83/82	Proportion of patients achieving treatment success, defined as either an increase in 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 glucose level
I8R-MC-IGBB	Pediatric patients, 4 to <17 years of age, with T1D	Multicenter, randomized, 2-period, crossover; insulin was used if necessary to attain a glucose <80 mg/dL (4.44 mmol/L) 0.5 or 1 mg GlucaGen HypoKit (Novo Nordisk USA); IM	NG 2 mg: 23 NG 3 mg: 36 IMG 0.5/1 mg: 24 Enrolled/ Completed: 48/47	Proportion of patients achieving treatment success, defined as an increase in glucose of ≥20 mg/dL (1.1 mmol/L) from glucose nadir within 30 minutes after receiving study glucagon, without receiving additional actions to increase glucose level
Clinical Bridging* and Confirmatory Study				

I8R-MC-IGBI	Adult patients, 18 to 64 years, with T1D	Multicenter, randomized, open-label, 2-period, crossover; insulin-induced hypoglycemia (insulin infusion was stopped when glucose was <60 mg/dL [3.3 mmol/L]) 1 mg GlucaGen HypoKit (Novo Nordisk UK); IM	NG 3 mg: 70 IMG 1 mg: 69 Enrolled/ Completed: 70/69	Proportion of patients achieving treatment success, defined as either an increase in glucose to ≥70 mg/dL (3.9 mmol/L), or an increase of ≥20 mg/dL (1.1 mmol/L) from glucose nadir, within 30 minutes after receiving study glucagon, without receiving additional actions to increase glucose level[a]. Safety, PK, and PD

Source: Adapted from table 2.5.1.1 from Applicant's Clinical Overview
**Study used to bridge older formulation used in studies IGBC and IGBB to to-be-marketed formulation*

Study Design- IGBI/IGBC:

Studies IGBI and IGBC had similar study designs. Both studies were open-label, randomized, cross-over studies with a non-inferiority design comparing the efficacy and safety of NG to CG. The primary endpoint of both studies was the percentage of patients who achieved treatment success, which was defined as an increase in glucose to ≥ 70 mg/dL or an increase of ≥20 mg/dL from nadir within 30 minutes after administration of glucagon. Noninferiority was achieved if the lower limit of the 2-sided 95% CI of the difference in proportion of success (NG-CG) was greater than the noninferiority margin of -10%.

At each study visit, subjects were given an IV infusion of regular insulin which was stopped once blood glucose levels reached < 60 mg/dL, with a target nadir blood glucose level of < 50 mg/dL. NG or CG was administered, and blood glucose levels were measured at 5,10, 15, 20, 25, 30, 40, 50, 60, and 90 minutes following administration of glucagon. There was a 7 to 28-day washout period between study visits.

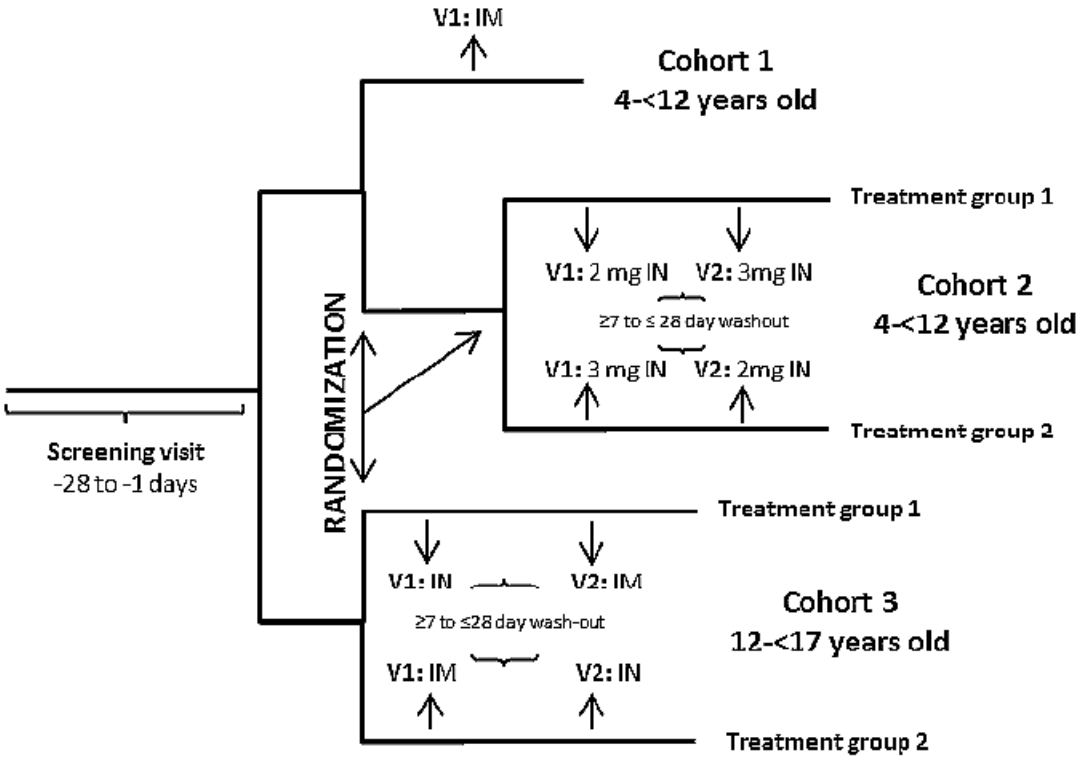
Study Design- IGBB:

Study IGBB was a randomized, quasi-blinded, quasi-crossover, multi-center, trial in pediatric patients with type 1 (the majority of patients) or type 2 diabetes. The study was considered quasi-blinded as the two NG doses studies were blinded, but glucagon administered intramuscularly versus intranasally were not blinded due to the method of administration. The study was quasi-crossover in that cohort 1 did not crossover, but cohorts 2 and 3 did. The primary objective was to assess the PK (glucagon) and PD (blood glucose) of NG in comparison with CG in a pediatric subjects aged 4 to <17 years old with T1DM.

At each visit, insulin was infused until plasma glucose levels reached < 80 mg/dL. Five minutes later, glucagon was administered. Blood glucose levels were measured at 5, 10, 15, 20, 30, 40, 60, and 90 minutes following administration of glucagon. Nasal and non-nasal scores were assessed at 15, 30, 60, and 90 minutes after glucagon administration.

The study design of IGBB is depicted in Figure 4.

Figure 4: Study Design Study IGBB



Source: Figure 9.1-1 CSR

Statistical Methods:
For both Studies IGBI and IGBC, the Applicant obtained the point estimate and 2-sided 95% CI from the 1-sample paired differences using the student t-distribution. Non-inferiority of NG was declared if the lower limit of the 2-sided 95% CI of the difference in proportion of success was greater than the noninferiority margin of -10%. In order to ensure the correct probability of the confidence interval containing the underlying true difference in the proportion of success, Dr. Roberto Crackel, the statistical reviewer, used the correction proposed by Agresti and Min, in which 0.5 was added to each cell count.

The study data for Study IGBB were to be analyzed descriptively and were considered exploratory. While no primary endpoint was prespecified, mean time to reach glucose increase ≥20 mg/dL was proposed by the Applicant for labelling.

The disposition of subjects in Studies IGBI, IGBC, and IGBB is displayed below in Table 5.

Table 5: Subject Disposition for 3 mg NG- Studies IGBI, IGBC, IGBB

	Number (%) of Patients							
Study	IGBI		IGBC- T1DM		IGBC-T2DM		IGBB	
Treatment	NG	CG	NG	CG	NG	CG	NG	CG
Randomized and received at least 1 dose of study drug	70 (100)	70 (100)	77 (100)	76 (98.7)	6 (100)	6 (100)	36 (100)	24 (100)
Primary Analysis Population	66 (94.3)	66 (94.3)	75 (97.4)	75 (97.4)	5 (83.3)	5 (83.3)	36 (100)	24 (100)

Source: adapted from Statistical Reviewer's analysis

There were 7 patients in total who were excluded from the primary analysis, 4 from Study IGBI and 3 from Study IGBC, of whom 2 had T1DM and 1 had T2DM. The reasons for subject exclusion from the primary analysis in Studies IGBI and IGBC were failure to achieve a nadir blood glucose of < 70 mg/dL, subject withdrawal from the study prior to receiving both study drugs, or premature administration of carbohydrates. Dr. Crackel has reviewed the efficacy data of these subjects, and concludes the exclusion of these subjects had no impact on the result of the primary endpoint.

Study Results

Study IGBI:

There were 66 patients who were included in the analysis and received both NG and CG. There was 100% success rate for both arms. The difference in proportion of success was 0.00 with a 95% CI of (-0.029, 0.029) according to the analysis conducted by Dr. Crackel, and since the lower bound of the CI was greater than pre-specified non-inferiority margin of -0.10, the non-inferiority of NG to CG was established. As the statistical reviewer's analysis used the Agresti and Min correction, the 95% CI are different than the Applicant's (-0.029, 0.029). The difference in the proportion of success, and therefore the conclusions regarding non-inferiority, remain unchanged from the Applicant's analysis.See Table 6, for further details.

Table 6: Proportion of Subjects who Achieved Success in Study IGBI

	BAQSIMI (N=66)	**IMG (N=66)**
# of success (%)	66	66
Success criterion met n, (%):		
≥ 70 mg/dL	66 (100%)	66 (100%)
Increase by ≥ 20 mg/dL from nadir	66 (100%)	66 (100%)
Difference in Proportion of success (95% C.I.) (Sponsor's analysis)	0.00 (0.00, 0.00)	
Difference in Proportion of success (95% C.I.) (Statistical reviewer's analysis)	0.00 (-0.029, 0.029)	

a There were 4 randomized patients excluded from the analysis. See Section 3.2.5 below for details
Source: Table 9 from Statistical Reviewer

Study IGBC:

There were 75 T1DM patients who were included in the analysis and received both NG and CG. There was 74 patients (98.7%) in the NG arm who achieved success, and 75 patients (100%) in the CG who achieved success. The difference in proportion of success was -0.013 with a 95% CI of (-0.049, 0.023) in Dr. Crackel's analysis, and since the lower bound of the CI was greater than pre-specified non-inferiority margin of -0.10, the non-inferiority of NG to CG was established. As previously discussed, using the Agresti and Min correction, the 95% CI (-0.049, 0.023) are different than the Applicant's. The difference in the proportion of success, and therefore the conclusions regarding non-inferiority, remain unchanged from the Applicant's analysis. See Table 7, for further details.

Table 7: Proportion of Subjects who Achieved Success in Study IGBC

	BAQSIMI (N=75[c])	**IMG (N=75[c])**
# of successes (%)	74 (98.7%)	75 (100%)
Success criterion met n, (%):		
≥ 70 mg/dL	72 (96.0%)	74 (98.7%)
Increase by ≥ 20 mg/dL from nadir	74[a] (98.7%)	75[b] (100%)
Difference in Proportion of success (95% C.I.) (Sponsor's analysis)	-0.013 (-0.040, 0.013)	
Difference in Proportion of success (95% C.I.) (Statistical reviewer's analysis)	-0.013 (-0.049, 0.023)	

a There were 2 patients on BAQSIMI who achieved ≥ 20 mg/dL from nadir but did not achieve ≥ 70 mg/dL
b There was 1 patient on IMG who achieved ≥ 20 mg/dL from nadir but did not achieve ≥ 70 mg/dL
c There were 2 randomized patients excluded from the analysis. See Section 3.5.2 below for details
Source: Table 7 from Statistical Reviewer

Study IGBB:

The results from Study IGBB were descriptive only, as there was no pre-specified primary efficacy endpoint. The results for the mean time to increase blood glucose by ≥ 20 mg/dl is displayed below, in Table 8. Since the starting blood glucose in Study IGBB was 80 mg/dl, the increase to blood glucose ≥ 70 mg/dl is not applicable for this study.

Table 8: Mean time to reach blood glucose increase ≥ 20 mg/dL- Study IGBB

Increase from Nadir	Mean Time (mins) to Reach Glucose Increase ≥ 20 mg/dL					
	4 to < 8 yrs old		8 to < 12 yrs old		12 to < 17 yrs old	
	IMG (N=6)	BAQSIMI (N=12)	IMG (N=6)	BAQSIMI (N=12)	IMG (N=12)	BAQSIMI (N=12)
≥ 20 mg/dL	10.0	10.8	12.5	11.3	12.5	14.2

Source: Table 7 from Statistical Reviewer

The mean time to achieve an increase in blood glucose ≥ 20 mg/dl was similar across the three age groups, and was similar between NG and CG. Although Study IGBB was an underpowered exploratory study, as discussed in Dr. Sista's Clinical Pharmacology review, after applying body-weight allometry scaling, age and gender had no impact on the PK of NG. The Applicant also developed a PK/PD model using data from the clinical studies, and based on the model, as well as data from Study IGBB, the PK/PD of NG is expected to be similar between pediatric and adult patients. The results from Study IGBB support the efficacy of NG in pediatric patients.

Overall, Dr. Crackel concludes that the applicant has demonstrated the non-inferiority of NG to CG in the percentage of patients who achieved treatment success, which was defined as an increase in glucose to ≥70 mg/dL or an increase of ≥20 mg/dL from nadir within 30 minutes after administration of glucagon. I agree with his conclusions.

Efficacy of 2 mg NG

(b) (4)

which would allow for a dose as low as 2.0 mg to be delivered, rather than 3.0 mg, the efficacy of 2 mg NG is considered here. The applicant was asked to provide efficacy and clinical pharmacology data for 2 mg NG from the clinical development program, as well as simulated glucagon exposure and glucose response for 2 mg NG.

The 2 mg NG dose was evaluated in 3 clinical studies (see Appendix 1); IGBA, IGBB, and IGBD, although different versions of the drug product were used in these studies, rather than the to-be-marketed drug product studies in IGBI. Study IGBD evaluated the PK and PD of NG in healthy volunteers and did not assess glycemic response. Studies IGBA and IGBB studied NG in patients with T1DM, but since both studies used different definitions for assessing glycemic response, the definition used in Study IGBC was assessed post-hoc for Studies IGBA and IGBB. Treatment success was defined as increase in blood glucose from nadir to at least 70 mg/dL or an increase in blood glucose of at least 20 mg/dL from nadir within 30 minutes of glucagon treatment. As the study procedures for Study IGBB did not require the blood glucose level to be decreased below 70 mg/dL, the second part of the definition for treatment success, i.e. increase of ≥20 mg/dL from nadir within 30 minutes post glucagon dosing, was used.

In Study IGBA, 18 subjects were included in the analysis and received both 2 mg NG and CG. There were 16 patients (88.9%) in the NG arm who achieved success, and 18 patients (100%) in the CG arm who achieved success. There were 4 subjects exposed to 2 mg NG who did not have detectable serum glucagon levels, which included the 2 subjects who did not achieve treatment success. In Study IGBB, 24 subjects received CG, and 22 subjects and received 2 mg NG. There were 22 patients (100%) in the NG arm who achieved success, and 24 patients (100%) in the CG who achieved success. SeeTable 9.

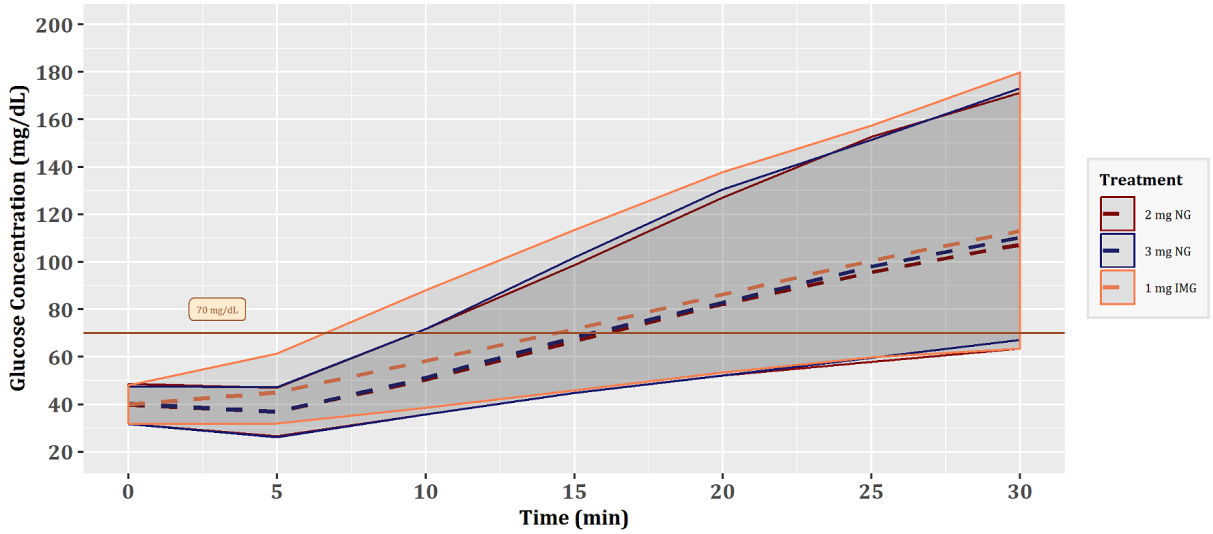
Table 9: Proportion of Patients Achieving Blood Glucose Increase of ≥20 mg/dL from Nadir within 30 minutes Post Glucagon Dosing

Study	CG n/N (%)	NG 2mg n/N (%)	NG 3mg n/N (%)
IGBA	18/18 (100.0)	16/18 (88.9)	8/8 (100.0)
IGBB	24/24 (100.0)	22/22 (100.0)	36/36 (100.0)

Source: Table 1 from Applicant's Reponse to Information Request November 30, 2018

The Applicant also simulated glucagon exposure and glucose response for the 2 mg dose of NG. The simulations used PK and PD parameters of Study IGBI, amd responses were simulated from 1,000 patients, to assess the probability of treatment success. For patients with a baseline blood glucose of 40 mg/dL, the simulated resulted indicate that 2 mg NG would result in 97% of patients achieving treatment success at 30 minutes postdose. The predicted glucagon exposure, as well as glucose response, of 2 mg and 3 mg of NG compared to IM glucagon (i.e. CG) were similar. The predicted glucose response is seen below in Figure 5.

Figure 5: Predicted Glucose Response of NG 2mg, 3 mg, and IMG 1 mg Over Time



Source: generated by Clinical Pharmacology reviewer

The post-hoc analyses of the clinical data for the 2 mg dose of NG, combined with the modelled exposure response data, support the efficacy of the 2 mg dose. Although there were 2 subjects who did not have a response to NG, no substantial glucagon levels were detected for these patients, suggesting these subjects did not receive NG. There were 2 additional subjects who did have a response to NG but who did not have detectable glucagon levels for unclear reasons. The Applicant suggests the glucagon assay used in this study was less sensitive that the glucacon assay used later in the development program. Regardless, while 2 mg dose is not intended for marketing purposes, efficacy data for the 2 mg dose, which would represent the lowest possible dose delivered from the intended 3 mg device, is reassuring. This ensures that in a "worst-case scenario" of drug product at the lower limit of shelf-life specifications, in which a dose of 2 mg is delivered, the product which is

intended for rescue from a potentially life-threatening hypoglycemic episode, produces a clinically meaningful response.

The Office of Scientific Investigations conducted inspections in support of this application, which consisted of two domestic clinical sites (representing three study sites) as well as the sponsor and contract research organization (CRO). The inspection of the sponsor, CRO and the clinical investigators revealed no regulatory violations. The inspectional findings support the validity of the data, and the data is considered reliable. For further details, please see the OSI review by Dr. Cynthia Kleppinger.

8. Safety

During the clinical development program for NG, a total of 461 patients received NG, of which 365 had T1DM. There were 421 patients out of the total of 461 patients who received the 3 mg dose of NG. There were 58 patients out of the total 461 patients who were aged 4-<18 years old. See Appendix 1 for a complete table of studies conducted with NG. As NG is intended for the treatment of severe hypoglycemia, which is a life-threatening disease, and is intended for short-term use, the ICH guidance for industry *E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions* is not applicable, and the safety database for NG is considered to be acceptable. The assessment of overall safety was conducted by Dr. Andreea Lungu. In my CDTL review, I will briefly review the overall safety findings and discuss selected safety findings unique to this product, namely nasal and ocular symptoms associated with intranasal administration. Please refer to Dr. Lungu's review for a detailed discussion of safety findings.

Description of studies reviewed:
Studies discussed in the safety review were IGBI, IGBC, and IGBB. Study IGBI was the only study conducted using the to-be-marketed drug product, and is considered the pivotal study. Studies IGBC (conducted in adults) and IGBB (conducted in adults and pediatric subjects), were considered supportive. The Applicant conducted two actual use studies, one in adults and one in pediatrics. Safety data from the actual use studies was not collected in a rigorous manner, and is therefore not discussed in this review, but is discussed in Dr. Lungu's review.

Safety Summary
The overall incidence of AEs in Studies IGBI, IGBC, and IGBB were similar in frequency between NG and CG, and were anticipated based on the known safety profile of injectable glucagon. There was a higher incidence of nasal and ocular AEs with NG, which is expected given the route of administration, and these nasal and ocular symptoms had mostly resolved by 90 minutes postbaseline.

The Applicant utilized a Nasal and Non-Nasal Symptom Score Questionnaire in order to capture details related to the timing and duration of nasal and ocular adverse events. This questionnaire was used in Studies IGBI, IGBC, and IGBB, however, in Study IGBI, these symptoms were not to be reported in the AE dataset (unless they were SAEs), but were only documented in the questionnaire. For this reason, the AE datasets for Study IGBI do not fully capture nasal and ocular AEs, which made up a large proportion of TEAEs in subjects exposed to NG. For purposes of labeling, I agree

with Dr. Lungu's recommendation that the Nasal and Non-Nasal Symptom Score Questionnaire should be used in addition to reported TEAEs to allow for a more complete and accurate representation of AEs associated with NG.

Deaths:
There was a single death reported in the NG clinical development program. The patient was a 66 year old male with T1DM, who was enrolled in the actual use study B002. The patient had two hypoglycemic episodes during the study, with blood glucose values of 41 mg/dl and 36 mg/dl, but recovered after administration of NG. The patient was diagnosed with Klebsiella pneumonia more than a month after last administration of study product, and subsequently developed acidosis and multiple organ failure, and died three days later. I agree with Dr. Lungu's assessment that the death was not related to the study drug.

Serious Adverse Events:
There was one reported serious adverse event (SAE) in an adult male from Study IGBG. The patient was a 54 year old male with a history of T2DM, managed on insulin isophane, metformin, sitagliptin, and acarbose. After receiving a total of 2 doses of NG 6 mg during separate study visits, the patient received his third dose of 6 mg of NG. The same day, the patient developed increasing pain in his right leg, and noted the presence of a red plaque, and developed difficulty walking. He presented to the Emergency Room the following day, where he was diagnosed with cellulitis and treated with parenteral antibiotics. I agree with Dr. Lungu's assessment that there is no evidence this event was caused by the study drug.

There was a second reported SAE that occurred in a pediatric patient from Study IGBB. The patient was a 7 year old male with a history of T1DM for 4 years, and was managed on insulin aspart administered via insulin pump. The patient's baseline blood glucose was 88 mg/dl, following which he received 1 mg of IM glucagon. His blood glucose increased, and was 230 mg/dl at 1 hour and 215 mg/dl after 90 minutes. He was given a meal, along with bolus insulin, and developed symptoms consistent with severe hypoglycemia, and became nauseous and vomited. He then became disoriented and drowsy, and uncooperative with oral intake. His blood glucose was 55 mg/dl, and subsequently dropped to 32 mg/dl. He was given 90 grams of carbohydrates and recovered. As the patient received IM glucagon, and not NG, this SAE was unrelated to study drug, and was likely related to the study procedures, including the bolus insulin he was administered, and use of IM glucagon.

Treatment-emergent Adverse Events

Studies IGBI and IGBC

Treatment emergent adverse events (TEAEs) reported by subjects were similar in Studies IGBI (NG 48.6%; CG 50.7%) and IGBC (NG 55.4%; CG 45.1%); the most common TEAEs were gastrointestinal and nervous sytem disorders such as nausea, vomiting, and headache. The incidence of TEAEs were similar between NG and CG in Study IGBI, however, there was a greater incidence of TEAEs reported by subjects in the NG group in Study IGBC. The lower incidence of TEAEs in Study IGBI compared to Study IGBC was likely related to the preferential reporting of nasal and ocular symptoms on the symptom questionnaires, rather than as AEs in Study IGBI, which resulted in a reduction in the number of TEAEs reported as AEs in that study. See Table 10 for additional details.

Table 10: Treatment-emergent Adverse Events by System Organ Class, Preferred Term in Study IGBI and IGBC Reported by at least 5% of Patients

	Study IGBC		Study IGBI	
System Organ Class Preferred Term	CG (N=82) n (%)	NG 3 mg (N=83) n (%)	CG (N=69) n (%)	NG 3 mg (N=70) n (%)
Patients reporting ≥1 TEAE	37 (45.1)	46 (55.4)	35 (50.7)	34 (48.6)
Gastrointestinal disorders	30 (36.6)	29 (34.9)	30 (43.5)	23 (32.9)
Nausea	22 (26.8)	18 (21.7)	29 (42.0)	22 (31.4)
Vomiting	9 (11.0)	13 (15.7)	12 (17.4)	10 (14.3)
Nervous system disorders	8 (9.8)	18 (21.7)	7 (10.1)	11 (15.7)
Headache	7 (8.5)	17 (20.5)	7 (10.1)	11 (15.7)
Respiratory, thoracic, and mediastinal disorders	1 (1.2)	16 (19.3)	1 (1.4)	3 (4.3)
Nasal discomfort	0	8 (9.6)	1 (1.4)	0
Nasal congestion	1 (1.2)	7 (8.4)	0	0
Eye disorders	1 (1.2)	8 (9.6)	0	2 (2.9)
Lacrimation increased	1 (1.2)	7 (8.4)	0	0
General disorders and administration site conditions	7 (8.5)	8 (9.6)	0	0
Fatigue	7 (8.5)	7 (8.4)	0	0
Infections and infestations	0	0	3 (4.3)	4 (5.7)
Nasopharyngitis	0	0	2 (2.9)	4 (5.7)

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.
Sources: CLUWE: //statsclstr//lillyce/prd/ly900018/i8r_mc_igbc/final/output/shared/tfl/igbc_smtea111.rtf; CLUWE: lillyce/prd/ly900018/i8r_mc_igbi/final/output/shared/t_aef1.

Source: Table 2.7.4.15 from Applicant's Summary of Clinical Safety

IGBB- Pediatric Study

TEAEs were reported in 55.6% of subjects who received NG in the 3 mg dose, and 75.0% of subjects who received CG. The highest incidence of reported TEAEs were gastrointestinal disorders, with nausea and vomiting the most frequently reported PTs, with a greater incidence of gastrointestinal TEAEs reported in subjects in the CG group. Other TEAEs that were frequently reported were headache and dizziness, and nasal discomfort and nasal congestion, all of which were more common in NG group in comparison to the CG group. For additional details, see Table 11.

Table 11: Treatment-emergent Adverse Events by System Organ Class, Preferred Term- 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: CLUWE: //statsclstr//lillyce/prd/ly900018/idb/output/shared/smtea112.rtf.

Source: Table 2.7.4.9 from Applicant's Summary of Clinical Safety

Nasal/Ocular Questionnaire

Studies IGBI/IGBC

The most commonly reported symptoms in the Nasal and Non-Nasal Symptom Questionnaire with an increase to severe during any postbaseline time point reported by subjects treated with NG in both Studies IGBI and IGBC were watery eyes (IGBI 10.0%, IGBC 8.4%), nasal congestion (IGBI 5.7%, IGBC 7.2%), nasal itching (IGBI 4.3%, IGBC 2.4%), and itchy eyes (IGBI 2.9%, IGBC 2.4%). There were no severe symptoms reported at 90 minutes postbaseline, which was the last time point collected in Study IGBI, while nasal congestion remained severe severe in Study IGBC at 90 minutes postbaseline in 3 subjects (3.6%) treated with NG. See Table 12 for further details.

Table 12: Shifts of Increasing Nasal and Non-Nasal Symptom Severity from Baseline to Maximum Post-Dose Severity from Symptom Questionnaires in Studies IGBI and IGBC

Symptom	Study IGBC NG 3 mg (N=83) n (%)	Study IGBI NG 3 mg (N=70) n (%)
Runny Nose	27 (32.5)	26 (37.1)
Nasal Congestion	38 (45.8)	27 (38.6)
Nasal Itching	26 (31.3)	34 (48.6)
Sneezing	13 (15.7)	17 (24.3)
Watery Eyes	46 (55.4)	44 (62.9)
Itchy Eyes	19 (22.9)	14 (20.0)
Redness of Eyes	23 (27.7)	15 (21.4)
Itching of Ears	3 (3.6)	2 (2.9)
Itching of Throat	10 (12.0)	9 (12.9)

Abbreviations: N = total number of patients; n = number of patients in the specified category; NG = nasal glucagon.
Sources: CLUWE://statsclstr/lillyce/prd/ly900018/i8r_mc_igbc/final/output/shared/tfl/igbc_smnqs11.rtf; CLUWE: lillyce/prd/ly900018/i8r_mc_igbi/csr1/output/shared/t_qsshiftm.doc.

Source: Table 2.7.4.16 from Applicant's Summary of Clinical Safety

IGBB- Pediatric Study

The most commonly reported symptoms in Study IGBB in the Nasal and Non-Nasal Symptom Questionnaire with an increase to severe during any postbaseline time point reported by subjects treated with NG were watery eyes (52.8%), nasal congestion (50.0%), itchy eyes (30.6%), and nasal itching (30.0%). Nasal congestion, nasal itching, itchy eyes, and sneezing were reported as shifting to severe in 1 subject each, while watery eyes was reported as shifting to severe in 3 subjects. There were 3 reporeted severe symptoms reported at 90 minutes postbaseline, which included nasal itching, watery eyes, and itchy eyes. See Table 13 for further details.

Table 13: Shifts of Increasing Nasal and Non-Nasal Symptom Severity from Baseline to Maximum Post-Dose Severity from Symptom Questionnaires in 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: CLUWE://statsclstr/lillyce/prd/ly900018/idb/output/smnqs112.rtf.

Source: Table 2.7.4.13 from Applicant's Summary of Clinical Safety

9. Advisory Committee Meeting

Not applicable.

10. Pediatrics

The applicant conducted a pediatric assessment for children aged 4 to less than 17 years of age (Study IGBB). In the agreed iPSP, the applicant had requested a deferral for study in children < 4 years of age, however the agreed iPSP had not been updated with study timelines. The pediatric assessment in children ages 4 to less than 17 was discussed with PeRC on March 13, 2019. The applicant's pediatric assessment for children ages 4 to less than 17 years of age was found to be acceptable. The applicant was asked to provide an updated timeline for the proposed study in children < 4. The applicant responded with a proposal for a deferred pediatric study in children 1-4 years of age, and a request for a waiver for children < 1 years old, as studies would be highly impracticle. The Division agrees with the proposed waiver. A postmarketing requirement will be issued for the deferred study at the time of approval.

11. Other Relevant Regulatory Issues

Not applicable.

12. Labeling

Prescribing Information

The applicant has proposed the following indication for NG: for the treatment of severe hypoglycemia in adult and pediatric patients with diabetes. I agree that the submitted data supports the use of NG for the proposed indication for pediatric subjects aged 4 and older, however the applicant has not yet performed studies on children younger than 4 years old, and has requested a waiver for children under the age of 1 years old.

The applicant has proposed a contradindication for patients with a known hypersensitivity to glucagon, as well as in patients with pheochromocytoma. Warnings and Precautions include pheochromocytoma, insulinoma, hypersensitivity and allergic reactions, and glycogen stores and hypoglycemia. The applicant has not proposed to include Necrolytic Migratory Erythema (NME) in the Warnings and Precautions, as this is associated with continuous intravenous infusion, which would not be applicable for NG, which is administered intranasally. I agree with the applicant's proposed contraindication and warnings and precautions, as they are consistent with labeling for approved injectable glucagon products, with the appropriate exception for NME.

The clinical trial data proposed by the applicant to describe AE data (b) (4) . I recommend data from the symptom questionnaires be included in labeling to provide a more accurate description of nasal and ocular AEs with use of NG.

The description of clinical studies should present the confidence intervals (CI) using the Agresti and Min correction, as discussed in Dr. Crackel's review. The applicant should also present mean nadir glucose values using the average of all nadir glucose measurements, in order to be consistent with Study IGBI. Data from the real use studies should not be included, as there were a number of protocol violations which makes me question the interpretability of the data from these studies.

Other Labeling:
The applicant has proposed the proprietary name BAQSIMI. This name was reviewed by Dr. Ariane Conrad of DMEPA, who has found the name to be acceptable.

As discussed in Section 3, the applicant was advised to revise the proposed labeling and container labels, which were then evaluated in a supplemental human factors study. DMEPA recommended additional changes to be implemented to improve the clarity and reasability of important information. The applicant implemented the recommended modifications, and the revised carton and container labeling were reviewed by DMEPA, and were found to be acceptable.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

No REMS is recommended for NG. No serious safety concerns associated with the use of NG were identified that would require a REMS.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

Under the Pediatric Research Equity Act (PREA), I recommend a PMC for a study to evaluate safety, efficacy, and pharmacokinetics of BAQSIMI in pediatric patients (b) (4) age 1 year to less than 4 years.

14. Recommended Comments to the Applicant

None

Appendix 1

Overview of Clinical Studies Supporting Registration of Nasal Glucagon

Study ID	Population	Design Comparator; Route of Administration	Number of Patients Receiving Study Drug	Key Endpoints
Pivotal Studies				
I8R-MC-IGBC	Adult patients, 18 to 65 years, with T1D or T2D	Multicenter, randomized, open-label, 2-period, crossover; insulin-induced hypoglycemia (insulin infusion was stopped when glucose was <60 mg/dL [3.3 mmol/L]) 1 mg GlucaGen HypoKit; (Novo Nordisk USA); IMG	NG 3 mg: 83 IMG 1 mg: 82 Enrolled/Completed: 83/82	Proportion of patients achieving treatment success, defined as either an increase in glucose to ≥70 mg/dL (3.9 mmol/L), or an increase of ≥20 mg/dL (1.1 mmol/L) from glucose nadir, within 30 minutes after receiving study glucagon, without receiving additional actions to increase glucose level[a]. Safety, PK, and PD
I8R-MC-IGBB	Pediatric patients, 4 to <17 years of age, with T1D	Multicenter, randomized, 2-period, crossover; insulin was used if necessary to attain a glucose <80 mg/dL (4.44 mmol/L) 0.5 or 1 mg GlucaGen HypoKit (Novo Nordisk USA); IMG	NG 2 mg: 23 NG 3 mg: 36 IMG 0.5/1 mg: 24 Enrolled/Completed: 48/47	Proportion of patients achieving treatment success, defined as an increase in glucose of ≥20 mg/dL (1.1 mmol/L) from glucose nadir within 30 minutes after receiving study glucagon, without receiving additional actions to increase glucose level[a,b]. Safety, PK, and PD
Clinical Bridging and Confirmatory Study				
I8R-MC-IGBI	Adult patients, 18 to 64 years, with T1D	Multicenter, randomized, open-label, 2-period, crossover; insulin-induced hypoglycemia (insulin infusion was stopped when glucose was <60 mg/dL [3.3 mmol/L]) 1 mg GlucaGen HypoKit (Novo Nordisk UK); IMG	NG 3 mg: 70 IMG 1 mg: 69 Enrolled/Completed: 70/69	Proportion of patients achieving treatment success, defined as either an increase in glucose to ≥70 mg/dL (3.9 mmol/L), or an increase of ≥20 mg/dL (1.1 mmol/L) from glucose nadir, within 30 minutes after receiving study glucagon, without receiving additional actions to increase glucose level[a]. Safety, PK, and PD

Study ID	Population	Design Comparator; Route of Administration	Number of Patients Receiving Study Drug	Key Endpoints
Supportive Studies				
I8R-MC-IGBD	Healthy adult subjects, 18 to 55 years	Single-center, randomized, open-label,4-period, crossover 1 mg Glucagon for Injection (rDNA origin) (Eli Lilly Canada Inc); SCG	NG 0.5 mg: 15 NG 1 mg: 14 NG 2 mg: 16 SCG 1 mg: 15 Enrolled/Completed: 16/13	Safety, PK, and PD
I8R-MC-IGBA	Adult patients, 18 to 55 years, with T1D	Single-center, randomized, open-label, 3-period, crossover; insulin-induced hypoglycemia 1 mg Glucagon for Injection (rDNA origin) (Eli Lilly Canada Inc.); SCG	NG 1 mg: 12 NG 2 mg: 18 NG 3 mg: 8 SCG 1 mg: 18 Enrolled/Completed: 18/18	Efficacy, safety, PK, and PD
I8R-MC-IGBE	Adult subjects, 18 to 50 years, healthy other than experiencing symptomatic manifestation of the common cold	Single-center, open-label, 2-period, parallel No comparator Concomitant administration of nasal decongestant (ND; oxymetazoline). NG given on 2 occasions to subjects with and without symptoms of common cold and after a single dose with concomitant administration of ND.	NG 3 mg: 36 NG 3 mg with ND: 18 Enrolled/Completed: 36/35	Safety, PK, and PD
I8R-MC-IGBF	Adult patients, 18 to 70 years, with T1D or T2D	Single-center, randomized, open-label, 3-period, parallel 1 mg GlucaGen HypoKit (Novo Nordisk, Canada); IMG	NG 3 mg: 49 IMG 1 mg: 26 Enrolled/Completed: 75/73	Safety and immunogenicity[c]

Study ID	Population	Design Comparator; Route of Administration	Number of Patients Receiving Study	Key Endpoints
I8R-MC-IGBG	Adult patients, 18 to 70 years, with T1D or T2D	Single-center, randomized, open-label, 4- period, crossover. Single 3-mg dose versus repeated 3-mg doses of NG given on 4 occasions.	NG 3 mg (single dose): 27 NG 6 mg (repeated 3 mg dose): 32 Enrolled/Completed: 32/25	Safety, PK, PD, and immunogenicity[c]
I8R-MC-IGBH[d]	Adult patients, 18 to 70 years, with T1D or T2D	Single-center, randomized, open-label, 4- period, crossover. Single 3-mg dose versus repeated 3-mg doses of NG. No comparator	NG 3 mg (single dose): 3 NG 6 mg (repeated 3 mg dose): 9 Enrolled/Completed: 12/0	Safety, PK, and PD
Actual-Use Studies				
I8R-MC-B002	Adult patients, 18 to 75 years, with T1D	Multicenter, single-arm, open-label No comparator	NG 3 mg: 87 Enrolled/Completed[e]: 129/101	Proportion of patients awakened or returned to normal status within 30 minutes after receiving study
I8R-MC-B001	Pediatric patients, aged 4 to <18 years of age, with T1D	Multicenter, single-arm, open-label No comparator	NG 3 mg: 22 Enrolled/Completed: 26/12	Proportion of patients awakened or returned to normal status within 30 minutes after receiving study glucagon Safety

Abbreviations: IMG = intramuscular glucagon; ND = nasal decongestant; NG = nasal glucagon; PD = pharmacodynamics; PK = pharmacokinetics;

rDNA = recombinant deoxyribonucleic acid; SCG = subcutaneous glucagon; TID = type 1 diabetes mellitus; T2D = type 2 diabetes mellitus; UK = United Kingdom; USA = United States of America.

a Nadir defined as the minimum glucose value at the time of or within 10 minutes following glucagon administration.

b The original efficacy outcome measure in the protocol and statistical analysis plan was "proportion of patients achieving ≥25 mg/dL (1.4 mmol/L) rise in glucose above basal level". To better facilitate evaluation of the efficacy in pediatric patients, glucose criteria similar to what was used in the adult pivotal study (Study IGBC) were applied retrospectively to Study IGBB.

c Subsequent to study completion, the Sponsor developed a new assay which was used to assess immunogenicity.

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

safety data collected prior to termination of this study are included in the clinical study report included with this submission. Exposure and reasons for discontinuation are also included in the Clinical Summary of Safety.

[e] Fourteen patients completed Study B002 without a hypoglycemic event and thus were never treated with NG.

Source: Table 2.5.1.1 from Applicant's Clinical Overview

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