NDA Multi-Disciplinary Review and Evaluation

Application Type	Efficacy Supplement
Application Number(s)	NDA 210134, Supplement 004
Priority or Standard	Priority
Submit Date(s)	September 17, 2024
Received Date(s)	September 17, 2024
PDUFA Goal Date	March 17, 2025
Division/Office	DDLO/OCHEN
Review Completion Date	See stamp date
Established/Proper Name	Glucagon
(Proposed) Trade Name	BAQSIMI
Pharmacologic Class	Antihypoglycemic agent
Applicant	Amphastar Pharmaceuticals, Inc.
Dosage form	Nasal powder
Applicant proposed Dosing Regimen	3 mg
Applicant Proposed Indication(s)/Population(s)	Treatment of severe hypoglycemia in adult and pediatric patients with diabetes ages 1 year and above
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of severe hypoglycemia in adults and pediatric patients with diabetes aged 1 year and older
Recommended Dosing Regimen	3 mg

Table of Contents

Table of Tables

Table of Figures

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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
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
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
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
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
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
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
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
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Nasal glucagon (BAQSIMI) is an antihypoglycemic agent. It contains glucagon, a single-chain polypeptide containing 29 amino acid residues and is identical to human glucagon. It is a preservative-free, white powder for intranasal administration in an intranasal device containing one dose of 3 mg glucagon. It was approved on July 24, 2019, for the treatment of severe hypoglycemia in adult and pediatric patients with diabetes ages 4 years and older. The Applicant has submitted this efficacy supplement to seek approval to expand the indicated patient population to include pediatric patients aged 1 year and older with diabetes. The Applicant also submitted this efficacy supplement to address the Pediatric Research Equity Act (PREA) and fulfil the postmarketing requirement (PMR) 3621-1: An open-label pediatric study to evaluate safety, efficacy, and pharmacokinetics of BAQSIMI in pediatric patients age 1 year to less than 4 years.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant provided substantial evidence of effectiveness to support expanding the indicated patient population to include pediatric patients with diabetes aged 1 year and older. The effectiveness of BAQSIMI in the pediatric population aged 1 to 4 years (inclusive) is based on FDA's previous finding of effectiveness of the drug in adults, together with scientific evidence that justifies such reliance. The scientific evidence that justifies this reliance is derived from Study I8R-MC-IGBO (hereafter referred to as Study IGBO), a phase 1, open-label, multicenter, single-arm, study with the primary objective of assessing the safety and tolerability of a single dose of nasal glucagon (NG) 3 mg in pediatric patients aged 1 to less than 4 years with type 1 diabetes mellitus (T1D). The secondary objectives were to assess the pharmacodynamics (PD) and pharmacokinetics (PK) of NG 3 mg in children aged 1 to less than 4 years with T1D. The scientific evidence is the PK and PD results in the proposed patient population, compared to the PK and PD results in previously studied populations for whom the drug is currently indicated (i.e., pediatric and adult patients with diabetes aged 4 years and older).

The PK results demonstrated that the glucagon concentrations observed in subjects enrolled in Study IGBO were similar to those observed in pediatric patients aged 4 to less than 17 years and adults with diabetes after intranasal administration of 3 mg NG. The PD results demonstrated that the observed change from baseline in glucose in subjects enrolled in Study IGBO was similar to the observed change from baseline in glucose in pediatric patients aged 4 to less than 17 years after intranasal administration of 3 mg NG. Finally, the review considered the exploratory efficacy findings from Study IGBO. All subjects in Study IGBO achieved treatment success, defined as an increase in glucose ≥20 mg/dL from baseline within 30 minutes of NG administration.

Although the observed glucagon concentrations between the proposed pediatric patient population and previously studied populations for whom the drug is currently indicated were similar, the observed glucagon concentrations in the proposed pediatric patient population were lower than modeled predictions, which were calculated prior to incorporating the PK data from Study IGBO. The pharmacokinetic model incorporated well known, and empirically validated relationships between body weight, glucagon clearance, and glucagon volume of distribution.

When the PK data from Study IGBO was incorporated into the pharmacokinetic model, an effect of patient age (less than or equal to 4 years old, or greater than 4 years old) on bioavailability of glucagon was required to predict the observed data (i.e., patients less than or equal to 4 years of age were assumed to have lower bioavailability of nasal glucagon). The underprediction of observed PK exposures based on the naïve model is considered reassuring; the risks of under dosing to treat a life-threatening event far outweigh the risks of higher glucagon exposure.

When considering the collective evidence, it is scientifically appropriate to extrapolate the efficacy from adult and pediatric patients with diabetes aged 4 years and older for whom the drug is currently indicated to the proposed pediatric patient population aged 1 year and older with diabetes.

1.3. Benefit-Risk Assessment

The benefit-risk integrated assessment for NG for the treatment of severe hypoglycemia in pediatric patients with diabetes aged 1 to less than 4 years is generally unchanged from the original benefit-risk integrated assessment for adult and pediatric patients with diabetes ages 4 years and above.

The definition of severe hypoglycemia in pediatric patients is similar to the definition of severe hypoglycemia in adults and is defined as a hypoglycemia event associated with severe cognitive impairment (including coma and convulsions) requiring assistance by another person to administer carbohydrates, glucagon, or administer intravenous (IV) dextrose. Younger age is considered a risk factor for severe hypoglycemia. It is a medically significant and potentially life-threatening complication of diabetes treatment that, if left untreated, can lead to seizures, coma, or death.

Currently available treatments for severe hypoglycemia in pediatric patients with diabetes are limited to IV dextrose and injectable glucagon or its peptide analog.[1] IV dextrose requires administration by trained personnel within a hospital or emergency medical setting. Thus, injectable glucagon or its peptide analog are the only treatment options 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

[1] Although dasiglucagon, a peptide analog of glucagon, is approved for use in pediatric and adult patients with diabetes, it is currently only indicated for use in pediatric patients with diabetes aged 6 years and above.

sufficient cognitive function to safely consume oral carbohydrates. Although some glucagon products are available in ready-to-use formulations, all require injection by a layperson.

This efficacy supplement included results from a phase 1, open-label, multicenter, single-arm, study. Although it was designed with the primary objective of assessing the safety and tolerability of a single dose of NG 3 mg in pediatric patients aged 1 to less than 4 years with T1D, the secondary objectives addressed PD and PK of NG 3 mg in the study population. The PK and PD results in the proposed patient population were compared to the PK and PD results in previously studied populations for whom the drug is currently indicated (i.e., pediatric and adult patients with diabetes aged 4 years and older).

The PK results demonstrated that the observed glucagon concentrations observed in subjects enrolled in Study IGBO were similar to those observed in pediatric patients aged 4 to less than 17 years and adults with diabetes after intranasal administration of 3 mg NG. The PD results demonstrated that the observed change from baseline in glucose in subjects enrolled in Study IGBO was similar to the observed change from baseline in glucose in pediatric patients aged 4 to less than 17 years after intranasal administration of 3 mg NG. Finally, the review considered the exploratory efficacy findings from Study IGBO. All subjects in Study IGBO achieved treatment success, defined as an increase in glucose ≥20 mg/dL from baseline within 30 minutes of NG administration.

A population pharmacokinetic model, incorporating data from IGBO, studies in adolescents, and studies in adults, provides supportive evidence that the PK in pediatric patients aged 1 to 4 years old (inclusive) is similar to adults and adolescents. Although the observed glucagon concentrations between the proposed pediatric patient population and previously studied populations for whom the drug is currently indicated were similar, the observed glucagon concentrations in the proposed patient population were lower than modeled predictions. The explanation for this finding is not certain but may be due to a smaller nasal mucosal surface area, which may lead to lower bioavailability of NG. It is possible that in the postmarket setting, patients may be exposed to higher concentrations of glucagon than observed in this study. This possibility is acceptable because NG is intended to be used in an emergency setting to treat a life-threatening event and the risk of reduced exposure leading to a reduction in efficacy outweighs the concerns for higher glucagon exposure. Additionally, if patients are exposed to higher concentrations of glucagon than those observed in Study IGBO, it is also reassuring that there was no correlation between adverse events and glucagon exposure in the original NG program.

When considering the entirety of data, it is scientifically appropriate to extrapolate the efficacy from adult and pediatric patients with diabetes aged 4 years and older for whom the drug is currently indicated to the proposed pediatric patient population aged 1 year and older with diabetes.

Available glucagon products have similar safety profiles, and the most common adverse reactions include injection site reactions, nausea, vomiting, and headache. These adverse reactions were also observed in the pediatric patients studied in the original NG program with the exception of injection site reactions. Instead, because NG is administered

intranasally and not as an injection, its use was associated with an increase in nasal and ocular adverse reactions (e.g., nasal discomfort, nasal congestion, watery eyes, etc.). The safety profile of NG observed in Study IGBO was comparable to that observed in adults and pediatric patients aged 4 to less than 17 years. Additionally, the PK results demonstrated similar exposure between subjects enrolled in Study IGBO and those observed in pediatric patients aged 4 years to less than 17 years and adults with diabetes after intranasal administration of 3 mg NG based on the observed glucagon concentrations.

1.4. Recommended Regulatory Action

The Division of Diabetes, Lipid Disorders, and Obesity (DDLO) clinical team, consisting of Ann Miller, MD (Clinical Reviewer), Justin Penzenstadler, PharmD (Cross-Disciplinary Team Lead), and John Sharretts, MD (Division Director, DDLO) agrees on approval of sNDA 210134 (Supplement-004) to expand the indication of BAQSIMI to patients aged 1 to 4 years of age (inclusive). The reviewers from the Office of Clinical Pharmacology concur with approval. The new labeling for BAQSIMI will include the amended indication, updated information in section 8.4 (Pedatric Use) and a description of the trial results in section 14 of the Prescribing Information (PI).

1.5. Patient Experience Data

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

			Section of review where discussed, if applicable
☐	**The patient experience data that were submitted as part of the application include:**		
	☐	Clinical outcome assessment (COA) data, such as	
		☐ Patient reported outcome (PRO)	
		☐ Observer reported outcome (ObsRO)	
		☐ Clinician reported outcome (ClinRO)	
		☐ 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.**		

2 Therapeutic Context

2.1. Analysis of Condition

The International Society for Pediatric and Adolescent Diabetes (ISPAD) Clinical Practice Guidelines 2022 define severe hypoglycemia as a hypoglycemia event associated with severe cognitive impairment (including coma and convulsions) requiring assistance by another person to administer carbohydrates, glucagon, or administer IV dextrose.[2] This definition is similar to the definition of severe hypoglycemia in adults outlined by the American Diabetes Association (ADA)[3].[4]

Younger age is considered a risk factor for severe hypoglycemia. The T1D Exchange Clinic Network found that one or more severe hypoglycemia events within 12 months occurred more commonly in subjects aged 2-<6 years old than in the older age groups (9.6% in 2-<6 years, 5.2% in 6-<13 years, 6.3% in 13-<18 years, and 6.9% in 18-<26 years, p=0.005).[5] Similarly, an analysis of data from the DPV (Diabetes Patienten Verlaufsdokumentation) found that older age was associated with moderately decreased risk of severe hypoglycemia (6% risk reduction per 1-y age increase).[6]

Severe hypoglycemia is a medically significant and potentially life-threatening complication of diabetes treatment that, if left untreated, can lead to seizures, coma, or death. Severe hypoglycemic episodes may also lead to negative psychosocial consequences and compensatory behaviors. Fear of hypoglycemia is a physiological and psychological barrier to achieving optimal glycemia and may result in emotional morbidity for children with T1D and their caregivers.

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[2] Abraham MB, Karges B, Dovc K, Naranjo D, Arbelaez AM, Mbogo J, Javelikar G, Jones TW, Mahmud FH. ISPAD Clinical Practice Consensus Guidelines 2022: Assessment and management of hypoglycemia in children and adolescents with diabetes. Pediatr Diabetes. 2022 Dec;23(8):1322-1340. doi: 10.1111/pedi.13443. PMID: 36537534; PMCID: PMC10107518.

[3] The ADA standards of care in diabetes guidelines classify hypoglycemia by levels. Level 3 hypoglycemia is defined as a severe event characterized by altered mental and/or physical functioning that requires assistance from another person for recovery, irrespective of glucose level.

[4] American Diabetes Association Professional Practice Committee. 6. Glycemic Goals and Hypoglycemia: Standards of Care in Diabetes-2025. Diabetes Care. 2025 Jan 1;48(Supplement_1):S128-S145. doi: 10.2337/dc25-S006. PMID: 39651981; PMCID: PMC11635034.

[5] Cengiz E, Xing D, Wong JC, Wolfsdorf JI, Haymond MW, Rewers A, Shanmugham S, Tamborlane WV, Willi SM, Seiple DL, Miller KM, DuBose SN, Beck RW; T1D Exchange Clinic Network. Severe hypoglycemia and diabetic ketoacidosis among youth with type 1 diabetes in the T1D Exchange clinic registry. Pediatr Diabetes. 2013 Sep;14(6):447-54. doi: 10.1111/pedi.12030. Epub 2013 Mar 8. PMID: 23469984; PMCID: PMC4100244.

[6] Karges B, Rosenbauer J, Kapellen T, Wagner VM, Schober E, Karges W, Holl RW. Hemoglobin A1c Levels and risk of severe hypoglycemia in children and young adults with type 1 diabetes from Germany and Austria: a trend analysis in a cohort of 37,539 patients between 1995 and 2012. PLoS Med. 2014 Oct 7;11(10):e1001742. doi: 10.1371/journal.pmed.1001742. PMID: 25289645; PMCID: PMC4188517.

2.2. Analysis of Current Treatment Options

Currently available treatments for severe hypoglycemia in pediatric patients are limited to IV dextrose and injectable glucagon or its peptide analog. IV dextrose requires administration by trained personnel within a hospital or emergency medical setting. Thus, injectable glucagon or its peptide analog are the only treatment options 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. Although some glucagon products are available in ready-to-use formulations, all require injection by a layperson. The currently approved glucagon products, including a peptide analog of glucagon, for treatment of severe hypoglycemia in pediatric patients with diabetes are listed below. The pediatric age group for which the product is approved is emphasized in bold font.

Table 1 FDA Approved Glucagon Treatments for Severe Hypoglycemia in Pediatric Patients

Product Name	Efficacy Information	Recommended Dosing	Important Safety and Tolerability issues
Glucagon: For subcutaneous (s.c.), intramuscular (IM), or intravenous (IV) injection. Administer intravenously only under medical supervision. NDA 201849 ANDAs 204468 and 208086[7]	Approved for use in **pediatric and adult patients with diabetes**	NDA 201849 • In adults and pediatric patients weighing >25 kg or pediatric patients with unknown weight ≥ 6 years of age: 1 mg • In pediatric patients weighing <25 kg or for pediatric patients with unknown weight <6 years of age: 0.5 mg ANDAs 204468 and 208086 • Adults and pediatric patients weighing ≥20 kg: 1 mg • Pediatric patients weighing <20 kg: 0.5 mg or dose equivalent to 20 to 30 mcg/kg	The most common adverse reactions include injection site reactions, nausea, vomiting, headache, dizziness, asthenia, pallor, diarrhea, somnolence, and generalized allergic reactions
Gvoke (glucagon): For s.c. injection only NDA 212097	Approved for use in pediatric and adult patients with diabetes **ages 2 years and above**	• For adults and pediatric patients aged 12 years and older: 1 mg • For pediatric patients aged 2 to under 12 years of age: ○ For pediatric patients who weigh <45 kg: 0.5 mg ○ For pediatric patients who weigh ≥45 kg: 1 mg	The most common adverse reactions in pediatric patients include nausea, hypoglycemia, vomiting, headache, abdominal pain, hyperglycemia, injection site reactions, and urticaria
Zegalogue (dasiglucagon)[8]: For s.c. injection only NDA 214231	Approved for use in pediatric and adult patients with diabetes **aged 6 years and above**	• 0.6 mg	The most common adverse reactions in pediatric patients include nausea, vomiting, headache, and injection site pain

[7] The reference listed drug (RLD) for ANDAs 204468 and 208086 is Glucagon (NDA 020928). The RLD is discontinued but was not discontinued or withdrawn for safety or effectiveness reasons.
[8] Dasiglucagon is a peptide analog of glucagon where seven amino acid substitutions have been introduced into the native 29 amino acid gluagon peptide chain

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

BAQSIMI (glucagon) nasal powder received U.S. marketing approval on July 24, 2019, for the treatment of severe hypoglycemia in patients with diabetes ages 4 years and above. At the time of approval, the following PMR was issued in the approval letter:

3621-1	An open-label pediatric study to evaluate safety, efficacy, and pharmacokinetics of BAQSIMI in pediatric patients age 1 year to less than 4 years

3.2. Summary of Presubmission/Submission Regulatory Activity

September 22, 2020	The Applicant submitted the draft study protocol for study I8R-MC-IGBO (i.e., Study IGBO) to IND 110674 for Agency review. The Applicant referenced PMR 3621-1 and considered this the first milestone for the pediatric assessment. The study was a phase 1, single dose, single arm, multi-center study with the primary objective to assess the safety and tolerability of a single 3 mg dose of NG in pediatric subjects aged 1 to <4 years with T1D. The goal was to have 6 evaluable subjects.
December 4, 2020	The Agency sent the Applicant an information request about Study IGBO asking the Applicant to justify the proposed 3 mg dose and provide the predicted (median with 95% CI) glucagon exposure for patients age 1 to <4 years. Additionally, the Agency asked the Applicant to clarify whether the device approved for use in adults and pediatric patients aged 4 years and older is appropriate for use in younger patients.
January 27, 2021	The Agency sent the Applicant an information request about Study IGBO requesting the following information: 1. Justify the chosen sample size in the context of expected PK variability with NG delivery in this patient population. Additionally, the Agency asked what the Applicant's plan was for evaluation of the efficacy of BAQSIMI (e.g., extrapolation) in this patient population.

	2. The Agency advised the Applicant to consider including patients on multiple daily injections (MDI) in addition to patients on insulin pumps. 3. The Agency had concerns regarding the length of the proposed fast for children age 1-4 years as it may lead to hypoglycemia. The Agency asked the Applicant to clarify why (b) (4) hour fasting prior to dosing was necessary. The Agency advised that a 3 hour fasting period may be adequate to limit the glucose excursions due to ingestion of food. 4. The Agency asked the Applicant to clarify the frequency of assessments for the safety laboratories, including liver monitoring outlined in Section 10. 5. The Agency asked the Applicant to submit the Informed Consent form if available.
March 11, 2021	FDA issued the Acknowledge Final Protocol for Postmarketing Requirement letter. This letter stated the Agency received and reviewed the submissions containing the proposed protocol for Study I8R-MC-IGBO for the PMR cited in the July 24, 2019 approval letter. The Agency agreed that this protocol constituted the Final Protocol for the PMR.
September 17, 2024	The Applicant submitted an efficacy supplement (NDA 210134, S-004) to expand the pediatric patient population for BAQSIMI from pediatric patients from 4 years to 17 years to 1 year to 17 years. The Applicant submitted the trial results from Study I8R-MC-IGBO to support this supplemental NDA.

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

4.1. Nonclinical Pharmacology/Toxicology

The Applicant did not propose any new changes to the nonclinical section of the label. Therefore, a nonclinical review for this submission was not applicable.

4.2. Office of Scientific Investigations (OSI)

The review team determined that inspections by the Office of Scientific Investigations (OSI) and the Office of Study Integrity and Surveillance (OSIS) were not needed for this study. The reason for this determination included the study's small size of only 7 subjects and the fact that PK was a secondary endpoint, not a primary endpoint.

4.3. Product Quality

The following was excerpted from the Product Quality Review (Drs Sarah Zimmerman and Rohit Kolhatar, PANORAMA date 3/7/2025):

An IR was issued to the Applicant on November 4, 2024 to provide an Environmental Assessment. An IR Response received in SD647 on November 06, 2024 provides a categorical exclusion request for the proposed change. The firm claims categorical exclusion based on 21 CFR 25.31 (b) and 21 CFR 25.31 (c), that the proposed change would not increase the EIC above 1 ppb, and the proposed change does not significantly alter the concentration or distribution of the substance, its metabolites, or degradation products in the environment, respectively. The firm claims no extraordinary circumstances that exist that could require environmental assessment.

There are no proposed changes to the drug product quality information as a result of the proposed change. CDRH assessed the current actuator nozzle size for the proposed pediatric indication and found the current actuator acceptable for the proposed change in indication (02/10/2025, Ryan Kau).

There are no proposed labeling changes to CMC relevant sections 3, 11, and 16. Final labeling is deferred to OND.

The proposed change is acceptable from a CMC perspective.

4.4. Clinical Microbiology

There was no new information related to clinical microbiology submitted in this application.

4.5. Devices and Companion Diagnostic Issues

BAQSIMI (glucagon) is a prefilled, single-use, delivery device that is intended to deliver a 3 mg dose of glucagon to the nasal mucosa of a patient experiencing severe hypoglycemia. After removing the device from the secondary packaging, the user inserts the device nozzle into the patient's nostril and presses the button on the bottom of the device, (b) (4) expels the drug product into the nose.

The Applicant did not propose any changes to the drug product, including the nasal spray device. Nevertheless, DDLO consulted the Center for Devices and Radiological Health (CDRH) and the Division of Pediatrics and Maternal Health (DPMH) to provide input on the determination of whether the device is fit for purpose for pediatric patients aged 1 to 4 years. The primary consideration for this younger pediatric population is the difference in size of the nasal passage.

The consultants concluded that the nasal spray appears fit for purpose. The CDRH reviewer compared the actuator nozzle tip of NG to Narcan (naloxone hydrochloride) nasal spray, which is an emergency use drug approved for use in pediatric patients of all ages. Compared to Narcan nasal spray, the NG nozzle tip is smaller, and the volume dispensed per dose in mL is lower. It is expected that a smaller nozzle would be able to administer NG into the nasal cavity. Therefore, the dimensions appear reasonable for the 1 year to less than 4 years of age population.

The DPMH review considered the novel dosage form of a nasal powder, whereas other products for nasal administration are typically sprays (i.e., liquid solutions). DPMH deferred to CDRH who noted that PK data could provide information on the absorption of the drug. CDRH concluded that if the PK data were acceptable, then that would address whether absorption is affected in a meaningful way.

Finally, CDRH considered the safety of the device in pediatric patients aged 1 to less than 4 years. The review concluded that the nozzle tip and the body of the nozzle diameters would make it highly unlikely for a user to advance the device far enough to cause significant trauma.

For additional information, please refer to the Subject Matter Expert (SME) Review by Ryan Kau and the DPMH memo by Sonaly McClymont.

5 Review Strategy

The primary documents reviewed were the Applicant's submissions to NDA 210134 S-004 and the Applicant's responses to multiple information requests. These documents included the Study IGBO clinical study report (CSR), datasets, summaries of clinical efficacy and safety, and the final study protocol and all amendments. The primary objective of Study IGBO was to assess the safety and tolerability of a single dose of NG 3 mg in pediatric subjects aged 1 to less than 4 years with T1D. The secondary objectives were to assess the PD and PK of NG 3 mg in children aged 1 to less than 4 years with T1D.

We acknowledge that Study IGBO was a small study that only enrolled seven pediatric subjects. Therefore, the review team considered all data to determine whether the safety and efficacy of NG in the populations for whom it is currently approved (i.e., adult and pediatric patients with diabetes ages 4 years and older) could be extrapolated to the proposed patient population. PK and PD of glucagon after nasal or parenteral delivery have been previously characterized in patients with diabetes aged 4 years and older ("*Population PK and PD analyses of Nasal Glucagon Studies IGBA, IGBB, IGBC, IGBD, IGBG, and IGBI*", dated 14 December 2018, NDA 210134, Sequence No. 0019). The clinical pharmacology review considered the how the PK and PD data for the 3 mg dose of NG in the proposed pediatric patient population aged 1 to less than 4 years of age compared to the PK and PD results for the 3 mg dose of NG in the previously approved populations including older children and adults (Study IGBB (pediatric population 4 to less than 17 years, n=18) and Study IGBI (adult population, n-63), respectively). Additionally, modeling and simulation of PK and PD data were further used to support the dosing in the proposed age group.

The Division consulted DPMH and CDRH to determine if the device was fit for purpose for the proposed expanded population. The Division also consulted labeling experts (DMPP and DMEPA) to determine if the patient labeling and instructions for use were fit for purpose for the proposed expanded population.

Finally ,the review considered the safety findings from Study IGBO and the results of the exploratory efficacy endpoint to further inform the determination of whether it was scientifically appropriate to extrapolate the efficacy and safety from adult and pediatric patients with diabetes aged 4 years and older for whom the drug is currently indicated to the proposed pediatric patient population aged 1 year and older with diabetes.

6 Study I8R-MC-IGBO

6.1. Study Design

Overview and Objective

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

Primary Objective: To assess the safety and tolerability of a single dose of NG 3 mg in children aged 1 to <4 years with T1D

Secondary Objectives:

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

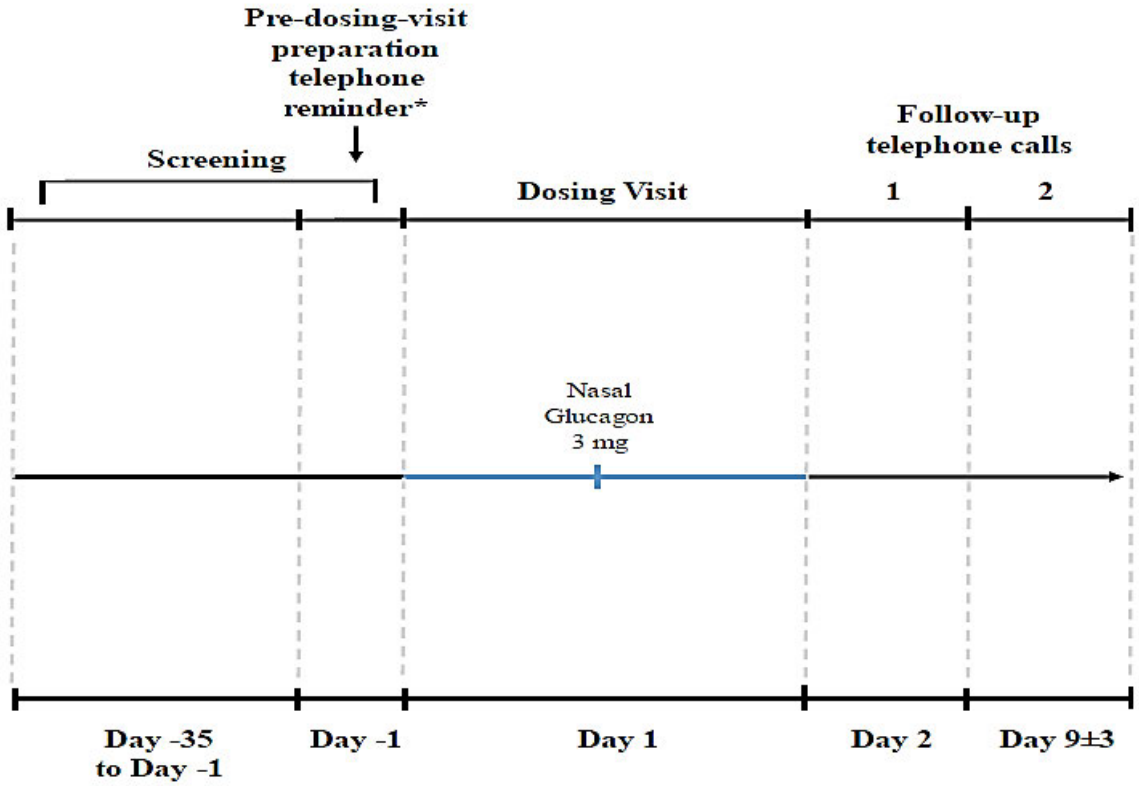
Exploratory Objective: To assess the efficacy of a single dose of NG 3 mg in pediatric subjects aged 1 to <4 years with T1D

> ***Reviewer comment:*** *The study objectives are consistent with the PMR and previous Agency agreement.*

Trial Design

Study IGBO was a phase 1, open-label, multicenter, single-arm, study to evaluate the safety and tolerability of a single dose of 3 mg NG in pediatric subjects aged 1 to <4 years with T1D. The study planned to enroll at least 9 subjects with an approximate maximum of 20 subjects so that at least 6 evaluable subjects completed the study. The length of the study was approximately 7 weeks which included screening, dosing, and follow-up (Error! Reference source not found.).

Figure 1 Study IGBO Study Design



Source: Study IGBO CSR, Figure IGBO.3.1

Screening
The screening visit and all associated assessments and procedures took place as shown in the schedule of assessments (Error! Reference source not found.).

Dosing
Subjects were recommended to fast overnight before the dosing visit on Day 1, to achieve a target range blood glucose (BG) of 70 to 140 mg/dL prior to dosing. At a minimum, subjects were to have no food or beverage intake other than water within 3 hours before dosing. BG was measured at the study site to determine whether the subject's baseline BG level was within the target range. If the blood glucose was below the target range, rescue treatment was considered. If it was above the target range, the investigator had the option to choose one of the following:

- In the case of pump users, increase the basal insulin rate of the subject's insulin pump, or initiate a small bolus dose to achieve target blood glucose
- In the case of MDI users, administer a small correction bolus via s.c. injection of insulin or IV infusion of insulin diluted in normal saline to achieve target blood glucose
- Wait and allow blood glucose to decrease to target level if BG is already decreasing
- Reschedule the visit

Reviewer comment: *The product is indicated for the treatment of severe hypoglycemia. However, the subjects' predose BG was not consistent with hypoglycemia. The Applicant avoided inducing hypoglycemia in the subjects to ensure that subjects were exposed to no more than minimal risk. The Applicant's predose BG range of 70-140 mg/dL was based on premeal target glucose values recommended by the ISPAD of 70-130 mg/dL, with +10 mg/dL for the upper BG limit.[9] Given the subject population included in this study and the primary objective to assess safety, this design is reasonable.*

Study Treatment
3 mg NG was administered intranasally once within 5 minutes of the predose BG measurement by the site staff (i.e., investigator or designee, under medical supervision). The tip of the device was gently inserted into the nostril and the plunger of the device was pushed firmly until the green line no longer showed. The subject did not need to inhale after dosing as the protocol stated the drug is absorbed from the nasal cavity. Dose modification was not allowed in the study because it was not possible to modify the dose with the current drug-device design.

Reviewer comment: *The Applicant's study documents clarified that the same drug-device combination product that is approved for use in adults, adolescents and children aged 4 years and older was used in this study. The administration of the drug as described in the protocol appears consistent with the instructions for use for the BAQSIMI product.*

Subject Monitoring
Subjects were monitored after dosing and discharged after 4 hours postdose safety monitoring was complete.

Reviewer comment: *The median half-life of NG in adults is approximately 35 minutes and slightly lower (21 to 31 minutes) in the pediatric patient population (4 to <17 years).[10] Based on these data, the subjects were monitored at the site for a reasonable amount of time to collect safety, PK, and PD data.*

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[9] DiMeglio, L. A., Acerini, C. L., Codner, E., Craig, M. E., Hofer, S. E., Pillay, K., & Maahs, D. M. (2018). ISPAD Clinical Practice Consensus Guidelines 2018: Glycemic control targets and glucose monitoring for children, adolescents, and young adults with diabetes. Pediatric Diabetes, 19(S27), 105–114. https://doi.org/10.1111/pedi.12737
[10] Baqsimi (glucagon) U.S. prescribing information

Follow-Up
The site staff conducted follow-up telephone calls with the parent or legal guardian to discuss any potential side effects or adverse events on Days 2 and 9 ± 3 days.

Applicant's Rationale for Study Design
The Applicant designed Study IGBO without an active comparator to eliminate unnecessary procedures and minimize distress and discomfort for the study subjects. The Applicant rationalized that NG 3 mg demonstrated similar safety and PD responses across all completed adult and pediatric studies (age range 4 to <17 years) in which injectable glucagon was used as an active comparator.

> ***Reviewer comment:*** *The study design is consistent with the PMR and previous Agency agreement and is appropriate to meet the stated objectives.*

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

In the previous IGBB study:

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

Although 3 mg NG in 1 to <4 year old participants is expected to result in higher systemic glucagon concentrations than those observed with 3 mg NG in older pediatric patients, this transient high systemic exposure is expected to be safe, based on literature. This safety prediction is based on published data with intravenous administered glucagon in adults (Graf *et al*. 1999[11]), which showed exposures that were multiples higher than the projected maximum exposure following NG administration in pediatric patients aged 1 to <4 years, with no safety concerns. Despite this transient high glucagon concentration, the 3 mg dose was predicted to result in an increase of >20 mg/dL within 30 minutes from baseline glucose in 100% of subjects, as desired for an emergency-use product. Additionally, the smaller nasal mucosal surface area for NG absorption in proposed pediatric patients may result in lower than predicted exposures and so the risk of transient higher glucagon outweighs the uncertainty related to absorption and lower efficacy for this emergency use indication.

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[11] Graf CJ, Woodworth JR, Seger ME, *et al. Pharmacokinetic and glucodynamic comparisons of recombinant and animal-source glucagon after IV, IM, and SC injection in healthy volunteers*. J Pharm Sci. 1999;88(10):991-995

This proposed dose of 3mg in the pediatric population aged 1-<4 years was previously reviewed and found acceptable by the Clinical and Clinical Pharmacology review teams (Clinical Review (IND 110674, 03/10/2021, Reference ID: 4759773, Andreea Lungu & Mitra Rauschecker) and Clinical Pharmacology Review (IND 110674, 03/01/2021, Reference ID: 4754694, Manoj Khurana and Jaya Vaidyanathan).

Eligibility Criteria
Key Inclusion Criteria

- Subjects aged 1 to <4 years at the time of signing the informed consent form and throughout the study who have a diagnosis of T1D based on medical history for at least 6 months and a hemoglobin A1C ≤9.5% at screening
- Subjects who having been receiving insulin therapy via MDI or continuous subcutaneous insulin infusion (CSII) using a pump and have been stable on the therapy and route of administration for at least 3 months prior to screening
- Are in good general health with no conditions that could influence the outcome of the trial and no prior history of choanal atresia, nasal/pharyngeal blockage, or anomaly

Key Exclusion Criteria

- History of pheochromocytoma or insulinoma
- History of epilepsy or seizure disorder
- Have 1 or more congenital anomalies to the anatomy of the nose, or require changes to the anatomy of the nose (e.g., are eligible for nasal pharyngeal surgery)
- History or presence of laryngopharyngeal reflux
- In the 3 months before screening, have had an episode of severe hypoglycemia, defined as a hypoglycemia event with severe cognitive impairment (including coma and convulsions) requiring assistance by another person to actively administer carbohydrates, glucagon, or take other corrective actions
- Are regularly administered a systemic beta-blocker, indomethacin, warfarin, or drugs classified as anticholinergics, or corticosteroids
- Are using closed-loop insulin therapy, *unless* such a device is set to 'open loop/manual' mode and the automated low glucose suspend or predictive low glucose suspend are disabled on the day of the dosing visit until all PK and PD samples have been collected

Reviewer comment: *The eligibility criteria appear appropriate to meet the study objectives. The exclusion of subjects with anomalies in nasal anatomy appears reasonable given the secondary objectives of the study (i.e., collection of PK and PD endpoints).*

Administrative Structure
The Applicant's clinical pharmacologist or clinical research physician (CRP)/scientist monitored safety data throughout the course of the study. The Applicant reviewed serious adverse events (SAEs) within time frames mandated by company procedures. The

Applicant's clinical pharmacologist or CRP periodically reviewed vital signs, safety, and adverse events (AEs). There was no data monitoring committee.

> ***Reviewer comment:*** *It is inevitable that all parties involved in the study (e.g., subjects, caregivers, investigators, Applicant employees) had knowledge of treatment assignments given the open label design. This could lead to bias in the adverse event collection and reporting. However, PK endpoints are objective measurements. The extrapolation of safety to this proposed patient population from the larger phase 3 trials based on considerations of the PK findings from this study is less subject to bias and can support the safety findings from this study.*

Study Endpoints

The primary endpoint of Study IGBO was incidence of treatment-emergent adverse events (TEAE). A TEAE was defined as an event that first occurs or worsens in severity on or after the date of first dose of study drug. Adverse events (AEs) were collected from signing of the informed consent form (ICF) until the completion of the second follow-up phone call (i.e., at the screening visit, at the dosing visit (i.e., Day 1), and via a follow-up telephone call on Day 2 and Day 9 ± 3 days). An AE was defined as any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. Investigators and qualified designees were responsible for detecting, documenting, and recording events that met the definition of an AE or serious adverse event (SAE). AEs were reported by the investigative site staff or the subject's parent/legal guardian. Open-ended and nonleading verbal questioning of the subject, subject's parent/legal guardian, and investigator assessment were the preferred methods to inquire about AE occurrences. After the initial AE, investigators were required to proactively follow up on AEs with each subject's parent/legal guardian at subsequent visits/contacts that were serious, considered related to study intervention, study device, or device constituent or study procedures. All SAEs were followed up until resolution, stabilization, the event was otherwise explained, or the subject was lost to follow-up.

The investigator also assessed each AE for intensity and categorized intensity as one of the following:

- Mild: an event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities
- Moderate: an event that causes sufficient discomfort and interferes with normal everyday activities
- Severe: an event that prevents normal everyday activities.

> ***Reviewer comment:*** *The AE and SAE definitions were appropriate. Ascertainment of AEs was adequate to meet the study objective.*

In addition to AEs, assessment of safety included physical examinations, vital signs, and clinical laboratory assessments.

- Although an age-appropriate physical examination was conducted at screening only, a visual nasal inspection was performed at screening and on Day 1. On Day 1, the predose inspection, administration of NG, and postdose inspection were done by the same person.
- Vital signs included blood pressure and pulse rate and were collected at screening, Day 1 predose, and 45 minutes postdose.
- Clinical safety laboratory assessments[12] were assessed for all subjects at the screening visit only. Subjects underwent additional tests at any time during the study if deemed necessary by the Investigator. Subjects did not need to fast for laboratory samples.

Finally, the safety assessments included BG monitoring. During and after dosing, BG levels were measured at the bedside for safety. Bedside glucose safety measurements were taken with either the subject's own continuous glucose monitoring (CGM) device[13] or with an approved point-of-care glucometer using capillary blood samples.

The planned timepoints for all safety assessments are provided in the schedule of assessments (Error! Reference source not found.).

> ***Reviewer comment:*** *The clinical protocol review noted that the approach of collecting clinical chemistry samples at the screening visit only is consistent with clinical experience with glucagon therapy and the overall conduct of the NG clinical program in adult and older pediatric patients. The safety assessments including physical exams, vital signs, and laboratory assessments are reasonable.*

The secondary endpoints of Study IGBO were the following:

- Change from baseline (predose BG) of maximum blood glucose. Other blood glucose parameters:
  - BG_{max} (maximum observed blood glucose)
  - AUC (area under the concentration time curve)
  - TBG_{max} (time of maximum observed blood glucose)
- Model-estimated population PK parameters

The schedule of assessments (Error! Reference source not found.) specifies the times when venous blood samples were collected to determine the plasma concentrations of glucagon and the times when blood samples were collected for use in a study-approved rapid glucose analyzer (YSI or equivalent) to determine the plasma concentrations of glucose.

The protocol outlined one exploratory endpoint which was the proportion of subjects

[12] Hematology (included hematocrit, hemoglobin, leukocytes, and platelets) and clinical chemistry (included sodium, potassium, chloride, glucose, blood urea nitrogen, albumin, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, creatinine, magnesium, bicarbonate, phosphorus, and HbA1c)
[13] If the subject has been using an approved CGM in accordance with the device label for at least 1 month prior to the dosing visit, the CGM was allowed to be used for safety monitoring

achieving treatment success defined as an increase of BG ≥20 mg/dL from baseline (predose BG) within 30 minutes postdose.

Figure 2 Study IGBO Schedule of Assessments

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

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

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

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

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

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

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

Source: I8R-MC-IGBO(a) study protocol

Statistical Analysis Plan

The study was not powered to conduct any statistical testing. PK and PD analyses were conducted on data from all enrolled subjects who received the study drug and had evaluable PK or PD data. The PD parameters were summarized using standard descriptive statistics. The PK and PD data were analyzed using a population PK approach via nonlinear mixed-effects modeling with NONMEM.

Efficacy was assessed as an exploratory endpoint. The incidence of "treatment success" was defined as an increase in plasma glucose ≥20 mg/dL from baseline within 30 minutes postdose. The Applicant calculated the proportion of subjects achieving treatment success.

Safety analyses were conducted for all enrolled subjects who received at least one dose of the study drug, whether or not they completed all protocol requirements. If the frequency of events allowed, safety data were summarized using a descriptive methodology.

An interim analysis was conducted after 3 subjects completed the study. The analysis evaluated the data relating to the primary and secondary objectives. If there were no safety concerns, study enrollment resumed.

Protocol Amendments

There were no important modifications/amendments to the study protocol that would have had an impact on the integrity of the trial or the interpretation of the results.

6.2. Study Results

Compliance with Good Clinical Practices

The Applicant provided attestation that the study was conducted in accordance with the protocol and the consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines, applicable ICH GCP guidelines, and applicable laws and regulations. The Applicant provided attestation that the informed consent met the requirements of 21 CFR 50.

Financial Disclosure

The Applicant adequately disclosed financial interests/arrangements with clinical investigators. The submitted financial disclosure statement has been noted. Refer to the Financial Disclosure template in Section 13.2.

Patient Disposition

The study enrolled 7 subjects; all subjects received the planned 3 mg dose of NG and completed the study.

Protocol Violations/Deviations

There were two protocol deviations related to PK and PD collection:

- A missing PK collection at the 60-minute postdose time point for 1 subject
- Collection of the baseline PD sample 2 minutes outside of the predefined window for 1 subject

Reviewer comment: *The missing PK collection is unlikely to affect the interpretation of the primary endpoint and the safety evaluation. The collection of the baseline PD sample 2 minutes outside of the predefined window is also unlikely to affect the interpretation of the results.*

Demographic Characteristics

The study was conducted at 5 centers in the United States. The demographics and baseline characteristics of the subjects who completed Study IGBO are shown in Table 2. The Applicant notes that the subject reported as 4 years old was actually younger than 4 years old at screening and throughout the study, per protocol, but age was reported as 4 years due to the rounding of age in months for age derivation.

Table 2 Demographic and Baseline Characteristics of Subjects in Study IGBO; Safety Population

		3 mg nasal glucagon
Number of subjects studied		7
Age (years)	Mean (SD)	2.98 (0.82)
	Range	1.8 – 4.0
Sex	Male	4 (57.1%)
	Female	3 (42.9%)
Ethnicity	Not Hispanic or Latino	6 (85.7%)
	Hispanic or Latino	1 (14.3%)
Race	White	7 (100%)
Site ID	00001	1 (14.3%)
	00002	1 (14.3%)
	00004	1 (14.3%)
	00007	2 (28.6%)
	00008	2 (28.6%)
Country of Enrollment	United States of America	7 (100.0%)
Weight (kg)	Mean (SD)	15.49 (2.36)
	Range	12.2 – 18.6
Height (cm)	Mean (SD)	93.39 (7.23)
	Range	81.6 – 102.0
Body mass index (kg/m^2)	Mean (SD)	17.77 (1.95)
	Range	15.0 – 19.6
Duration of T1D (years)	Mean (SD)	1.36 (0.67)
	Range	0.7 – 2.5

Abbreviations: SD = standard deviation; T1D = type 1 diabetes
Age in years is derived from the age of the subject in months rounded to 1 decimal place.
All subjects met the inclusion criteria of age <4 years at the time of informed consent and study completion.
Source: Adapted from study IGBO CSR, Table IGBO 4.1

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

All subjects were receiving insulin therapy by either MDI or CSII.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The treatment was administered in a clinical research setting. Therefore, compliance is not considered an issue.

Efficacy Results – Primary Endpoint

The primary endpoint was related to safety, not efficacy. Safety is discussed in Section 8.

Data Quality and Integrity

Data quality and integrity of the safety data are discussed in Section 8.3. The secondary endpoints were related to PD and PK of a single dose of NG 3 mg.

The data quality presented in the population PK and PK/PD model reports is acceptable for labeling descriptive PK in pediatrics aged 1 to 4 years of age and generating individual exposure metrics. The simulation results were not represented in the population PK and PK/PD reports but was summarized in the summary of clinical pharmacology report. However, this simulation was not based on the population PK and PK/PD model mentioned above, and the results are not acceptable. The updated simulation results are discussed in section 7.2 Comprehensive Clinical Pharmacology Review and section 13.4.2 Pharmacometrics Review.

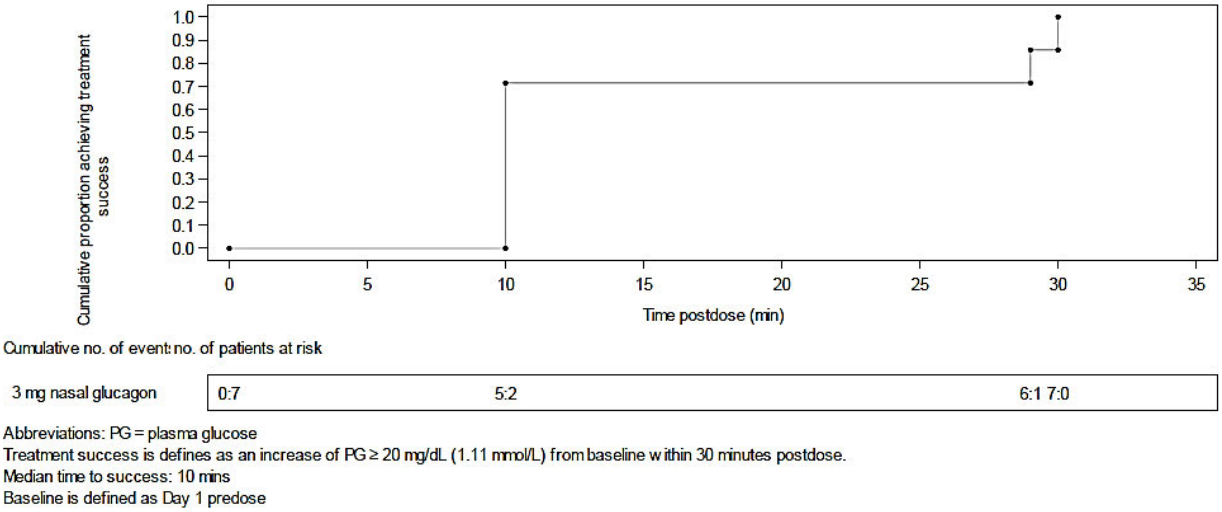
Efficacy Results – Secondary and other relevant endpoints

Subjects Achieving "Treatment Success"

"Treatment success" was an exploratory endpoint defined as an increase in plasma glucose of at least 20 mg/dL from baseline within the 30 minutes postdose assessment window. Plasma glucose levels were measured prior to the administration of glucagon and at various time points after administration.

All subjects achieved treatment success. The time to increase in plasma glucose ≥20 mg/dL ranged from 10 to 30 minutes with a mean time of 15.6 minutes.

Figure 3 Kaplan-Meier Plot of Time to "Treatment Success" Following 3 mg Nasal Glucagon Administration in Study IGBO Study Population



Abbreviations: PG = plasma glucose
Treatment success is defines as an increase of PG ≥ 20 mg/dL (1.11 mmol/L) from baseline within 30 minutes postdose.
Median time to success: 10 mins
Baseline is defined as Day 1 predose

Source: Study IGBO CSR, Figure IGBO.5.1

7 Clinical Pharmacology Assessment

7.1. Summary of Clinical Pharmacology Assessment

Pharmacokinetics (PK) and pharmacodynamics (PD) of glucagon after nasal or parenteral delivery have been previously characterized in patients with diabetes aged 4 years and older ("Population PK and PD analyses of Nasal Glucagon Studies IGBA, IGBB, IGBC, IGBD, IGBG, and IGBI", dated 14 December 2018, NDA 210134, Sequence No. 0019). The current submission focused on the administration of Nasal Glucagon (NG or Baqsimi) in pediatric patients aged 1 to <4 years. IGBO was a conducted as a post-marketing requirement study (PMR 3621-1) for assessing the safety, tolerability, pharmacodynamics, and pharmacokinetics of NG in pediatric patients aged 1 to <4 years. Due to the limited sample size in this study IGBO (n=7), modeling and simulation of PK and PD data were further used to support the dosing in this age group. The clinical pharmacology review focused on the evaluation of the observed and simulated PK and PD data for 3 mg dose of NG in the proposed pediatric patient population aged 1 to <4 years of age. The PK and PD results for 3 mg dose of NG in previously approved population including older children and adults were used for comparison (Study IGBB (pediatric population 4-<17 years, n=18) and Study IGBI (adult population, n-63)).

7.1.1. Pharmacology and Clinical Pharmacokinetics

Glucagon absorption via the intranasal route, achieved mean peak plasma levels of 6130 pg/mL at around 15 minutes. The apparent volume of distribution was approximately 885 L. The median half-life was approximately 35 minutes. In pediatric patients (1 to<17 years), glucagon via the intranasal route, achieved mean peak plasma levels between 10 and 20 minutes. The median half-life was 21 to 31 minutes. Glucagon is known to be degraded in the liver, kidneys, and plasma. After administration of BAQSIMI in adult patients with diabetes, the mean maximum glucose increase from baseline was 140 mg/dL. In pediatric patients with type 1 diabetes (1 to <17 years), the mean maximum glucose increase from baseline was 132 mg/dL (1 to <4 years), 138 mg/dL (4 to <8 years), 133 mg/dL (8 to <12 years), and 102 mg/dL (12 to <17 years).

7.1.2. General Dosing & Therapeutic Individualization

General Dosing
The recommended dose of Baqsimi is 3 mg administered as one actuation of the intranasal device into one nostril. If there has been no response after 15 minutes, an additional 3 mg dose of Baqsimi from a new device may be administered while waiting for emergency assistance.

Therapeutic Individualization
Intrinsic factors do not affect the pharmacokinetics of glucagon. Therefore there are no recommendations for dose adjustment based on intrinsic factors. Beta-blockers, Indomethacin and Warfarin have been reported to have drug-drug interactions with

glucagon. Caution should be exercised when administering glucagon to patients on these regimens.

7.2. Comprehensive Clinical Pharmacology Review

7.2.1. Background

Baqsimi (nasal glucagon (NG)) is a single dose nasal dosing device containing 3 mg glucagon powder for nasal delivery. NG is approved as an antihypoglycemic agent indicated in the treatment of severe hypoglycemia in adult and pediatric patients with diabetes ages 4 and above.
The approval for use in adults mainly relied on study IGBI, which was a single-dose crossover study in adult patients with type 1 diabetes (T1D) that compared glucagon administered through either the nasal route (NG) or the intra-muscular route (GlucaGen) in the recovery from hypoglycemia induced by a controlled insulin infusion. With respect to pediatric population aged 4 to <17 years, the approval mainly relied on Study IGBB, which evaluated the PK, PD, safety, and tolerability of NG 2 mg and 3 mg in pediatric patients aged 4 to <17 years with T1D. Overall, the 3 mg dose of NG is approved for use in patients with diabetes aged 4 years and above.
The current submission is focused on the PMR study IGBO which is a single-dose study in pediatric patients aged 1-<4 years of age with type 1 diabetes. This study assessed the safety, tolerability, PK, and PD of NG in 7 participants, 4 males and 3 females, aged 1 to <4 years after receiving a single dose of 3 mg NG.

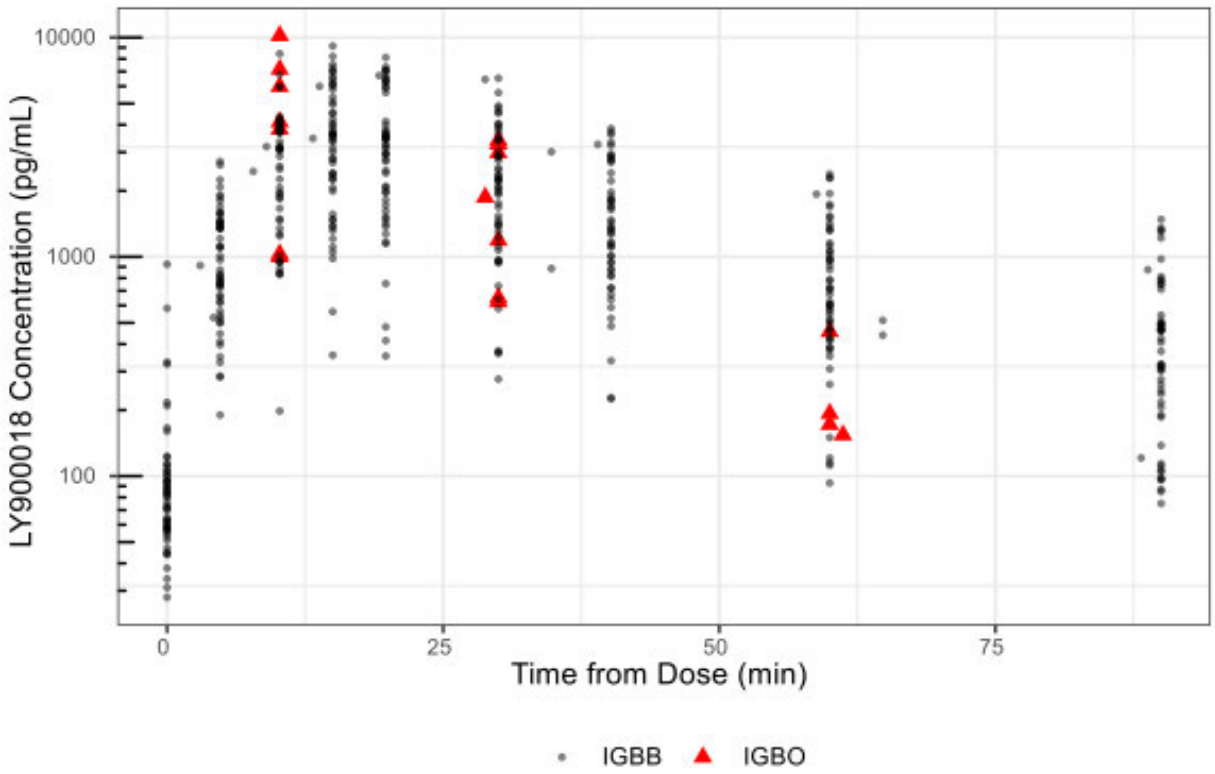
7.2.2. Key Review Questions

7.3.2.1 What are the pharmacokinetic and pharmacodynamic parameters of glucagon after a single 3 mg dose of NG in pediatric patients aged 1 to < 4years and how does it compare to older children and adults?

The primary objective of Study IGBO (PMR 3621-1) is to assess the safety and tolerability of a single 3 mg dose of NG in pediatric participants aged 1 to <4 years with type 1 diabetes (T1D). The secondary objectives are to assess the pharmacokinetics (PK) and pharmacodynamics (PD) of a single dose of NG 3 mg in children age 1 to <4 with T1D and an exploratory objective is to assess the efficacy. A total of seven patients with T1D (ages ranged between 1.8 to 4 years) received a single 3 mg dose of NG using the commercial (approved drug-device combination) product. Blood samples for glucagon PK and blood glucose measurements were obtained at 10, 30, 60 and 90 (glucose only) minutes after dosing. A population PK model (POPPK) was used to determine the area under the concentration-time curve (AUC) after the single 3 mg dose of NG.

The observed individual glucagon concentrations versus time profile following administration of NG in Study IGBO were similar to those observed in the previous pediatric study IGBB in children aged 4 to 17 years, as shown in the **Figure 4**.

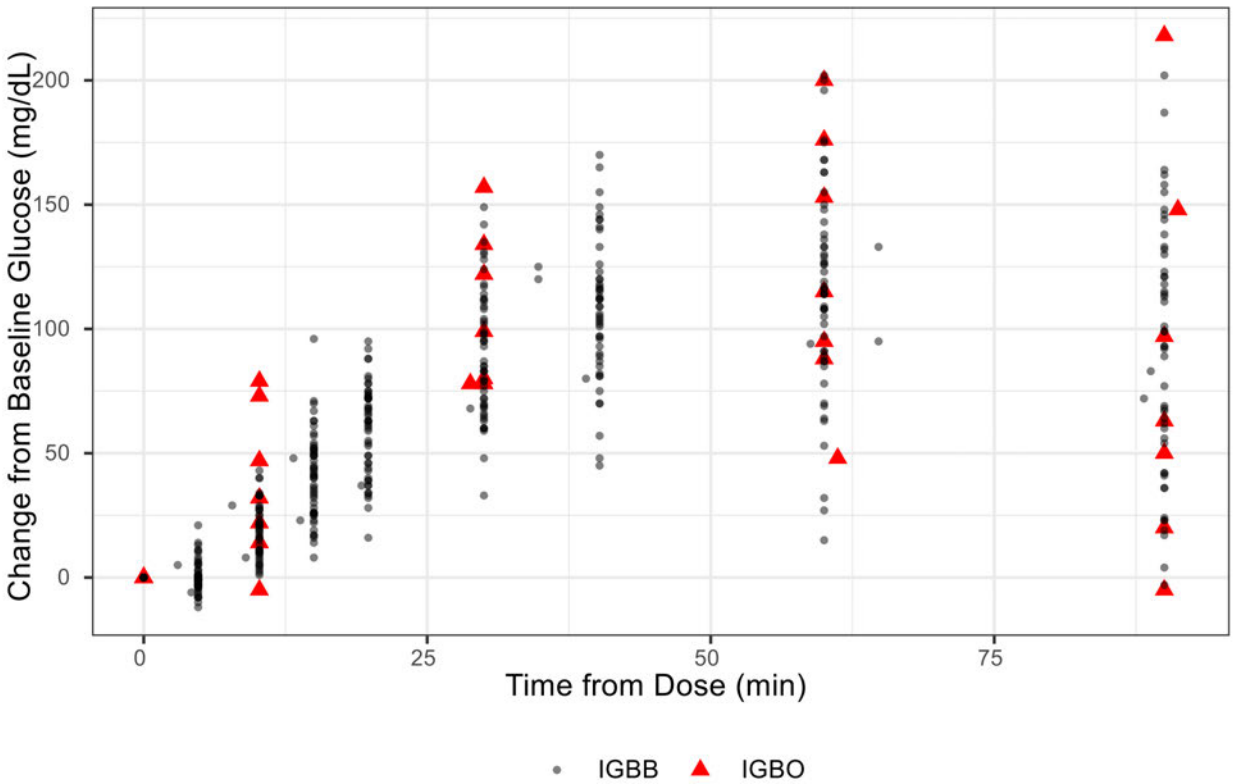
Figure 4 Observed glucagon concentrations over time in Study IGBO and Study IGBB



Source: (PopPK Modeling Report, eCTD 0639, M 5.3.5.1, Document ID: VV-CLIN-137745, Figure 1).

The maximum observed glucagon concentrations occurred at 10 minutes post-dose and using the POPPK model, the geometric mean AUC was determined as 1560 pg*h/mL in children aged 1 to <4 years.

Figure 5 Observed change from baseline glucose concentrations over time in Study IGBO and IGBB.

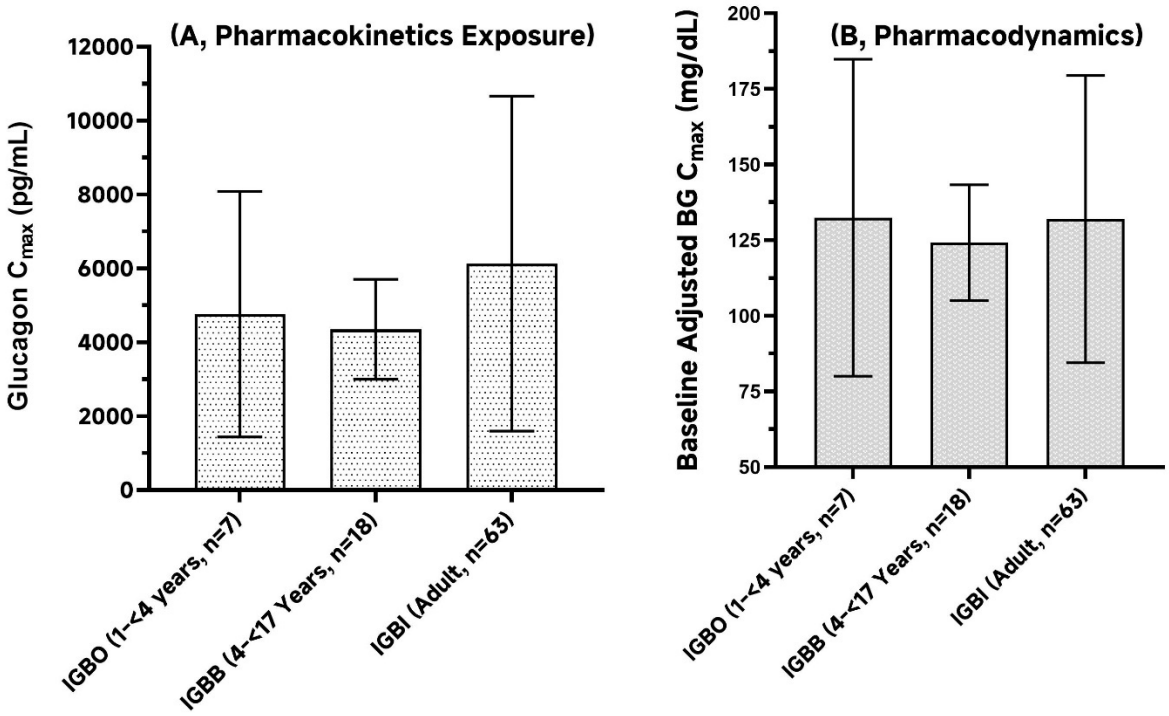


Source: PopPK Modeling Report, eCTD 0639, M 5.3.5.1, Document ID: VV-CLIN-137745, Figure 3.

The PD (individual observed change from baseline glucose) following administration of NG in Study IGBO were also similar to the previous paediatric study Study IGBB in children aged 4 to 17 years, as shown in **Error! Reference source not found.**. The mean maximum observed BG of 242 mg/dL was achieved at 55.6 minutes post-dose and represented an increase of 132 mg/dL (range: 78 mg/dL to 218 mg/dL) from the mean concentration at baseline.

A cross-study comparison of the PK and PD data for a single 3 mg dose of NG from Study IGBO with data from older children aged 4 to <18 years (IGBB) and adults (IGBI) is presented in **Error! Reference source not found.**. The Study IGBI used the commercial NG product and was conducted after insulin-induced hypoglycemia in adult patients with T1DM. As summarized in **Error! Reference source not found.**, the mean Cmax of glucagon and the mean baseline-adjusted Cmax of blood glucose in pediatric patients aged 1-<4 years (IGBO) is in general comparable with those observed in older children aged 4-<17 years (IGBB) and adult patients (IGBI).

Figure 6. Cross-study comparison of the observed PK (glucogan Cmax of glucagon) and observed PD response (baseline adjusted blood glucose BGmax) after a single 3 mg dose of NG in studies IGBO (1-<4 years), IGBB (Years 4-<17 years) and IGBI (adults)



Source: (Reviewer's analysis, Sourced from IGBO (Document ID: VV-CLIN-126141, I8R-MC-IGBO, NDA 210134, eCTD 0639, M 5.3.5.1), IGBB (AMG504-1, NDA 210134, eCTD 0000, M 5.3.5.1) & IGBI (I8R-MC-IGBI, NDA 210134, eCTD 0000, M 5.3.5.1) Clinical Study Reports (CSRs));
The observed (Mean, SD) for glucagon Cmax (pg/mL) in studies IGBO (1-<4 years), IGBB (Years 4-<17 years) and IGBI (Adults) were (4760, 3320) pg/mL, (4350, 1352) pg/mL and (6130, 4536) pg/mL, respectively. The observed (Mean, SD) for baseline adjusted blood glucose BGmax (mg/dL) in studies IGBO (1-<4 years), IGBB (Years 4-<17 years) and IGBI (Adults) were (132, 52) mg/dL, (124, 19) mg/dL and (132, 48) mg/dL, respectively.

In general, the observed PK and PD data for a single 3 mg dose of NG in pediatric patients aged 1-<4 years is comparable to that observed in older children and adults.

7.3.2.2 Is the proposed NG dose of 3 mg appropriate for use in pediatric patients with diabetes aged 1 to <4 years of age?

Yes, the proposed NG dose of 3 mg in patients aged 1 to <4 years is acceptable. The Study IGBO provided PK and PD observations for single dose of NG in seven patients with age ranging between 1.8 to 4 years. Regarding the sample size, the Applicant had estimated the between-subject variability for the clearance to be 29.9% and the power for this study to be at least 70% to have the 95% confidence interval within 60% and 140% of the geometric

mean estimate of clearance (as described by Wang et al. 2012). This approach was previously deemed adequate (Reference ID: 4759773, 03/10/2021).

The appropriateness of this dosing regimen was further evaluated by comparison of predicted glucagon PK exposures (Cmax, Tmax, AUC) and extrapolation of efficacy from the previously approved population of older children aged 4 to < 18 years. The final PopPK model and PK/PD models were used to predict glucagon exposures, glucose response and treatment success rate for pediatric patients between 1 to 18 years of age following 3 mg NG dosing of Baqsimi using data from Study IGBO and Study IGBB (in children aged 1 to 18 years). The modeling and simulation results also show that body weight based allometric scaling of CL and V was applicable in Study IGBO and no additional covariates were required in the PD model. Children aged 1 to <4 years have smaller nasal mucosa surface area for nasal glucagon absorption which may lead to lower bioavailability of NG.
Body weight distribution in the 1 to <4 year age group was based on World Health Organization growth reference tables. The results are shown in Table 3, Table 4 and

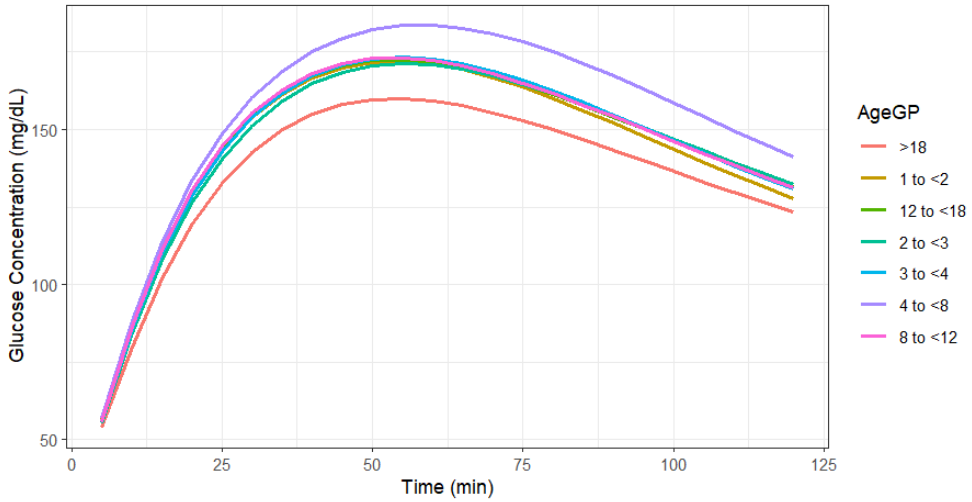
Figure 7.

Table 3. Predicted glucogan PK parameters based on PopPK modeling and simulations after a single 3 mg NG dose of Baqsimi for pediatrics 1 to 18 years of age.

Age (Years)	Weight (kg)	Tmax (min)	GeoMean Cmax (CV%) (pg/mL)	GeoMean AUC (CV%) (pg*h/mL)
1 to < 2	11	12.8	3771.7 (85.8%)	2432.8 (75.3%)
2 to < 3	13.4	13.4	3008.9 (76.2%)	2074.9 (70.5%)
3 to < 4	15.5	14.0	2767.5 (80.4%)	1943.8 (68.8%)
4 to < 8	21.5	14.5	5845.0 (89.1%)	3949.1 (75.0%)
8 to < 12	43.2	15.1	3020.2 (86.6%)	2186.9 (82.4%)
12 to < 18	61.2	16.2	2255.3 (52.7%)	1707.0 (51.1%)

Source: Reviewer's analyses.

Figure 7. Simulated time course profiles of glucose concentrations after a single 3 mg NG dosing of Baqsimi with a baseline glucose level of 40 mg/dL.



Source: Reviewer's analyses.

Table 4. Summary of Simulations for Percent of Patient Achieving Treatment Success following 3 mg NG dosing of BAQSIMI

Dose	Age group (Years)	Treatment Success (%)
3 mg NG	1 to <2	100
3 mg NG	2 to <3	100
3 mg NG	3 to <4	99.9
3 mg NG	4 to <8	99.9
3 mg NG	8 to <12	99.8
3 mg NG	12 to <18	98.9

Source: IR response from the sponsor received on 02/21/2025. NDA 210134, Sequence 0654.

Based on the simulated results, the Cmax, AUC, and time course profiles of glucose concentrations are comparable between children 1 to 4 years and those 4 to < 18 years. Approximately 100% children are predicted to reach treatment success which is in alignment with the observed efficacy results presented in Section 6.2 of this review. Thus, based on the observed and predicted concentrations of glucagon and glucose, we conclude that 3 mg dose of NG is acceptable for use in children aged 1 to < 4 years of age.

From a safety evaluation perspective, Cmax was chosen as the focus of the safety assessment given that NG treatment is expected to have intermittent emergency use. The results from PopPK analyses (Table 3) show that the Cmax for pediatrics between 1 to < 4 years are comparable to those 4 to < 18 years, indicating no potential for safety concern due to higher exposures. In addition, no major safety events were observed in Study IGBO. Thus, 3 mg NG dose of BAQSIMI is considered to be safe for use in children aged 1 to < 4 years.

7.3. Clinical Pharmacology Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in NDA 210134 S-004 and supports the approval of BAQSIMI for the treatment of severe hypoglycemia in the extended patient population aged 1 year or older. The review team considers that Applicant has fulfilled the Post Marketing Requirement Study 3621-1 (Study IGBO).

8 Review of Safety

8.1. Safety Review Approach

The focus of the safety review was the data generated in Study IGBO. The purpose of this safety review was to identify any new safety signals that could potentially affect the benefit-risk assessment for the pediatric population of patients with T1D aged 1 to <4 years of age. As previously stated, the size of Study IGBO was small which limited its ability to detect safety signals. Therefore, the safety evaluation of NG in the expanded pediatric patient population also considered the PK results of Study IGBO and whether they could support extrapolation of the safety of NG from the larger NG phase 3 program to the new pediatric patient population.

The safety profile of NG was established in the original NG NDA review. In the original review, nausea, vomiting, and headache were common adverse events observed with the NG product which was consistent with other glucagon emergency use products. Headache was observed more commonly with NG compared to control glucagon in all clinical studies.

Symptoms related to the route of administration, such as nasal and ocular symptoms, were commonly observed with NG, some reported as severe and leading to treatment discontinuation.

Transient increases in blood pressure and heart rate have been reported for other glucagon products. In the adult and pediatric studies in the NG program, more NG-treated subjects shifted beyond the reference range values than control glucagon-treated patients. However, the incidence in both groups was small, and none of the values were considered clinically significant by the investigators or the Applicant.

8.2. Review of the Safety Database

Overall Exposure

As previously stated, 7 subjects were enrolled in the study and were exposed to the 3 mg dose of NG.

Adequacy of the safety database:

The number of subjects included in Study IGBO is small and make it difficult to draw conclusions about the safety of NG in this patient population. Therefore, review of safety for the expanded pediatric patient population was also based on the PK results of Study IGBO and the consideration of whether they could support extrapolation of the safety of NG from the larger NG phase 3 program to the proposed pediatric patient population.

8.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Given the size of Study IGBO and the limitations of drawing meaningful safety conclusions, the Applicant did not submit, nor did the review team require, safety datasets. The safety review was completed using the safety findings outlined in the CSR and from information requests.

Categorization of Adverse Events

The primary endpoint of the study was TEAEs. Therefore, the definition, recording, and categorization of AEs was discussed previously in Section 6.1. AEs were coded using MedDRA version 24.0. No adverse events of special interest were pre-specified, however, the protocol did state that nasal/respiratory and anosmia AEs would be identified using preferred terms and summarized.

Routine Clinical Tests

Routine clinical tests assessed in Study IGBO are described in Section 6.1.

8.4. Safety Results

Deaths

There were no deaths reported in Study IGBO.

Serious Adverse Events

There were no serious adverse events reported in Study IGBO.

Dropouts and/or Discontinuations Due to Adverse Effects

No subject discontinued due to an AE in Study IGBO.

Significant Adverse Events

There were no significant adverse events observed in Study IGBO consistent with the definition in the ICH guideline for industry E3 Structure and Content of Clinical Study Reports.

Treatment Emergent Adverse Events and Adverse Reactions

Treatment emergent adverse events observed in the safety population in Study IGBO are shown in Table 5, below. All AEs were considered mild. All events except 'post-tussive vomiting' and 'nausea' occurred postdose on Day 1 and resolved the same day. The 'post-tussive vomiting' event was observed on Day 2, approximately 36 hours postdose. The event of 'nausea' occurred 2 hours postdose on Day 1 but resolved approximately 20 hours after onset. All events resolved spontaneously. There were no events related to hypoglycemia or the device.

Table 5 Treatment Emergent Adverse Events Observed in the Safety Population Organized by System Organ Class and Preferred Term; Study IGBO

System Organ Class MedDRA preferred term	Number of adverse events* [number of subjects with adverse events] (percentage of subjects with adverse events) 3 mg Nasal Glucagon (N=7)
Gastrointestinal disorders	**5 [4] (57.1%)**
Abdominal discomfort	1 [1] (14.3%)
Dyspepsia	1 [1] (14.3%)
Nausea	1 [1] (14.3%)
Post-tussive vomiting	1 [1] (14.3%)
Vomiting	1 [1] (14.3%)
Respiratory, thoracic and mediastinal disorders	**3 [2] (28.6%)**
Epistaxis	1 [1] (14.3%)
Nasal discomfort	1 [1] (14.3%)
Sneezing	1 [1] (14.3%)
Eye disorders	**1 [1] (14.3%)**
Eye pruritis	1 [1] (14.3%)
Overall Total	**9 [5] (71.4%)**

Abbreviations: N = number of subjects
*Adverse events with a change in severity are only counted one time at the highest severity
MedDRA version 24.0
Source: Adapted from Study IGBO CSR, Table IGBO.8.1

> ***Reviewer comment:*** *The TEAEs observed in Study IGBO are consistent with the known safety profile of NG and no new safety signals are identified.*

Laboratory Findings

No additional laboratory testing other than the protocol specified tests at screening were collected for any of the subjects in Study IGBO.

Vital Signs

Heart rate and blood pressure were measured before the nasal glucagon dose and 45 minutes post dose. Although an increase in heart rate was observed in 5/7 (71.4%) subjects, none of these subjects had a measured heart rate considered abnormal. Increases in systolic blood pressure were observed in 5/7 (71.4%) subjects as well. In 3 subjects, the systolic blood pressure increased from normal to abnormal. An increase in diastolic blood pressure was only observed in one subject.

> ***Reviewer comment:*** *The observed elevations in heart rate and blood pressure are consistent with the BAQSIMI label which currently states that tachycardia and hypertension were observed adverse reactions across clinical trials. Additionally, none of the investigators considered the vital signs clinically meaningful at the scheduled assessment time of 45 minutes postdose and no events prompted further evaluation.*

Electrocardiograms (ECGs)

ECGs were not routinely collected in Study IGBO.

QT

Not applicable.

Immunogenicity

No immunogenicity assessments were performed in Study IGBO.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1.1. Nasal, Respiratory, and Anosmia Events

As previously stated, no adverse events of special interest were pre-specified, however, the protocol did state that nasal/respiratory and anosmia AEs would be identified using preferred terms and summarized. This is largely because in the original NG safety review, AEs related to the nasal route of administration were observed more frequently than in other glucagon development programs which have different routes of administration.

2 subjects reported nasal, respiratory, and anosmia AEs. 1 subject reported epistaxis at 1 minute postdose followed by sneezing at 7 minutes postdose. Both events resolved within 1 minute of onset. One subject reported nasal discomfort at 1 minute postdose. This resolved after 4 hours.

> ***Reviewer comment:*** *The TEAEs related to nasal, respiratory, and anosmia events observed in Study IGBO are consistent with the known safety profile of NG and no new safety signals are identified.*

8.6. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Nasal glucagon is an approved product. The most recent periodic safety update report (PSUR) covering the period of July 25, 2023 to July 24, 2024 was submitted on September 25, 2024. No new safety signals were identified during the reporting period based on an evaluation of the postmarketing data.

Expectations on Safety in the Postmarket Setting

Based on the totality of evidence, the clinical review team safety of BAQSIMI in the postmarket setting will remain similar with the approval of this supplement, and that pediatric patients with diabetes ages 1 year and above can safely use NG for the treatment of severe hypoglycemia.

8.7. Integrated Assessment of Safety

The safety profile of NG observed in Study IGBO was comparable to that observed in adults and pediatric patients aged 4 to less than 17 years for whom the drug is indicated. Additionally, the PK results demonstrated similar exposures between subjects enrolled in Study IGBO and pediatric patients aged 4 years to less than 17 years and adults with diabetes after intranasal administration of 3 mg NG based on the observed glucagon concentrations. We acknowledge that the observed glucagon concentrations in Study IGBO were lower than modeled predictions (see discussion in Section 1.3). It is possible that in the postmarket setting, patients may be exposed to higher concentrations of glucagon than observed in this study. This possibility is acceptable because this drug is intended to be used in an emergency setting to treat a life threatening event and the risk of reduced exposure leading to a reduction in efficacy outweighs the concerns for higher glucagon exposure. Additionally, if patients are exposed to higher concentrations of glucagon than those observed in Study IGBO, it is also reassuring that there was no correlation between adverse events and glucagon exposure in the original NG program.

9 Advisory Committee Meeting and Other External Consultations

There was no Advisory Committee held to discuss this efficacy supplement.

10 Pediatrics - PMRs

We recommend updating the status of postmarketing requirement 3621-1 to "fulfilled". Specifically, Study I8R-MC-IGBO entitled, "An Open-Label, Multi-Center, Single-Dose Study to Assess the Safety, Tolerability, Pharmacodynamics, and Pharmacokinetics of Nasal Glucagon in Pediatric Patients with Type 1 Diabetes Aged 1 to <4 years" fulfills requirement 3621-1.

This efficacy supplement, including the regulatory history, design, conduct, and results of Study I8R-MC-IGBO, was discussed with the Pediatric Review Committee (PeRC) on February 25, 2025. The PeRC concurred with DDLO's recommendation. The meeting minutes from the February 25, 2025, PeRC meeting are not finalized in DARRTS at the time of this review. However, the review team reviewed and concurred with the draft meeting minutes and concluded no additional edits were required.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Below is a summary of changes to the prescribing information (PI) for nasal glucagon.

- **Section 1: Indications and Usage**
  - The Applicant proposed the following indication statement: BAQSIMI is indicated for the treatment of severe hypoglycemia in adult and pediatric patients with diabetes ages 1 year and above.

  Reviewer comment: *In accordance with the guidance for industry,* Pediatric Information Incorporated Into Human Prescription Drug and Biological Product Labeling *(2019) we recommended the Applicant modify the language as follows: "BAQSIMI is indicated for the treatment of severe hypoglycemia in adults and pediatric patients with diabetes aged 1 year and older."*

- **Section 6: Adverse Reactions**
  - The Applicant proposed to summarize Study IGBO (b) (4) .

  Reviewer comment: (b) (4) *did not add any new information to the label because*

the adverse reactions observed in Study IGBO were comparable to those observed in adults and pediatric patients aged 4 to less than 17 years. We recommended (b) (4) *and addition of the following text, "The safety profile observed in this trial in pediatric patients was comparable to that observed in adults and pediatric patients aged 4 to less than 17 years* [see Clinical Pharmacology (12.2, 12.3)]*."*

- **Section 8.4: Pediatric Use**
  - To align with labeling best practices and provide greater specificity for the basis of approval for use in the pediatric population, DPMH recommended changes to the Applicant's proposed labeling language in subsection 8.4 based on information provided in the clinical review from the original approval of Baqsimi and the clinical trial data provided to support the current sNDA.

- **Section 14: Clinical Studies**
  - The Applicant proposed to summarize Study IGBO and present the exploratory endpoint result in textual format (i.e., the proportion of subjects who achieved treatment success defined as an increase of blood glucose ≥20 mg/dL from baseline (predose BG) within 30 minutes postdose).

Reviewer comment: *Although the efficacy findings from this study were exploratory, we agreed with the Applicant's proposed text in Section 14 (with minor edits) because it informs prescribers about the expected clinical effect of the drug in the 1 to less than 4 years old age group.*

In addition to the above changes to the label, minor labeling changes were made to modernize and ensure compliance with best practices/guidance. The labeling negotiations are documented in DARRTS. Drs. Patel and Birkemeier from the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the proposed Baqsimi Prescribing Information (PI), Patient Package Insert (PPI), and Instructions for Use (IFU) and determined that they are acceptable from a medication error perspective (DARRTs date 12/19/2024).

12 Risk Evaluation and Mitigation Strategies (REMS)

No risk evaluation and mitigation strategy is recommended for this product.

13 Appendices

13.1. References

References are provided as footnotes throughout this review.

13.2. Financial Disclosure

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

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 16		
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: N/A Significant payments of other sorts: N/A Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator in Sponsor of covered study: N/A		
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)

13.3. Clinical Pharmacology Appendices

13.4.1 Summary of Bioanalytical Method Validation and Performance

Plasma concentrations of glucagon in study samples were measured using a high-performance liquid chromatography tandem mass spectrometry (LC-MS/MS) method. The method validation summary for glucagon is shown below (***Table 6***).

The LC-MS/MS method involved extraction of glucagon from human plasma using solid-phase extraction in a 96-well format and desThr7-Glucagon as the internal standard. Glucagon and internal standard were identified and quantified using reversed-phase high performance liquid chromatography (HPLC) with MS/MS detection over a standard curve range of 100 pg/mL to 10000 pg/mL. The concentrations were calculated using peak area ratios, and the linearity of the calibration curve was determined using least squares regression analysis employing a weighted (1/x) linear regression.

Plasma glucose was measured using a study-approved rapid glucose analyzer (YSI Life Sciences or equivalent) to determine the plasma concentrations of glucose.

Table 6 Bioanalytical method validation summary for plasma concentration analysis for measuring Glucagon in Study l8R-MC-IGBO

API	Glucagon
Method	LC-MS/MS
Sample Matrix	Human plasma
Validated Method	XRI-W7-065(R2)
Internal Standard	desThr7-Glucagon
Laboratory Name	(b) (4)
LLOQ (ng/mL)	0.1
ULOQ (ng/mL)	10
Concentration/Validation range (ng/mL)	0.1 – 10
QC (pg/mL)	300, 354, 2000, 2050, 5000, 7500, 7550
Accuracy (bias, %)	90.1% to 111.2%
Precision (%)	4.3% to 6.9%
Incurred Sample Reanalysis (ISR) within acceptance criteria (± 10%)	100% (4 of 4)
Analvte Stability When Stored at -80° C (Days)	412
Samples collection & analysis time	Date of sample receipt: 04/26/2022 to 11/02/2023 Total samples received/analyzed: 20 Date of first sample analysis: 09/27/2022 Date of last sample analysis: 11/06/2023

	All samples were analyzed by 361 days after collection and were within the established stability period of 412 days.
Abbreviations	LLOQ Lower Limit of Quantification; ULOQ Upper Limit of Quantification

***Reviewers' comment**: The bioanalytical method validation is determined to be adequate (Bioanalytical Report for Study I8R-MC-IGBO, VV-CLIN-137767, NDA 210134, eCTD 0639, M 5.3.5.1). The method performance during sample analysis is determined to be acceptable based on results of the standard curve, QCs, and chromatograms. The sample analyses for study IGBO followed pre-established bioanalytical validation report XRI-W7-06S(R2) (Version 02, 2020/01/14) and the analysis results for Glucagon in study samples are acceptable, based on meeting the limits specified in "Guidance for Industry: Bioanalytical Method Validation, Docket Number: FDA-2013-D-1020, May 2018".*

13.4.2 Pharmacometrics Review

13.4.2.1 Population PK analysis

13.4.2.1.1 Review Summary

In this submission, population PK and PK/PD model were used to assess the plasma glucagon and glucose concentrations following dosing.

A population PK report for glucagon was submitted under the name of "I8R-MC-IGBO CSR Appendix Compliance Concern" (referred as final PopPK report), and relevant information was included in the Summary of Clinical Pharmacology report.

In general, the Applicant's population PK model described in the PopPK report (Model 1) is considered acceptable for the purpose of description of glucagon concentrations in plasma for pediatric patients between 1 to 4 years of age. However, the sponsor used a different model (Model 2) - reviewed in the previous review cycle for pediatrics 4 years and above - for simulating the exposure of glucagon in pediatrics between 1 to 4 years. As a result, several plots and tables presenting the simulation results in the Summary of Clinical Pharmacology report are not acceptable because of limitations of Model 2. The reviewer has conducted independent analyses and updated the simulation results and conclusion based on Model 1 regarding the estimated exposure of glucagon in pediatrics 1 to 4 years of age.

More specifically, the developed model was used to support the current submission as outlined in **Table 7**.

Table 7. Specific Comments on Applicant's Final Population PK Model

Utility of the Final Model		Reviewer's Comments
Derive exposure metrics for Exposure-response analyses	Glucagon: C_{max}, AUC Plasma Glucose: C_{max}, AUC	The sponsor's final population PK and PD/PD models (Model 1) are acceptable for describing time-course glucagon and glucose profiles following Baqsimi dosing for pediatrics 1 to < 18 years of age.

Source: Reviewer's summary.

13.4.2.1.2 Objectives

The primary objectives of the Applicant's analysis were to:

- To evaluate the population PK of glucagon in pediatrics 1 to 17 years of age.
- Generate individual plasma exposure estimates of glucagon in pediatric subjects.

13.4.2.1.2.1 Model Development

Data

The analyses were based on PK data from two studies (Studies IGBO and IGBB). The study design, study population, and timing of blood samples varied among the three clinical studies, and are briefly described in **Table 8**.

The data file from the Applicant's proposed final model for analysis contained 718 glucagon (700 from IGBB and 18 from IGBO) and 724 glucose (689 from IGBB and 35 from IGBO) concentrations from 55 participants. **Table 9** provides summary statistics of the baseline demographic covariates in the analysis dataset.

Table 8. Summary of Studies *w*ith PK Sampling Included in Population PK Analysis

Study ID	Phase	Title	Subject N	Dosing Regimen	Plasma PK Sampling Schedule
IGBO	1	An Open-Label, Multi-Center, Single-Dose Study to Assess the Safety, Tolerability, Pharmacodynamics, and Pharmacokinetics of Nasal Glucagon in Pediatric Patients with Type 1 Diabetes Aged 1 to <4 years	7	3 mg NG	• Glucagon 10, 30, and 60 min • Plasma Glucose Predose, 10, 30, 60 and 90 min
IGBB	1	Assessment of Intranasal Glucagon in Children and Adolescents with Type 1 Diabetes	48	2 mg NG and 3 mg NG, 0.5 mg or 1 mg IMG	• Glucagon 5, 10, 15, 20, 30, 40, 60 and 90 min • Plasma Glucose

					5, 10, 15, 20, 30, 40, 60 and 90 minutes

Source: Reviewer's summary.
NG: nasal glucagon
IMG: intramuscular glucagon

Table 9. Summary of Baseline Demographic Covariates for Analysis

Study IGBB						
Variable	N	Mean	Median	Min	Max	SD
Age (Years)	48	10	11	4.1	17	3.4
Weight (kg)	48	41	38	18	92	17
BMI (kg/m2)	48	19	19	15	29	3.3
Baseline glucacon (pg/mL)	48	94	72	24	371	76
Baseline glucose (mg/dL)	48	73	72	56	90	8
Sex	48	Female: 16 Male: 32				
Race	48	White: 45 Black or African American: 3 Multiple: 1				
Study IGBO						
Variable	N	Mean	Median	Min	Max	SD
Age (Years)	7	3	3.2	1.8	4	0.83
Weight (kg)	7	15	15	12	19	2.5
BMI (kg/m2)	7	18	18	15	20	2
Baseline glucose (mg/dL)	7	110	117	81	137	21
Sex	7	Female: 3 Male: 4				
Race	7	White: 4 Black or African American: 0 Multiple: 0				

Source: Reviewer's summary.

Applicant's Base Model

The population PK model for glucagon concentrations for adults and pediatric patients 4 years and above was verified in the previous review cycle (refer to the review by Dr. Suryanarayana Sista and Manoj Khurana) with pooled data from studies IGBA, IGBB, IGBC, IGBD, IGBG, and IGBI, supporting the initial application.

In this review, the base model for glucagon was a one-compartment model with first-order elimination, consistent with the population PK model in the previous review cycle. Body

weight-based allometric parameters were included as fixed values on clearance (power of 0.75) and volume of distribution (power of 1) parameters. A time lag parameter (ALAG) was introduced to better describe the nasal glucagon absorption. Additionally, baseline glucagon was also estimated in the model. The population PK analysis was conducted using NONMEM® software implementing the first order conditional with epsilon-eta interaction estimation method.

Covariate Analyses

Age as a continuous covariate was tested for impact on F1 and Ka parameters. After applying body-weight allometric scaling, age had no impact on glucagon PK. Age as a categorical, IGBO versus IGBB; 1 to <4 year olds versus > 4 year olds, was a significant covariate on F1.

Applicant's Final Model

The parameter estimates for the final covariate model are listed in **Table 10.** The goodness of fit plots and visual predictive check plots for the final covariate model for all data are shown in Figure 8 and Figure 9

Table 10. *Glucagon* Population PK Model Parameters

Parameter Description	Population Estimate (%SEE, 95% CI[a])	Inter-Patient Variability (%SEE[b])
Bioavailability		
F1 for IMG	1 (FIXED)	NE
Rate of Absorption		
Ka (hr^{-1}) of IMG	1.64 (9.09%, 1.27 - 1.88)	NE
Absorption Lag for NG		
ALAG1 (hr)	0.0622 (2.75%, 0.0578 - 0.0652)	NE
Clearance		
CL/F (L/hr)	297 (10.0%, 228 - 377)	49.5% (26.5)
Volume of Distribution		
V/F (L)	27.8 (10.9%, 22.8 – 35.7)	NE
Baseline Glucagon		
BLGCG (pg/mL)	82.7 (9.21%, 69.3 - 99.4)	73.8% (27.6)
Covariates		
Effect of Nasal administration on F1 (IGBB)[c]	-0.781 (2.47%, -0.829 - -0.735)	
Effect of Nasal administration on Ka[d]	0.44 (38.4%, 0.216 - 0.952)	
Effect of Study IGBO on F1[f]	-0.616 (17.5%, -0.682 - -0.211)	
Inter-occasion Variability on F1	55.7% (25.4%, 36.5 - 74.3)	
Inter-occasion Variability on Ka	46.3% (23.0%, 35.7 - 59.6)	
Residual Error (proportional)[e]	28.5 (12.9%)	

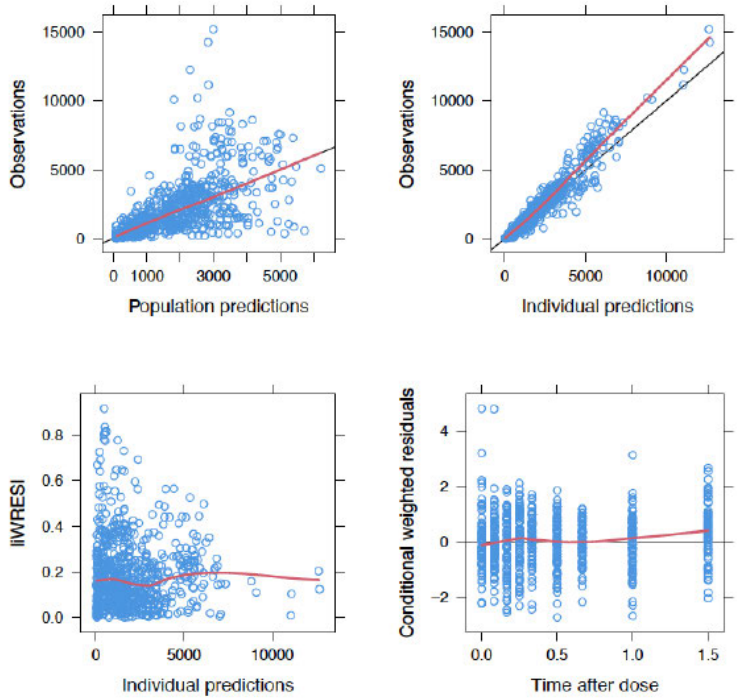
Abbreviations: ALAG1 = Absorption lag for NG; BLGCG = baseline glucagon; CL/F = apparent clearance; CI = coefficient of variation; CV = coefficient of variation; F1 = bioavailability; IMG = intramuscular glucagon; Ka = absorption rate constant; NE = not estimated; NONMEM = nonlinear mixed effects modeling program; SEE = standard error of the estimate; V/F = apparent volume of distribution.

a. 95% CI values obtained from bootstrap.

b. Reported as %CV, calculated by the equation 100 × $\sqrt{eOMEGA(N)} - 1$ where OMEGA(N) is the NONMEM output for the inter-subject variability of the Nth parameter
c. F1 = 1 × (1 + $I1$ × −0.781) , where I1 is set to 1 when route of administration is nasal and 0 for IMG
d. Ka = 1.57 × (1 + $I1$ × 0.51), where I1 is set to 1 when route of administration is nasal and 0 for IMG
e. Reported as %CV, calculated by the equation 100 × $\sqrt{SIGMA}$, where SIGMA is the NONMEM output for the variance of the proportional residual error.
f. F1 = 1 × (1 + $I1$ × −0.781) × (1 + $I2$ × −0.616), where I1 is set to 1 when route of administration is nasal and 0 for IMG and I2 is set to 1 when study is IGBO and 0 when study is IGBB.

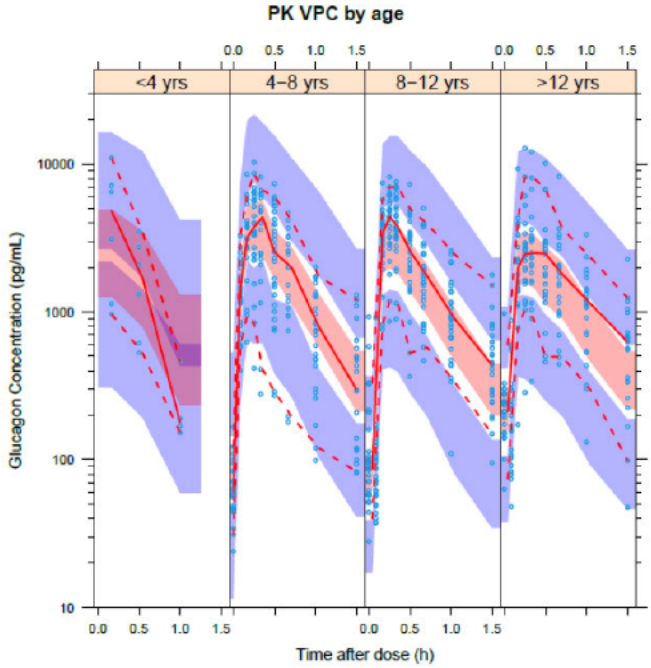
Source: Applicant's final PopPK report. Table 1, page 10.

Figure 8. Goodness of fit plot for the final population PK model



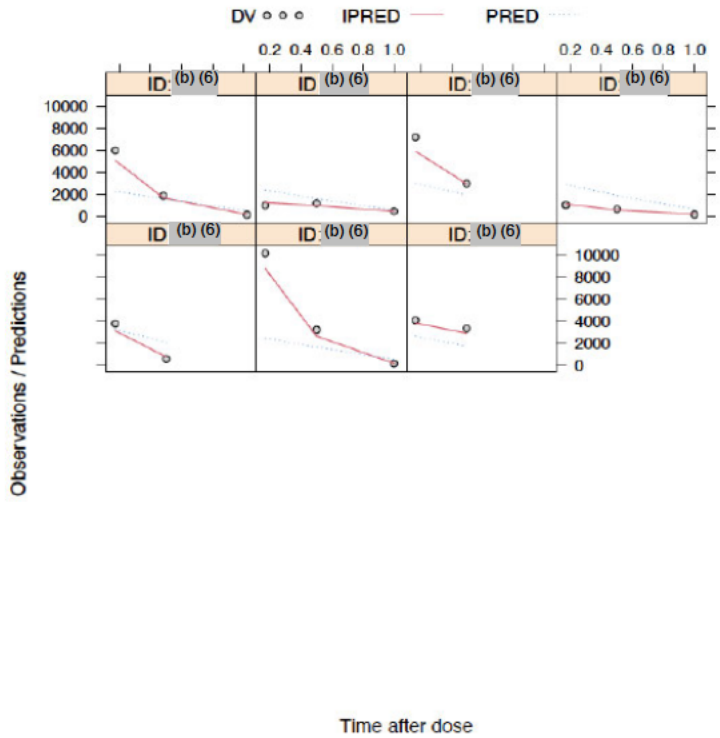
Source: Applicant's final PopPK report. Figure 5, page 17.

Figure 9. *V*isual *P*redictive *C*heck *(VPC) plot* for the *Glucagon* Population PK Model



Source: Applicant's final PopPK report. Figure 2, page 11.

Figure 10. Individual model predicted and observed glucagon profiles for study IGBO



Source: Applicant's final PopPK report. Figure 6, page 18.

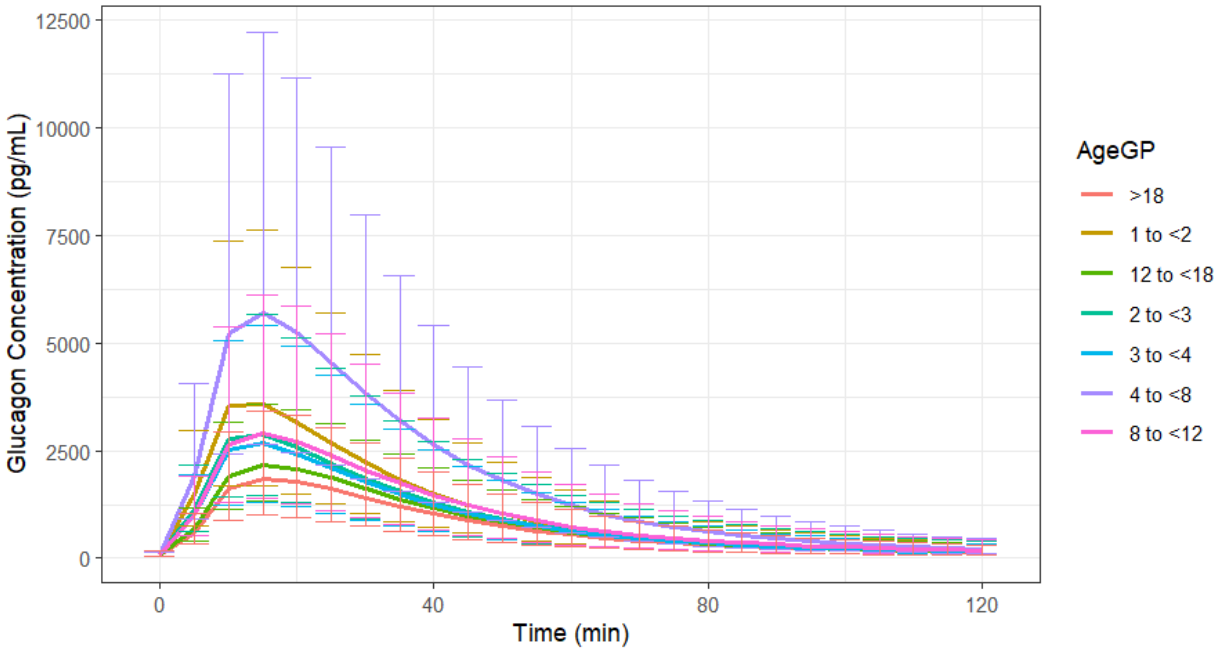
The final PopPK model was used to predict glucagon exposures for pediatric patients between 1 to 18 years of age following 3 mg NG dosing of Baqsimi. Body weight distribution in the 1 to 4-year of age groups was based on World Health Organization growth reference tables. The results are shown in ***Table 11*** and ***Figure*** 11.

Table 11. Predicted glucagon PK parameters based on PopPK modeling and simulations after a single 3 mg NG dose of BAQSIMI for pediatrics 1 to 18 years of age.

Age (Years)	Weight (kg)	Tmax (min)	GeoMean Cmax (CV%) (pg/mL)	GeoMean AUC (CV%) (pg*h/mL)
1 to < 2	11	12.8	3771.7 (85.8%)	2432.8 (75.3%)
2 to < 3	13.4	13.4	3008.9 (76.2%)	2074.9 (70.5%)
3 to < 4	15.5	14.0	2767.5 (80.4%)	1943.8 (68.8%)
4 to < 8	21.5	14.5	5845.0 (89.1%)	3949.1 (75.0%)
8 to < 12	43.2	15.1	3020.2 (86.6%)	2186.9 (82.4%)
12 to < 18	61.2	16.2	2255.3 (52.7%)	1707.0 (51.1%)

Source: Reviewer's analyses.

Figure 11. Simulated time course profiles of glucose concentrations after a single 3 mg NG dosing of Baqsimi.



Source: Reviewer's analyses.

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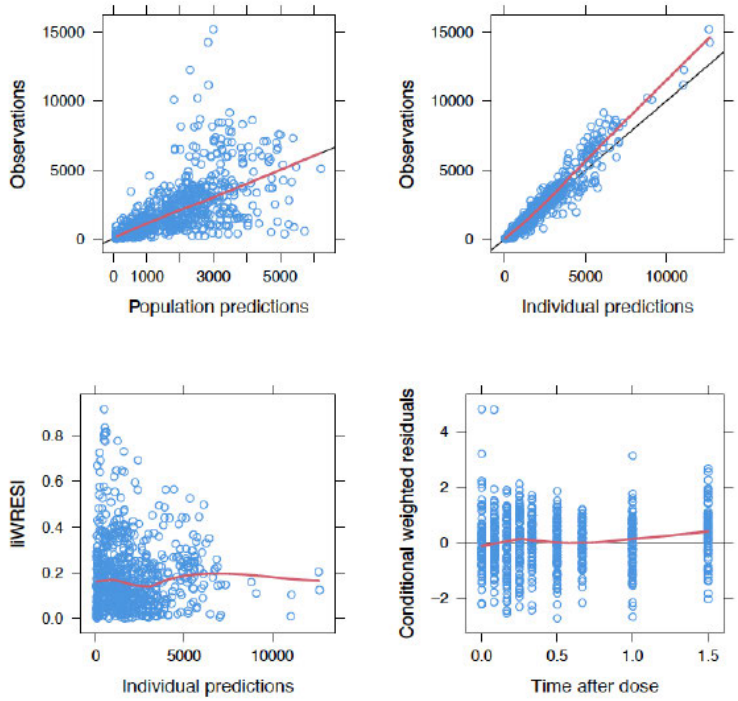
Reviewer's comments: *The population PK model for glucagon for adults and pediatric patients 4 years and above (Model 2) has been previously verified in the previous review cycle, and the current model focused on expanding the approved age range down to 1-year old (Model 1). Visual predictive check plots (Figure 8. Goodness of fit plot for the final population PK model*



Source: Applicant's final PopPK report. Figure 5, page 17.

Figure 9*) show that the population PK model (Model 1) has a good estimation for glucagon concentration across different age groups, as observed in the VPC plots, demonstrating that the predicted and observed concentrations align well within the prediction intervals. A covariate effect on nasal glucagon relative bioavailability was found to be significant, where children <4 years had lower bioavailability than children >4 years of age. Children aged 1 to <4 years have smaller nasal mucosa surface area for nasal glucagon absorption which may lead to lower bioavailability of NG (Xi et al. 2014).*
The review team determined that the Applicant's final population PK model (Model 1) for glucagon is considered acceptable for the purpose of description of glucagon exposure in plasma for pediatrics 1 to < 18 years. The model captures the central tendency of the data and is acceptable for empirical Bayesian estimates. The Applicant's analyses were verified by the reviewer, with no discordance identified.

*In the summary of clinical pharmacology (page 5, table 2.7.2.6.2-2), the sponsor predicted that the exposure of glucagon following 3 mg NG dosing was approximately 19200 (CV = 78.2%) pg/mL for Cmax and 8380 (CV = 70.7%) pg*h/mL for AUC0-1.5h, which is 3-4 fold higher than observed data in Study IGBO. The Agency sent out an information request for the sponsor to clarify these discrepancies. Based on the IR responses, the sponsor stated that the*

data presented in this table was the extrapolated results based on the previous PopPK model (Model 2) for pediatric patients (≥ 4 years) in the previous review cycle, which is not suitable for describing the glucagon concentration for pediatrics 1 to < 4 years of age. Therefore, the reviewer conducted independent analyses using the final population PK model (Model 1) , and the results show that pediatrics 1 to < 4 years had similar exposure of glucagon as compared to pediatrics 4 to < 18 years.

13.4.2.2 Exposure-Response Analysis

13.4.2.2.1 Exposure-Response Relationships for Efficacy

A PK/PD model between plasma glucagon and glucose concentrations was previously established for pediatrics ≥ 4 years. The PK/PD model was updated with the data from IGBO for estimation of glucose concentration in pediatrics 1 to < 4 years.

The final model included KIN where KIN=E0*KOUT, KOUT, Emax, and EC50 parameters, and a proportional residual error term. Model parameters are given in ***Table 12.***

Table 12. Pharmacodynamic Parameters in Final Model

Parameter Description	Population Estimate (%SEE, 95% CI[a])	Inter-Patient Variability % (%SEE[b])
E0 (mg/dL)	86.2 (34.0%, 57.4 - 135)	NE
K_{OUT} (h^{-1})	2.7 (32.6%, 1.84 - 4.27)	51.7% (54.9)
E_{MAX}	1.99 (69.9%, 0.808 - 3.82)	NE
EC_{50} (pg/mL)	301 (58.5%, 178 - 628)	185% (68.5)
Insulin effect on K_{OUT}	0.895 (63.6%, 0.403 – 1.68)	63.2% (110)
Half-life of insulin effect (h)	0.166 (41.7%, 0.0901 - 0.256)	NE
Covariate Impact		
Baseline glucose on K_{IN}[c]	0.0022 (82.3%, 0.000554 - 0.0111)	
Residual Error (proportional) [d]	10.3 (15.8%)	

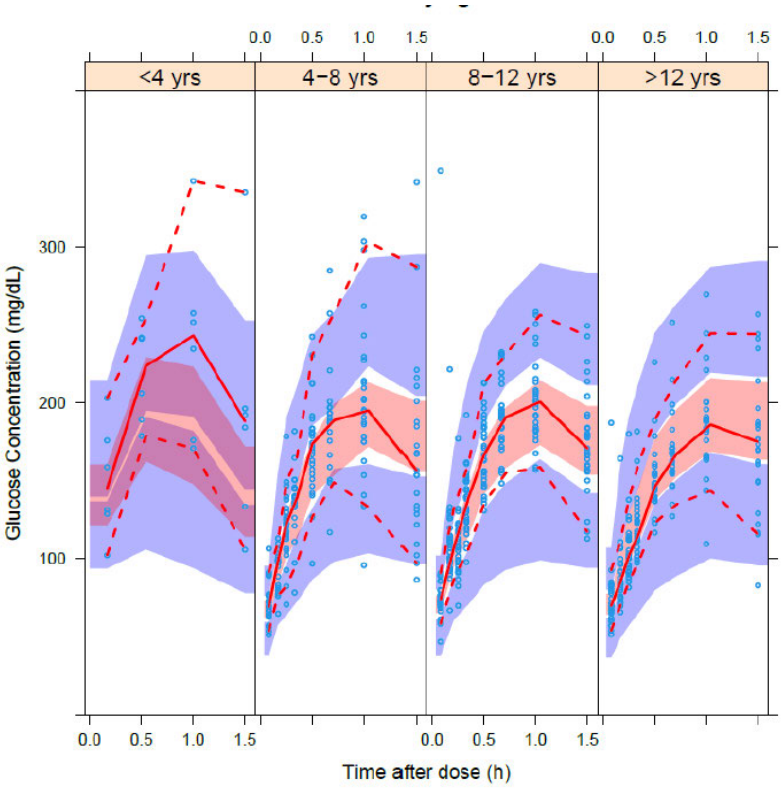
Abbreviations: CI = confidence interval; CV = coefficient of variation; E0 = estimated baseline glucose in absence of study induced hypoglycemia; EC50 = concentration for achieving half of maximum effect; EMAX = maximum effect of glucagon on glucose production rate; KIN = glucose production rate; KOUT = turnover rate of glucose;
NE = not estimated; SEE = standard error of the estimate.

a. 95% CI values obtained from bootstrap
b. Reported as %CV, calculated by the equation 100 × $\sqrt{eOMEGA(N)} - 1$ where OMEGA(N) is the NONMEM output for the inter-subject variability of the Nth parameter
c. KIN= $Kout * E0 \times EXP(0.0022 \times (baselineglucose - 72))$, where 72 is the population median baseline glucose in mg/dL
d. Reported as %CV, calculated by the equation 100 × $\sqrt{SIGMA}$, where SIGMA is the NONMEM output for the variance of the proportional residual error.

Source: Applicant's final PopPK report. Table 2, page 13.

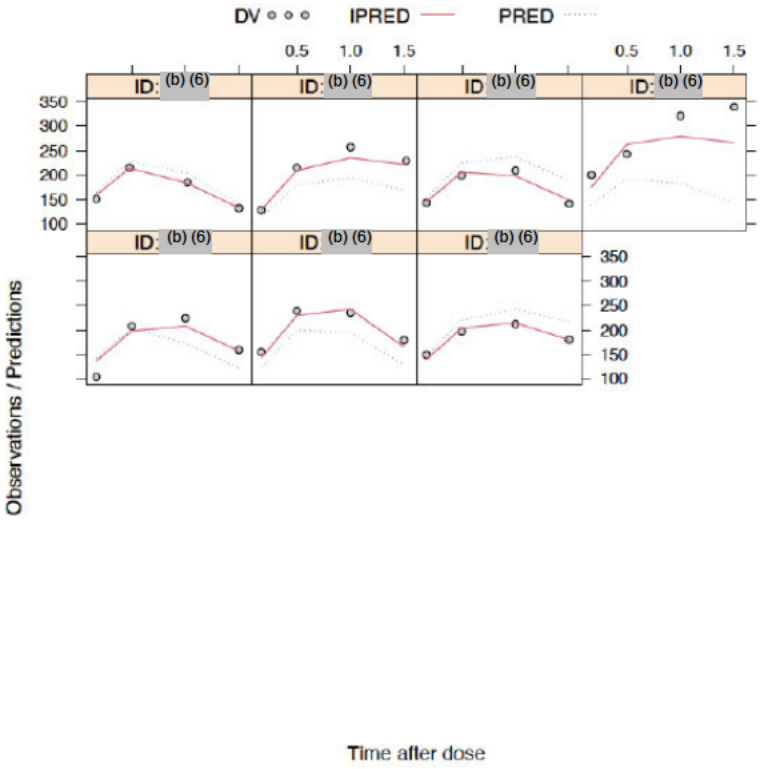
The visual predictive check plots for the final population PK/PD model for all data are shown in Figure 12.

Figure 12. Visual predictive check for the final glucose exposure-response model (prediction corrected)



Abbreviations: h = hours; PD = pharmacodynamic; VPC = visual predictive check. Note: The solid red line is the median and the dashed red lines are the 5th and 95th percentiles of the observed glucose concentrations; the red shaded region is the 90% confidence interval of median and the blue shaded region is the 90% confidence interval of the 5th and 95th percentiles of the model-predicted glucose concentrations.
Source: Applicant's final PopPK report. Figure 4, page 14.

Figure 13. Individual model predicted and observed glucose profiles for study IGBO



Source: Applicant's final PopPK report. Figure 8, page 22.

Based on the final PopPK/PD model, the time course profiles of glucose concentrations after a single 3 mg NG dosing of Baqsimi was simulated and presented in ***Figure 14.*** *The percent of patient achieving treatment success following 3 mg NG dosing of Baqsimi was also simulated and summarized in* ***Table 11.***

Figure 14. Simulated time course profiles of glucose concentrations after a single 3 mg NG dosing of Baqsimi for pediatrics with a baseline glucose concentration at 40 mg/dL.

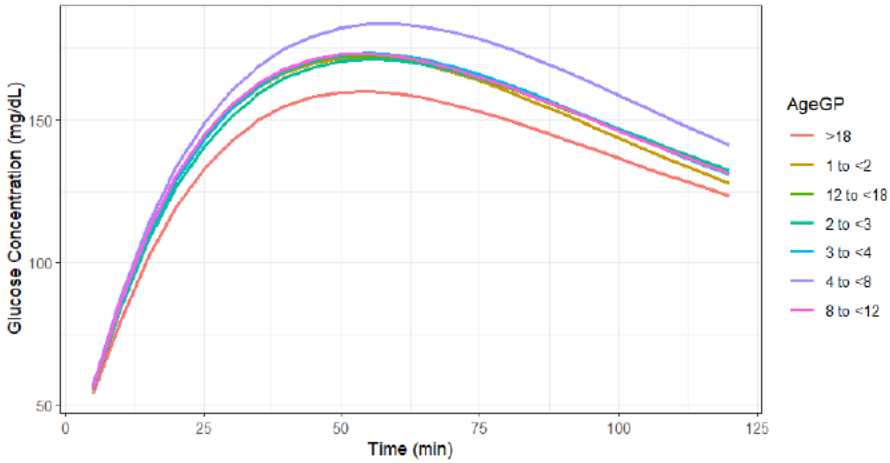


Table 5. Summary of Simulations for Percent of Patient Achieving Treatment Success following 3 mg NG dosing of *Baqsimi*.

Dose	Age group (Years)	Treatment Success (%)
3 mg NG	1 to <2	100
3 mg NG	2 to <3	100
3 mg NG	3 to <4	99.9
3 mg NG	4 to <8	99.9
3 mg NG	8 to <12	99.8
3 mg NG	12 to <18	98.9

Source: IR response from the sponsor received on 02/21/2025. NDA 210134, Sequence 0654.

Reviewer's comments: *The population PK/PD model for glucagon has been previously verified in the previous review cycle, and the current model focused on expanding the age range to 1 to < 4 years of age. Visual predictive check plots (Figure 12) show that the PK/PD model has a good estimation for plasma glucose concentration across different age groups, with the plots demonstrating that the predicted and observed concentrations align well within the prediction intervals.*

Therefore, the review team determined that the Applicant's PK/PD analysis for the relationship between glucagon and plasma glucose concentration is considered acceptable for the purpose of description of glucose exposure in pediatrics 1 to < 18 years. The model captures the central tendency of the data and is acceptable for empirical Bayesian estimates. The Applicant's analyses were verified by the reviewer, with no discordance identified.
The exposure and response projects presented in the summary of clinical pharmacology (page 3 to page 5) was based on the previous population PK/PD model for older kids (> 4 years), which is not suitable for describing PD response for pediatrics < 4 years of age. Therefore, the reviewer conducted independent analyses by simulating time course profiles of glucose concentrations following a single 3 mg NG dosing of Baqsimi, and Table 12 was an updated response from the sponsor regarding treatment success rate following dosing based on the information request from the Agency.

The results show that pediatric patients 1 to 4 years of age had similar glucose concentration profiles as compared to older kids. In addition, approximately 100% pediatric patients reached treatment success in the simulation, suggesting 3 mg NG dosing is appropriate for pediatrics 1 to < 4 years of age.

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/s/

JUSTIN A PENZENSTADLER
03/17/2025 12:29:41 PM

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03/17/2025 12:36:50 PM

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JOHN M SHARRETTS
03/17/2025 02:35:48 PM
I concur with the conclusions in this review.