Office of Clinical Pharmacology Review

NDA or BLA Number	210134
Link to EDR	\\CDSESUB1\evsprod\NDA210134\210134.enx
Submission Date	28 Jun 2018
Submission Type	*Standard Review*
Brand Name	BAQSIMI
Generic Name	Glucagon nasal powder
Dosage Form and Strength	Fixed ratio combination product (Drug/Device combination) containing 3 mg/unit dose of glucagon
Route of Administration	Intra-nasal
Proposed Indication	Treatment of severe hypoglycemia
Applicant	Eli Lilly and Company
Associated IND	*IND 110674*
OCP Review Team	*Suryanarayana Sista, PhD, Manoj Khurana, PhD*

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1. EXECUTIVE SUMMARY

This is an original NDA (drug-device combination) submitted by Eli Lilly and Company on June 28, 2018 seeking approval for intra-nasal (IN) glucagon under a proposed tradename of BAQSIMI for the treatment of severe hypoglycemia. Currently two approved products, to be administered as intramuscular injection, are available in the US for this indication.

BAQSIMI is a drug-device combination which is labeled to deliver 3 mg glucagon intra-nasally. Due to specifications (b) (4), the final delivered dose could theoretically be significantly lower than 3 mg. The Clinical Pharmacology review focused on 3 mg dose as claimed and also looked into exposure-response for a 2 mg dose compared to the approved 1 mg to cover the possible worst-case scenarios.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in NDA 210134. We recommend approval of BAQSIMI for the treatment of severe hypoglycemia. Key review issues with specific recommendations and comments are summarized below:

Review Issues	Recommendations and Comments
Supportive evidence of effectiveness	One pivotal trial conducted with the to-be-commericalized formulation provided primary evidence. Supportive evidence was obtained from (a) a second pivotal trial with a clinical trial formulation, (b) 4 dose selection studies for glucagon based on glucose response, (c) glucagon exposure and safety, and (d) a single dose study in otherwise healthy subjects with common cold symptoms.
General dosing instructions	BAQSIMI is indicated for the treatment of severe hypoglycemia in adult and pediatric patients with diabetes. The patient and/or caregiver should: • Insert the tip gently in one of the nostrils until finger(s) touch the outside of the nose. • Push the plunger all the way in, until the green line is no longer showing, which indicates that the dose has been administered. • After giving the dose, call for medical help right away.
Dosing in patient subgroups	Not Applicable
Bridge between the "to-be-marketed" (TBM) and clinical trial formulations	The pivotal trial (IGBI) utilized the TBM formulation.

1.2 Post-Marketing Requirements and Commitments

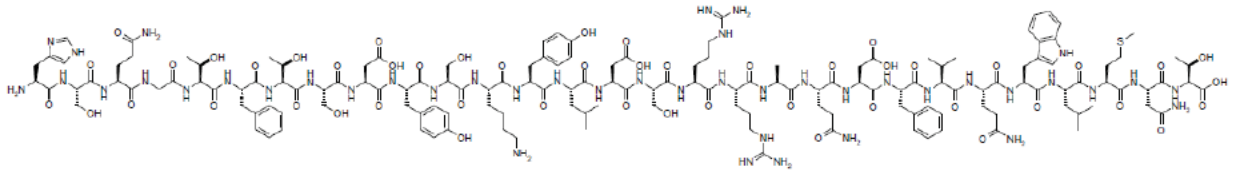
None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Glucagon is a naturally occurring peptide hormone consisting of 29 amino acids that is secreted by the alpha cells of the pancreas. Glucagon for Injection in this submission is a synthetic human glucagon manufactured by a [redacted] (b) (4) The test glucagon powder for intra-nasal use, and the reference product, Glucagon for injection are produced by recombinant DNA technology.

Glucagon is a polypeptide consisting of 29-amino acids. Chemically it is designated as L-Histidyl-L-seryl-L-glutaminyl-glycyl-L-threonyl-L-phenylalanyl-L-threonyl-L-seryl-L-aspartyl-L-tyrosyl-L-seryl-L-lysyl-L-tyrosyl-L-leucyl-L-aspartyl-L-seryl-L-arginyl-L-arginyl-L-alanyl-L-glutaminyl-L-aspartyl-L-phenylalanyl-L-valyl-L-glutaminyl-L-tryptophanyl-L-leucyl-L-methionyl-L-asparaginyl-L-threonine. Glucagon has the following structure:



Glucagon for the treatment of severe hypoglycemia has been marketed in the US since June 1998 under the brand name GLUCAGEN and September 1998 as Glucagon for Injection.

The extrahepatic effects of glucagon include relaxation of the smooth muscle of the stomach, duodenum, small intestine and colon. Glucagon increases plasma glucose levels and causes smooth muscle relaxation and an inotropic myocardial effect because of the stimulation of adenylate cyclase to produce cyclic adenosine monophosphate (cAMP). The cAMP initiates a series of reactions that leads to the degradation of glycogen to glucose. Hepatic stores of glycogen are needed for glucagon to exert an antihypoglycemic effect. Glucagon for Injection is a gastrointestinal motility inhibitor.

For adults and for pediatric patients weighing more than 44 lb (20 kg), glucagon 1 mg is administered by subcutaneous, intramuscular, or intravenous injection. For pediatric patients weighing less than 44 lb (20 kg), glucagon 0.5 mg or a dose equivalent to 20 to 30 mcg/kg is administered.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The proposed dosing recommends a single 3 mg intranasal dose of glucagon in both adult and pediatric patients. Based on exposure-response analysis, adequate clinical response will be maintained even under a "worst-case' scenario, where the delivered dose could be as low as 2 mg.

Dosing instructions to the patient and/or caregiver are as follows:

- Do not remove shrink wrap, open the tube, or test the device before use.
- Insert the tip gently in one of the nostrils until finger(s) touch the outside of the nose.
- Push the plunger all the way in, until the green line is no longer showing, which indicates that the dose has been administered.
- After giving the dose, call for medical help right away.

2.2.2 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.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology recommends the following labeling concepts be included in the final package insert. The ~~red strikeout font~~ is used to show the proposed text to be deleted and underline blue font to show text to be included or comments communicated to the sponsor.

12 CLINICAL PHARMACOLOGY

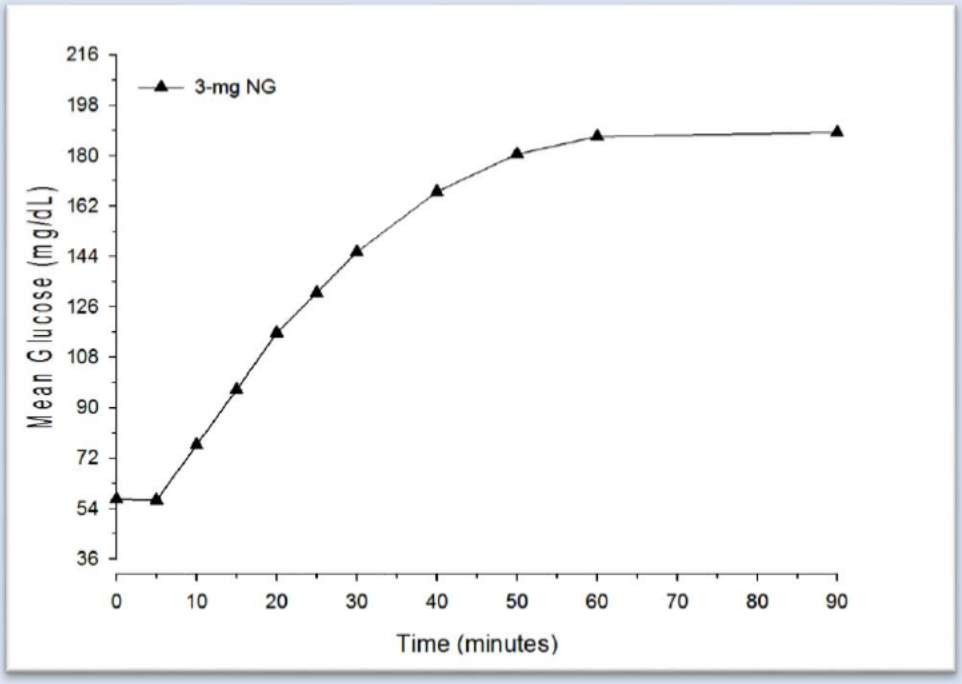
12.2 Pharmacodynamics

~~After administration of BAQSIMI in adult patients with~~ (b) (4) ~~diabetes~~ (b) (4) The mean time to treatment success in adult patients with type 1 diabetes was 16.2 and 12.3 minutes in the BAQSIMI and IMG 1 mg treatment groups, respectively. The mean maximum glucose increase was 140 mg/dL. All patients with type 2 diabetes (100%) achieved treatment success.

In pediatric patients with type 1 diabetes (4 to <17 years), (b) (4) .

Sex and body weight had no clinically meaningful effects on the pharmacodynamics of BAQSIMI.

Common cold with nasal congestion tested with or without use of decongestant did not impact pharmacodynamics of BAQSIMI.



Replace Figure 1

Replace this graph with one that compares both the 3 mg NG as well as 1 mg IMG

Figure 1 **Mean glucose concentration over time in adult Type 1 Diabetes patients with insulin induced hypoglycemia** (b) (4).

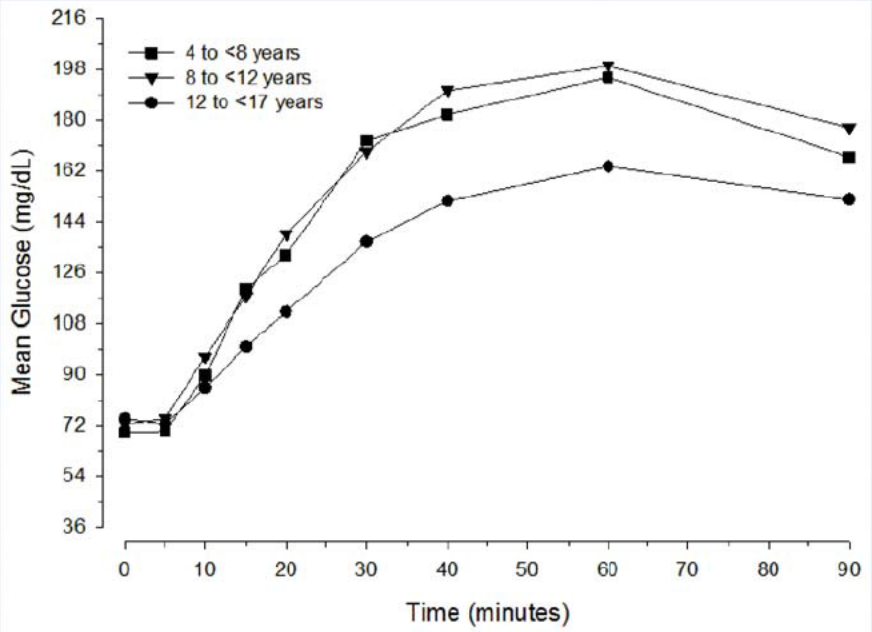


Figure 2 Mean glucose concentration over time in pediatric Type 1 Diabetes patients [redacted] BAQSIMI

12.3 Pharmacokinetics

Absorption

Glucagon absorption via the intranasal route, achieved mean peak plasma levels of 6130 pg/mL reached at 15 minutes.

Distribution

The apparent volume of distribution was approximately 885 L.

Metabolism

Glucagon is known to be degraded in the liver, kidneys, and plasma.

Elimination

The mean half-life was approximately [redacted] minutes.

Special Populations

[redacted]

Pediatrics

In pediatric patients (4 to <17 years), glucagon via the intranasal route, achieved mean peak plasma levels between 15 and 20 minutes. The mean half-life was 21 to 31 minutes.

Drug Interactions

Common Cold and use of Decongestant

Common cold with [redacted] use of decongestant did not impact the pharmacokinetics of BAQSIMI.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

The clinical development program comprises seven studies: four dose selection studies (three in adults and one in pediatric population), two dose confirmation studies in adults, and one supportive study in adult subjects. A total of 429 adult subjects participated in these clinical studies, including healthy volunteers (n = 52). T1DM patients (n = 307), and T2DM patients (n=44). A total of 70 pediatric patients participated in these studies. These studies provide information supporting proof-of-concept as well as the definitive efficacy and safety of glucagon in the target population for the treatment of severe hypoglycemia (Table 1).

Table 1 **Summary of Adult and Pediatric Exposure to Study Drug in Nasal Glucagon Clinical Studies (IGBA, IGBB, IGBC, IGBD, IGBE, IGBF, IGBG, IGBH, IGBI, B001, and B002)**

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

Abbreviations: CG = control glucagon; CSR = clinical study report; HV = adults without diabetes; N = total number of patients; NG = nasal glucagon; T1D = type 1 diabetes mellitus; T2D = type 2 diabetes mellitus.

a Included 1 mg intramuscular injection of glucagon or 1 mg subcutaneous injection of glucagon in adult studies, and 0.5 or 1 mg intramuscular injection of glucagon in the pediatric study.

b Number of total patients is not the sum of NG- and CG-treated patients because a patient may have received both NG and CG in a crossover study and is counted in each respective treatment group, but is only counted once in the total.

(Source: Module 2.7.4. Summary of Clinical Safety, Table 2.7.4.2, Page 18)

The regulatory history regarding these communications is summarized below:

Dates	Meeting Type	Key Communication Points
26 Nov 2010	Pre- Investigational New Drug (PIND) meeting request	Meeting denied
05 Apr 2012	IND	Allowed to proceed after the 30 day safety period
6 Jul 2012	End of Phase 2 (EOP2) meeting request	Meeting request denied and Sponsor asked to provide the full clinical study report (CSR) for the study entitled "A Single Site, Randomized, Three-way, crossover Phase 2 Study To Investigate The Safety And Efficacy Of 2 Dose Levels Of A Novel Glucagon Formulation Compared To Commercially Available Glucagon In Type 1 Diabetic Patients Following Insulin-Induced Hypoglycemia" for Agency's review
14 Dec 2012		Sponsor submitted the full CSR
24 Jan 2013	End of Phase 2 (EOP2) meeting request	Meeting request granted
15 Apr 2013	Face to face meeting	
12 Feb 2015	Pre-NDA Meeting request	Pre-NDA Type B meeting request from the previous Sponsor (Locemia Solutions) for IND 110674 AMG504-1, a novel, non-injectable glucagon for treatment of severe hypoglycemia
25 Feb 2015		Request granted for a pre-NDA Type B meeting for May 7, 2015

Dates	Meeting Type	Key Communication Points
01 May 2015	IR	Preliminary Meeting Comments sent to Sponsor
07 May 2015	Pre-NDA Type B meeting	
27 Sep 2016	Type C meeting request	Request to discuss regulatory pathways and an analytical testing strategy to demonstrate comparability between Phase 3 material and commercial drug product
09 Dec 2016		Agency agreed in principle, noting that it will ultimately be a review issue to the following proposals from the Sponsor: 1. Agreement that the proposed Study IGBI is appropriate to bridge to the previously-generated clinical data 2. Sponsor's approach outlined to compare the commercial Nasal Glucagon Drug Product to the Phase 3 Drug Product which would allow reliance on the data previously generated 3. Sponsor's proposal that Study IGBI meets its primary endpoint, the NDA may be submitted without further FDA interaction 4. The non-clinical and clinical development program as conducted with the addition of Study IGBI and the toxicology study to qualify drug product degradation impurities, represents "full reports of investigations to show whether or not the drug is safe and effective" and should be filed as a 505(b)(1) 5. No bridging toxicity study to a US-approved glucagon product is required
06 Jul 2016	Type C meeting request	Sponsor wanted to discuss a comparability exercise performed between two manufacturers of the active pharmaceutical ingredient and to discuss potential manufacturing changes
12 Jul 2016		Type C meeting request granted
16 Sep 2016		Agency response to CMC questions from the Sponsor.
04 Jun 2018	Request for Proprietary Name Review	A proposed proprietary name of BAQSIMI was submitted for Agency's review
28 Jun 2018	NDA Submitted	
24 Nov 2018	IR sent to Sponsor	Sponsor requested to conduct exposure-response modeling, and plot C_{max} and T_{max} as a function of glucagon API particle size in the formulation
30 Nov 2018	Response to IR of 24 Nov2018	Sponsor submitted CMC related IR response as well as plots of C_{max} and T_{max} as a function of glucagon API particle size in the formulation
14 Dec 2018	Response to IR of 24 Nov2018	Sponsor submitted the requested exposure-response modeling report
02 Jan 2019	IR sent to Sponsor	Datasets for the exposure-response modeling report were requested
09 Jan 2019	Response to IR of 02 Jan2019	Requested datasets were submitted to the NDA by the Sponsor
22 Feb 2019	IR sent to Sponsor	Sponsor asked to add the profiles of 1 mg IMG to the simulated profiles of 2 and 3 mg NG that was submitted on 14 Dec 2018.
26 Feb 2019	Agency communication	Clarification provided to Sponsor's questions re: 22Feb2019 IR
01 Mar 2019		Sponsor provided the requested information from IR of 22 Feb 2019
07 Mar 2019	IR sent to Sponsor	Scripts used to generate Figures Q1-1 to Q1-8 of the 01 Mar 2019 response was requested.
13 Mar 2019	Response to IR of 07 Mar 2019	Sponsor submitted the requested R scripts

3.2 General Pharmacological and Pharmacokinetic Characteristics

Prior Knowledge of Pharmacology of Glucagon:

Mechanism of Action:
The extrahepatic effects of glucagon include relaxation of the smooth muscle of the stomach, duodenum, small intestine and colon. Glucagon increases plasma glucose levels and causes smooth muscle relaxation and an inotropic myocardial effect because of the stimulation of adenylate cyclase to produce cyclic adenosine monophosphate (cAMP). The cAMP initiates a series of reactions that leads to the degradation of glycogen to glucose. Hepatic stores of glycogen are needed for glucagon to exert an antihypoglycemic effect.

Pharmacodynamics:
Graf et. al., (*J. Pharm Sci*, 1999; vol. **88**, No.10) compared the PK and PD parameters of recombinant glucagon and animal source glucagon. The PK and PD of recombinant glucagon was assessed following intravenous (IV) bolus administration of 0.25, 0.5, 1.0 and 2.0 mg dose with a 7-10 days interval between doses. The glucagon PK showed dose-proportional increase for Cmax and AUC in this dose range. Mean maximal plasma glucagon concentrations ranging from 37 to 368 ng/mL occurred within 0.05 h following the IV bolus dose. Glucagon was rapidly eliminated, with mean half-lives ranging from 0.13 to 0.30 h. The mean clearance was similar between the treatments (~59 L/h).

Mean maximal blood glucose concentrations in this study were similar for each treatment (129 to 136 mg/dL) and occurred within 0.36 h after the IV bolus dose of glucagon. This shows that the maximum glucodynamic effect is seen even at the lowest glucagon dose. Blood glucose levels returned to baseline values by 1 h in most subjects (Figure 1).

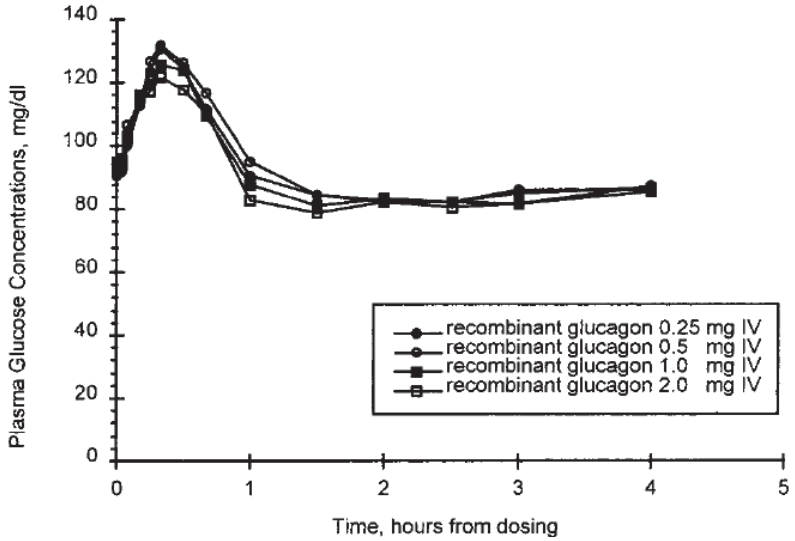


Figure 1 Mean blood glucose concentration versus time curves, all intravenous treatments.
*(Source: Graf et. al., (J. Pharm Sci, 1999; vol. **88**, No.10, Page 992)*

Further the PK and PD was compared for the IM and SC route and the absolute bioavailability was evaluated as compared to the IV glucagon. The mean glucagon concentrations suggest rapid absorption with either of the route of administrations (IM and SC), with maximum concentrations attained approximately 0.21 and 0.35 after dosing. Slight differences in glucagon concentrations were noted between the injection routes with higher plasma concentrations occurring after SC administration. All glucagon formulations produced nearly identical glucose response curves after SC or IM administration (Figure 2).

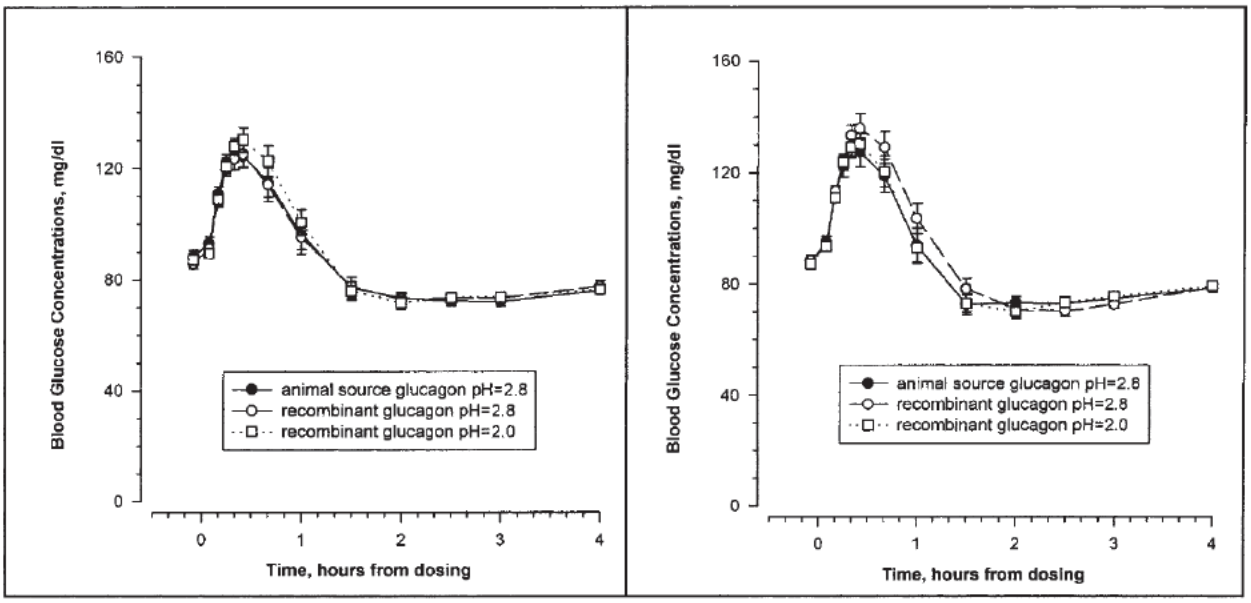


Figure 2 **Mean (±SE) blood glucose concentration versus time curves, all treatments. All glucagon doses were 1.0 mg. Left panel shows subcutaneous (SC) administrations; right panel shows intramuscular (IM) administrations**

(Source: Graf et. al., (J. Pharm Sci, 1999; vol. 88, No.10, Page 994)

Overall, the authors demonstrated that there is PK dose-proportionality of glucagon and that the glucose response appears to be saturated with even low doses of glucagon. Additionally, there appears to be no differences in the glucose profiles following either IM or SC route. Therefore, the clinical dose of 1 mg is ensured to achieve the maximum glucose response regardless of the route of administration.

Intranasal Glucagon:

Nasal glucagon is a combination product comprised of a [redacted] (b) (4) powder (drug powder) administered to the nasal mucosa via a delivery device.

Mean (± SD) PK (glucagon concentration-time in the left panel) and PD (glucose concentration-time in the right panel) profiles for intranasal glucagon are shown in Figure 3 below:

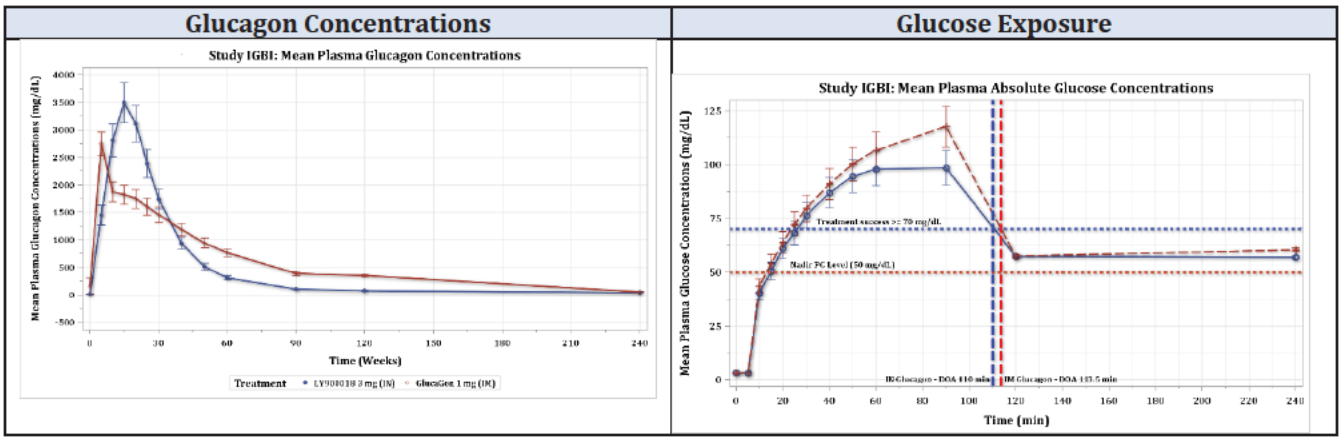


Figure 3 **Study IGBI: Mean Plasma Glucagon Concentrations and Glucose Exposure**

(Source: Reviewer generated plot)

Pharmacokinetics (Glucagon):

Glucagon was rapidly absorbed after nasal administration of 3 mg dose, and maximum glucagon concentrations (geometric mean of 6130 pg/mL) were attained by 15 minutes postdose and on average glucagon levels return to baseline by 90 minutes (Figure 3).

Pharmacodynamics (Plasma Glucose Increase From Baseline):

Mean glucose-time profiles shown in Figure 3 above show that the mean time to treatment success in adult patients with type 1 diabetes, defined as glucose concentrations above 70 mg/dL, was 16.2 and 12.3 minutes in the 3 mg IN and 1 mg IMG treatment groups, respectively. The mean maximum glucose increase was 140 mg/dL. The duration of action, defined as time after intra-nasal administration where glucose concentrations are maintained above 70 mg/dL, were similar for the 3 mg IN (110 min) and 1 mg IMG (113.5 min) treatment groups, respectively.

3.3 Clinical Pharmacology Questions

3.3.1 Does the clinical pharmacology information provide supportive evidence of effectiveness?

The data presented in this NDA provides supportive evidence of effectiveness for intranasal glucagon in the treatment of hypoglycemia (also see Clinical review by Dr. Lungu). However, there were questions as to whether the data provides a robust supportive evidence of effectiveness for IN-glucagon due to potency issues of the final formulation, and the final delivered dose being less than the claimed dose of 3 mg (also see Product Quality review by Dr. Ramaswamy. The Sponsor stated that a glucagon assay (b) (4) (NLT (b) (4)%), in conjunction with the (b) (4), results in not less than (b) (4) mg glucagon/device, a dose which they claimed to have produced a clinical response[1]. Due to issues that relate to the interpretability of the study findings and practical utility of the product that could deliver less than the claimed dose, the review of this application also tried to answer the following questions from a worst-case scenario perspective:

(b) (4)

- **Does a 2 mg dose of IN-glucagon produce adequate clinical response?**
- **How do doses of 2 mg and 3 mg IN-glucagon compare to 1 mg IMG in terms of glucagon exposure and blood glucose concentrations?**

Interpretability of efficacy data due to final delivered dose of IN-glucagon being less than the labeled claim of 3 mg was a major review issue. The Sponsor was asked to address this issue through a series of information requests (IRs).

The Agency pointed out that it did not have enough information to agree to the Sponsor's conclusion that a dose of 2.0 mg glucagon/device had been confirmed to produce a clinical response. The Agency noted that the 2 mg dose of intranasal (IN) glucagon was evaluated in the dose finding study IGBA, where 4 out of 18 patients exposed to 2 mg IN glucagon showed no substantial serum glucagon concentrations, and also pointed out that the inter-patient variability in glucagon exposure with the 2 mg dose was greater when compared to the 3 mg dose. In addition, the 2 mg IN glucagon dose was further evaluated in Study IGBB, where 22 evaluable exposures to the 2 mg IN glucagon dose were reported (in 11 patients aged 4-<12), and that, in all cases, an increase in glucose by at least 25 mg/dL over nadir was achieved by 20 minutes. It was, however, not clear how these exposures to 2 mg in various studies compared with each other, and with the to be marketed product (used in Study IGBI) , as numerous batches with variable particle size, and different devices were used along the course of the clinical program.

To help clarify this issue, the Sponsor was asked to submit the efficacy and clinical pharmacology data for the patients exposed to 2 mg IN glucagon in the IN-Glucagon development program, as well as the batches used, particle size distribution, and device used for administration to better understand how each of these components contributes to efficacy. To help understand how this data was applicable to the to be marketed product, the Agency recommended that the Sponsor compare this with modelled exposure data with the to be marketed product at the 2 mg dose. Additionally, the Sponsor was asked to clarify whether the observed inter-patient variability with the 2 mg dose observed in study IGBA was related to device delivery problems, particle size, or other reasons. In addition, th Sponsor was asked to plot C_{max} and T_{max} as a function of particle size of the formulations used in studies IGBA, IGBG, IGBB, IGBC, and IGBI.

The material used to supply Study IGBA contained particles with a D90 ≤ (b) (4) µm, larger than particles produced with the commercial process as represented by the 3 mg material in Study IGBI (X90 ≤ (b) (4) µm). Smaller particle size would result in larger surface area, which might explain th higher C_{max} observed in Study IGBI compared to previous studies. A plot of particle size versus C_{max} or T_{max} showed no consistent relationship (Figure 4, Figure 5).

Does a 2 mg dose of IN-glucagon produce adequate clinical response?

The Sponsor simulated glucagon exposure and glucose response for patients administered a 2 mg dose of NG commercial drug product. In these simulations, the PK and PD parameters were fixed to the estimated values for Study IGBI, the clinical study using commercially representative drug product. Baseline characteristics of Study IGBI were applied in the simulation. Glucagon exposure and glucose response after NG 2 mg were simulated from 1,000 patients, including all sources of variability in the model.

The simulation results were used to assess probabilities of "treatment success" of NG 2mg (commercial drug product). Treatment success was defined as either an increase from baseline BG of at least 20 mg/dL at 30 minutes post-dose, or an increase in BG to at least 70 mg/dL at 30 minutes post-dose. The simulation results show that, for patients with a baseline BG of 40 mg/dL, at 30 minutes post-dose, a single dose of NG 2 mg would lead to 97% of patients achieving treatment success, with 97% having at least a 20 mg/dL

BG increase and 92% having BG increase to at least 70 mg/dL. The median BG increase after NG 2 mg treatment was 67 mg/dL.

How do doses of 2 mg and 3 mg IN-glucagon compare to 1 mg IMG in terms of glucagon exposure and blood glucose concentrations?

Based on the Agency's IR, the Sponsor generated the PK and PD profiles of model predicted NG 3 mg and NG 2 mg compared to commercially representative drug product and IMG 1 mg. The model-predicted PD response was based on a median baseline glucose of 40 mg/dL. Results showed that PK and PD profiles of NG 2 mg, 3 mg and IMG 1 mg are similar during the initial 30 minutes after dose administration (Figure 6-Figure 8).

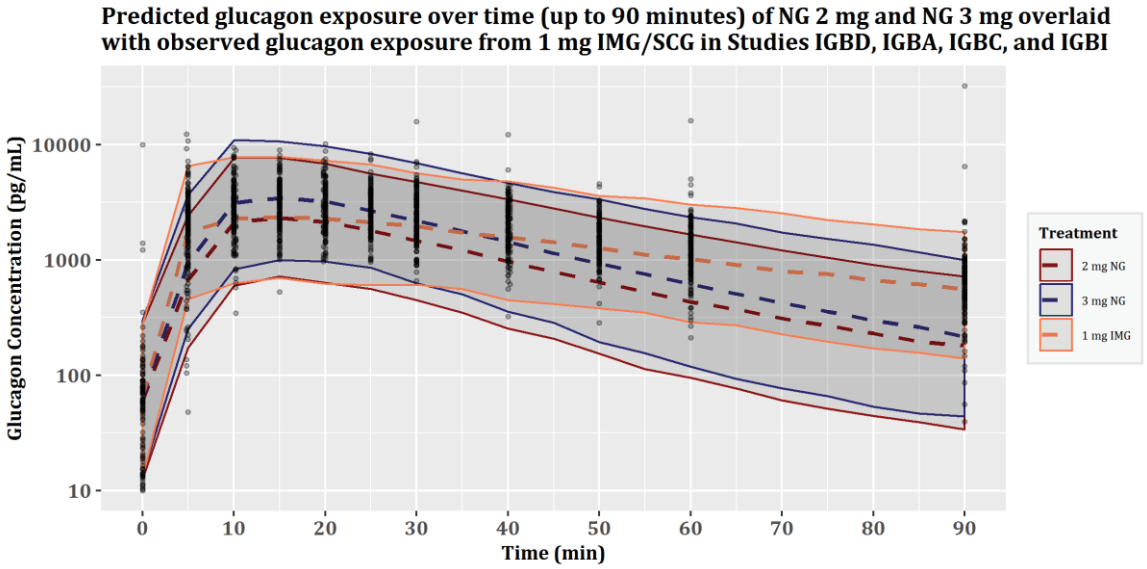


Figure 6 Predicted glucagon exposure over time (up to 90 minutes) of NG 2 mg, NG 3 mg overlaid with observed glucagon exposure from IMG/SCG 1 mg

(Source: Reviewer generated from data submitted as part of IR on 07 Mar 2018)

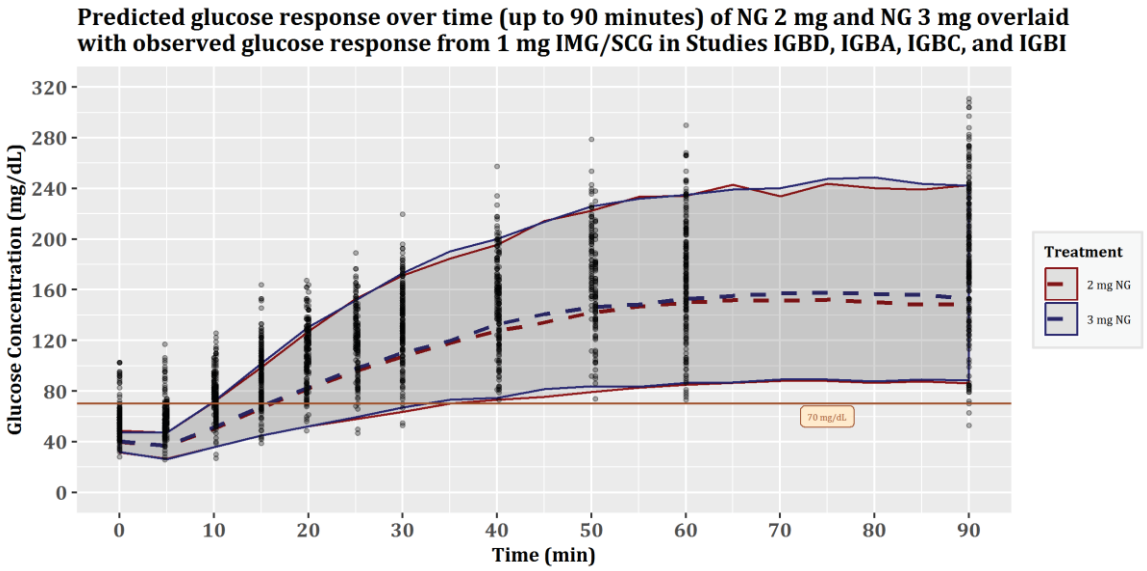


Figure 7 **Predicted glucose response over time (up to 90 minutes) of NG 2 mg, NG 3 mg overlaid with observed glucose response from IMG/SCG 1 mg**

(Source: Reviewer generated from data submitted as part of IR on 07 Mar 2018)

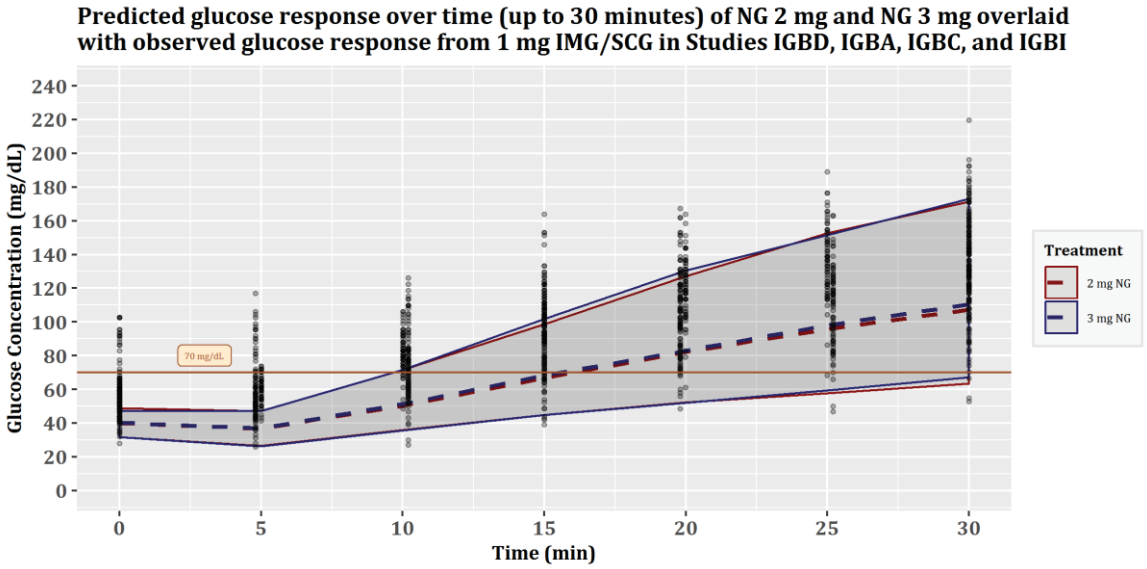


Figure 8 **Predicted glucose response over time (up to 30 minutes) of NG 2 mg, NG 3 mg overlaid with observed glucose response from IMG/SCG 1 mg**

(Source: Reviewer generated from data submitted as part of IR on 07 Mar 2018)

These graphical results are also supported by model predicted glucagon exposure and glucose response up to 30 minutes of administration of NG 3 mg, NG 2 mg, and IMG 1 mg summarized in Table 2. The PK exposure and PD response of NG 2 mg are comparable to that of IMG 1 mg at 30 minutes.

Table 2 Summary of Predicted PK and PD Parameters after Administration of NG 2 mg, NG 3 mg (with Commercially Representative Drug Product), and IMG 1 mg

Dose / Route	C_{max}[a] (pg/mL)	AUC(0-30 min)[a] (pg.h/mL)	$BG_{30\ min}$[a] (mg/dL)	Change from baseline to $BG_{30\ min}$[a]
3 mg / NG	6390 [59.3]	2090 [57.3]	117 [28.9]	73.5 [51.9]
2 mg / NG	4390 [61.1]	1410 [59.1]	112 [29.2]	68.6 [54.2]
1mg / IMG	4630 [61.0]	1640 [62.7]	118 [30.6]	74.6 [55.1]

Abbreviations: AUC(0-30min) = area under the concentration curve from time 0 to 30 minutes; BG_{30min} = blood glucose concentration at 30 minutes; C_{max} = maximum concentration; IMG = intramuscular glucagon; NG = nasal glucagon; PD = pharmacodynamics; PK = pharmacokinetics.

[a] Geometric mean [% coefficient of variation] is presented for C_{max}, BG_{30min} and AUC(0-30min).

(Source: Response to IR (111-quality-responses-to-questions-26-feb-2019), Table Q1-1, Page 6)

The PK/PD modeling demonstrates that NG 2 mg and NG 3 mg provide comparable glucagon exposure and glucose response to both simulated and observed IMG 1 mg data at 30 minutes. It is known that glucagon exposure and resulting glucose response reach saturation beyond certain dose. In case of IM administration, it was observed that saturation of response was observed beyond 0.25 mg. It appears from observed and modeled data in the NG glucagon program, that saturation of glucagon exposure and glucose response are observed at the 2 mg dose. This was also predicted from a dose-response curve (Figure 9).

However, this post-hoc analysis should only be restricted to scientific evaluation of the worst-case scenario and not be construed as the Agency's acceptance of any relaxed criteria towards the shelf-life related quality aspects of the product under question. Nor is it in the interest of the applicant to use this as an argument to choose/propose a relaxed criteria, as in long-term, it may create an issue for the applicant themselves in life-cycle management of their own product (e.g. bridging to their own product during manufacturing changes of the level that require bioequivalence demonstration). In addition, considering the life-saving nature of glucagon in the hypoglycemia related emergencies all efforts should be geared to ensure that the intranasal product is held to highest quality standards.

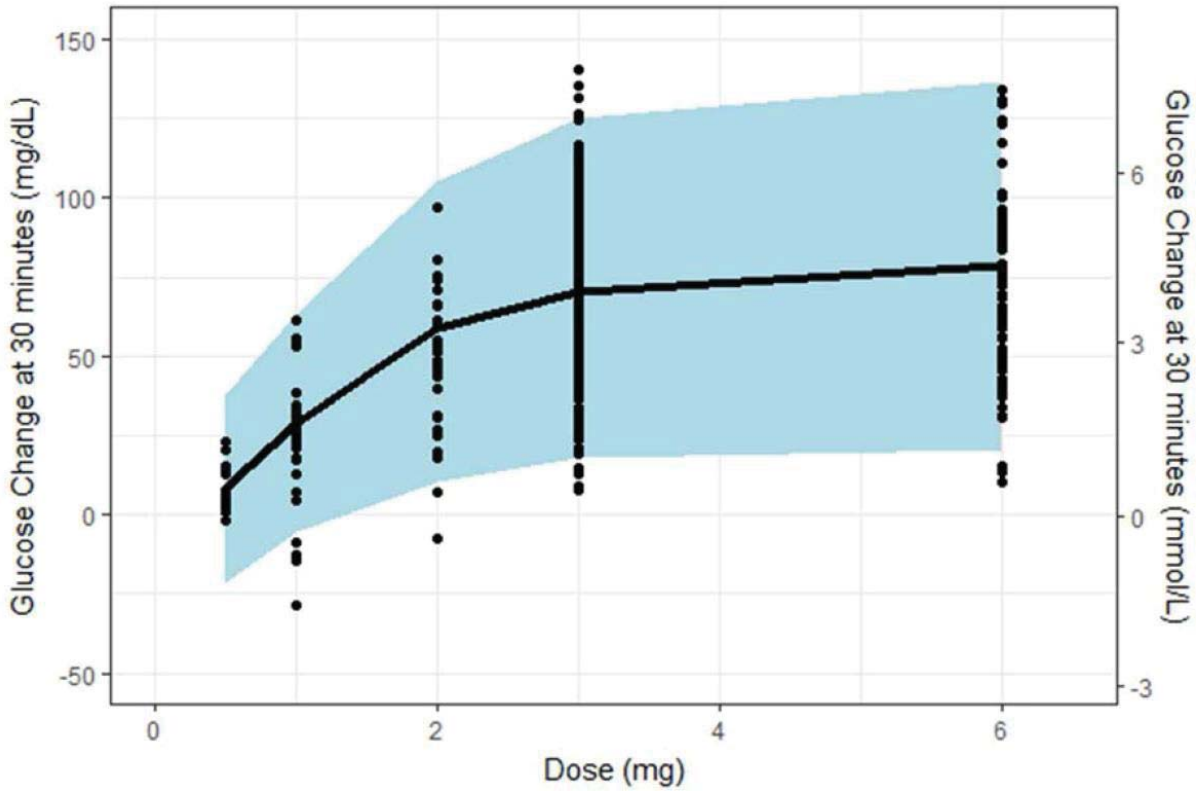


Figure 9 **Dose response (change from baseline of glucose at 30 minutes) of NG in adult population**

(Source: Module 2.7.2, Summary of Clinical Pharmacology Studies, Figure 2.7.2.1, Page 11)

3.3.2 Is the proposed general dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, based on modeling and simulation that the Sponsor provided in addition to the observed data from Study IGBI, the proposed general dosing regimen is appropriate for the general patient population for the treatment of severe hypoglycemia.

3.3.3 Is an alternative dosing regimen and management strategy required for subpopulations based on intrinsic factors?

After applying body-weight allometry scaling, age and gender had no impact on NG PK (Figure 10). Nasal glucagon 3 mg administered to all age groups of pediatric patients (4 to <8, 8 to <12, and 12 to <17 years) showed that in each group, NG 3 mg rapidly produced a maximal blood glucose increase, similar to that of weight-based IMG doses (0.5 mg or 1 mg). When nasal glucagon 2 mg and 3 mg were administered to 2 younger age groups (4 to <8, and 8 to <12 years), the 3 mg nasal glucagon produced a slightly higher glucose response than NG 2 mg. Pediatric patients showed similar tolerability to both NG 3 mg and NG 2 mg as weight-based IMG doses. An alternative dosing regimen and management strategy is not required for subpopulations based on intrinsic factors.

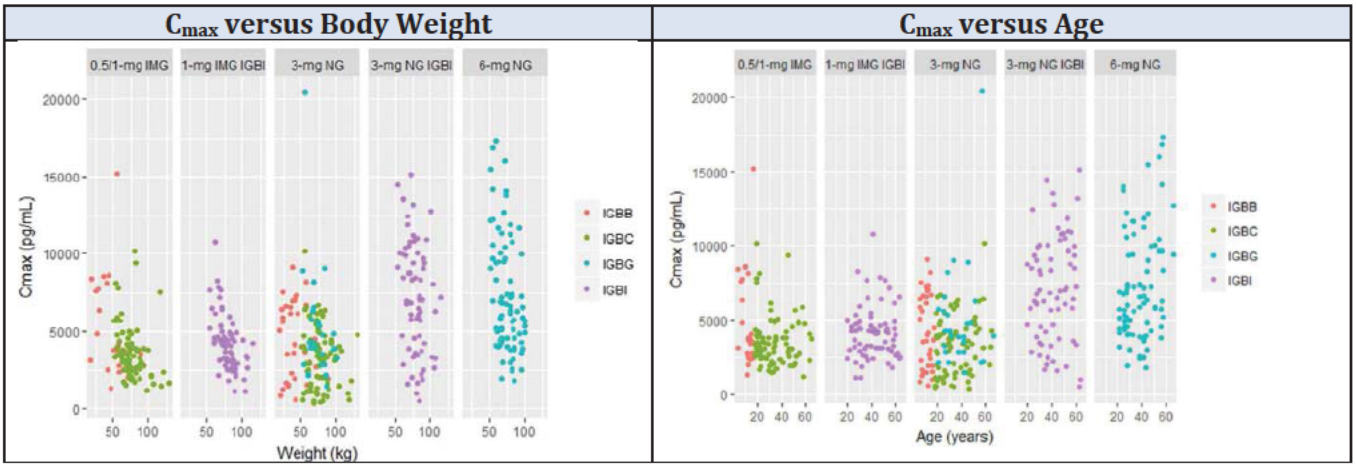


Figure 10 Scatter plot of C_{max} and T_{max} versus body weight (Studies IGBB, IGBC, IGBG, IGBI)
(Source: Module 2.7.2, Summary of Clinical Pharmacology Studies, Figure 2.7.2.24, Page 52, and, Module 2.7.2.5, Appendix to the Summary of Clinical Pharmacology Studies, Figure APP.2.7.2.4, Page 20)

3.3.4 Are there bioavailability differences between 3 mg NG and 1 mg IMG?

The relative bioavailability of Nasal (LY900018, 3 mg) or Intra-muscular (GlucaGen®, 1 mg) routes was evaluated in adult patients with type 1 diabetes mellitus (T1DM) during controlled insulin-induced hypoglycemia in Study IGBI. This was a multicenter, randomized, open-label, 2-treatment, 2-period, single-dose crossover study in 70 male or female patients 18 to 64 years of age with a diagnosis of T1DM for at least 2 years.

Subjects received one of the following treatments in a cross-over manner:

(a) A single 3-mg dose of nasal glucagon administered into 1 nostril with the patient lying fully reclined on their opposite side (that is, the patient was lying on their left side if the drug was administered into the right nostril). Nasal glucagon was supplied as a [redacted] (b) (4) powder contained within the nasal delivery device (lot numberC808058).

(b) A single 1-mg dose of GlucaGen® administered by IM injection into the deltoid muscle of the patient's nondominant arm while the patient was lying fully reclined on their opposite side (that is, the patient was lying on their left side if the drug was administered into the right arm). GlucaGen® was supplied as part of the GlucaGen® HypoKit® (Novo Nordisk A/S; prescribing information (lot number C829574). GlucaGen® was reconstituted with the provided diluent immediately prior to administration according to the instructions for use.

The primary objective of this study was to compare LY900018 (glucagon nasal powder or nasal glucagon) versus GlucaGen® in the percentage of adult patients with type 1 diabetes mellitus (T1DM) who achieve treatment success during controlled insulin-induced hypoglycemia.

The secondary objectives were to (a) assess the safety and tolerability of nasal glucagon versus GlucaGen®, (b) characterize the pharmacodynamics (PD) profiles of nasal glucagon versus GlucaGen®, and (c) characterize the pharmacokinetic (PK) profiles of nasal glucagon versus GlucaGen®.

The exploratory objectives of this study was to (a) characterize the PK profile of the dodecylphosphocholine (DPC) excipient of nasal glucagon, (b) assess the occurrence and severity of

hypoglycemia symptoms during controlled insulin-induced hypoglycemia, and (c) assess the awareness of hypoglycemia prior to its induction.

Glucagon:

Mean concentration-time profiles for glucagon from the two treatments are shown in Figure 11 below:

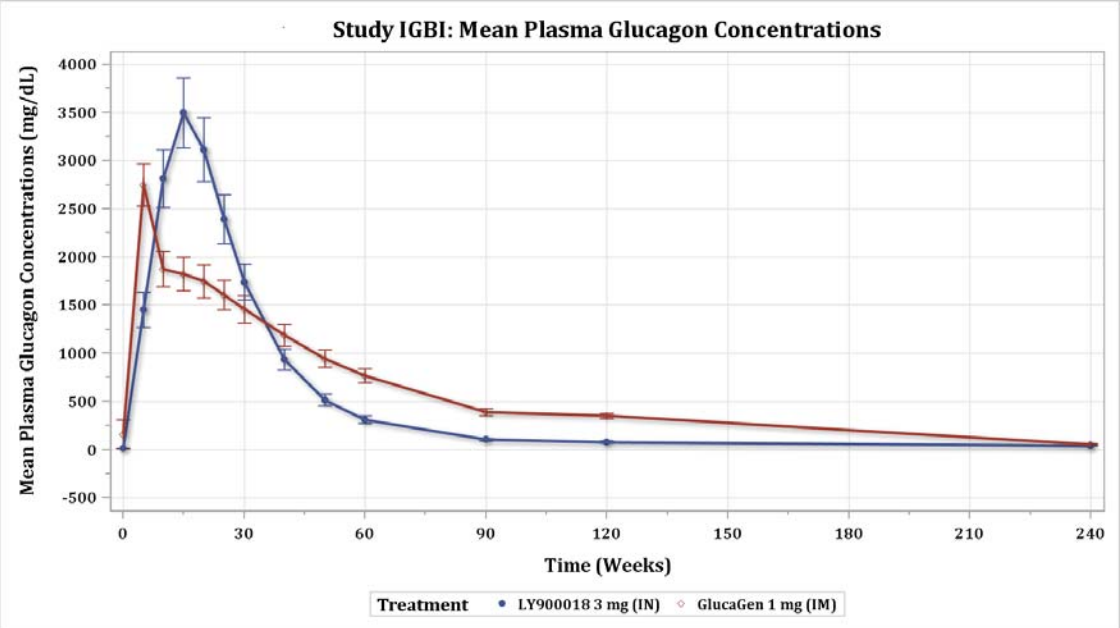


Figure 11 Study IGBI: Mean Plasma Glucagon Concentrations
(Source: Reviewer generated plot)

Glucagon was rapidly absorbed after both nasal and IM administration, and maximum glucagon concentrations were attained by 15 minutes postdose with both routes of administration. Nasal glucagon had a higher C_{max} compared to intramuscular GlucaGen® (geometric mean of 6130 pg/mL vs 3750 pg/mL, Figure 12), and it had a lower $AUC_{0\text{-tlast}}$ (2740 pg·hour/mL vs 3320 pg·hour/mL, Figure 13) and appeared to be cleared more rapidly. The median T_{max} was 15 minutes post-dose for both treatments (Figure 14).

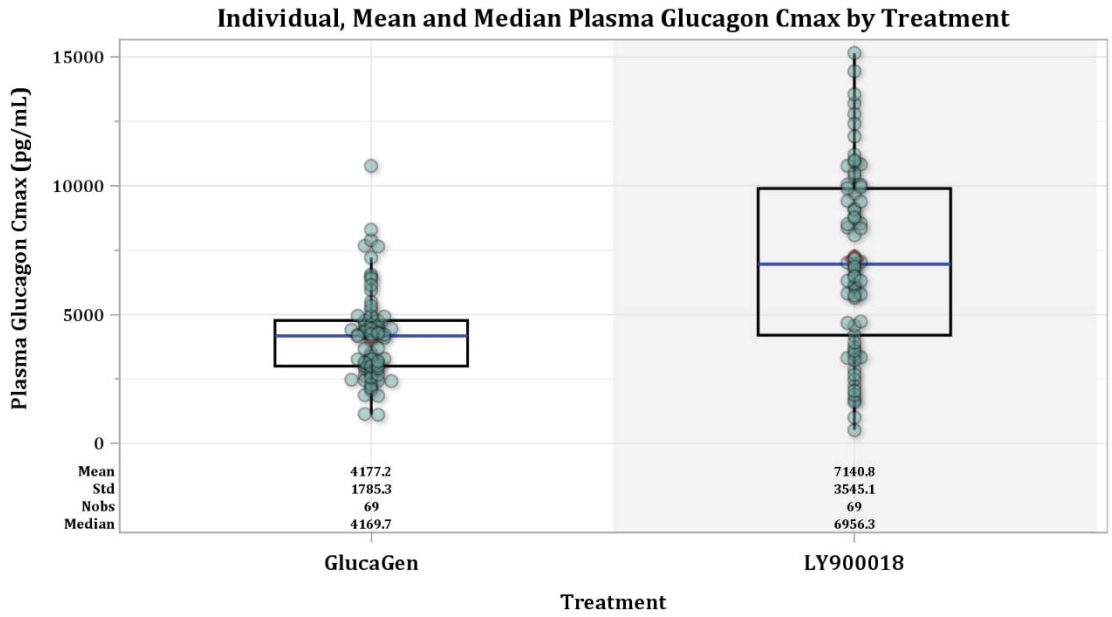


Figure 12 Individual, Mean and Median Plasma Glucagon C_{max} by Treatment

(Source: Reviewer generated plot)

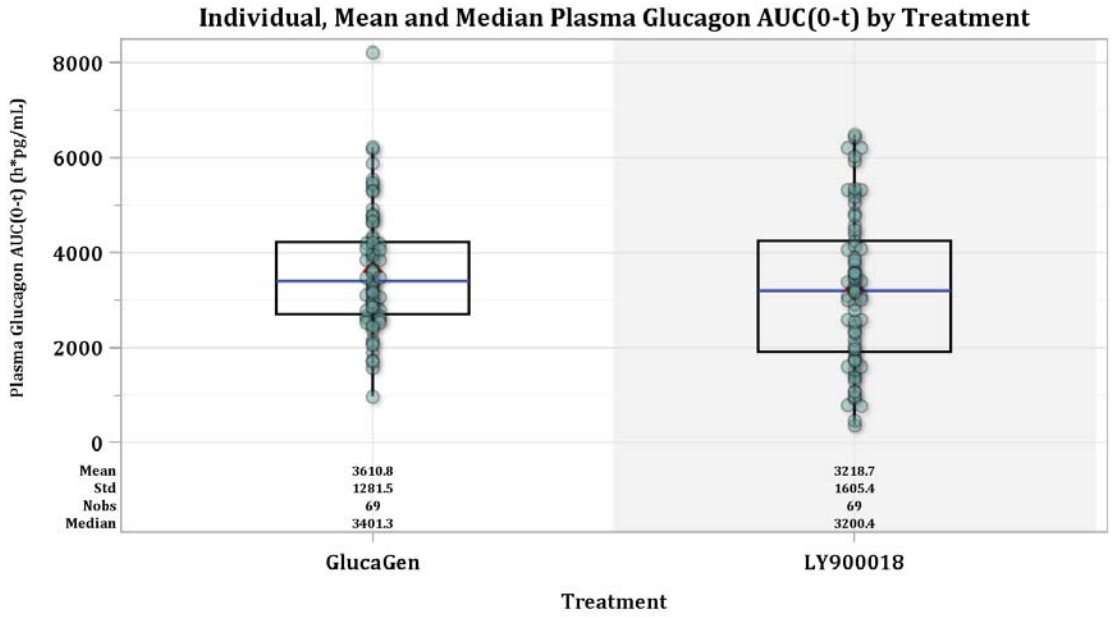


Figure 13 Individual, Mean and Median Plasma Glucagon $AUC_{(0-t)}$ by Treatment

(Source: Reviewer generated plot)

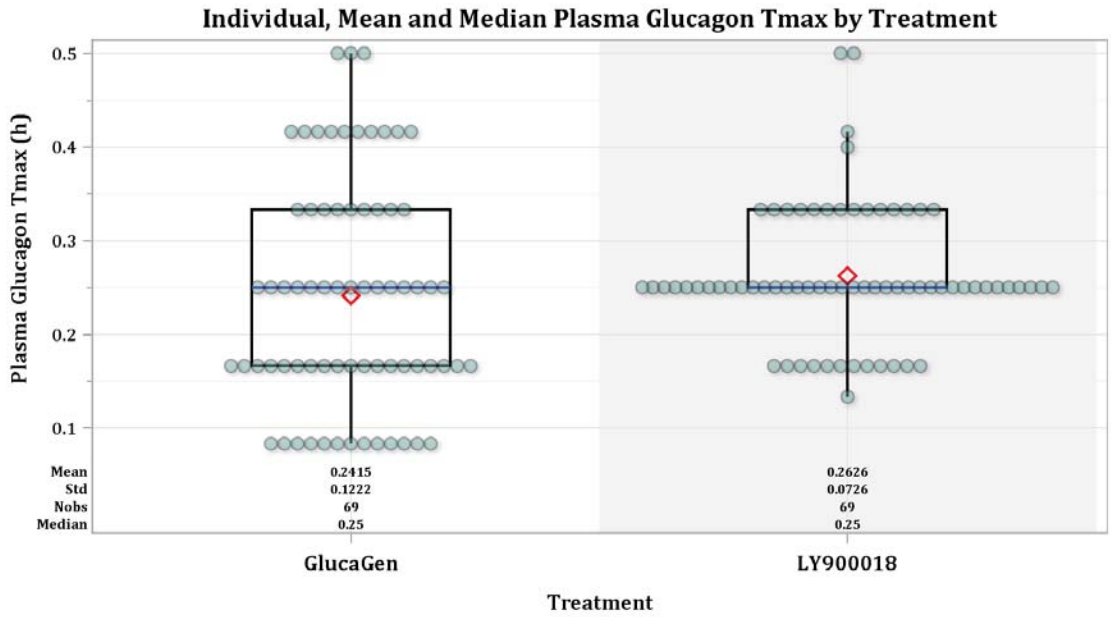


Figure 14 Individual, Mean and Median Plasma Glucagon T_{max} by Treatment
(Source: Reviewer generated plot)

A Forest plot of relative bioavailability of glucagon from 3 mg NG compared to 1 mg IMG is shown below in Figure 15:

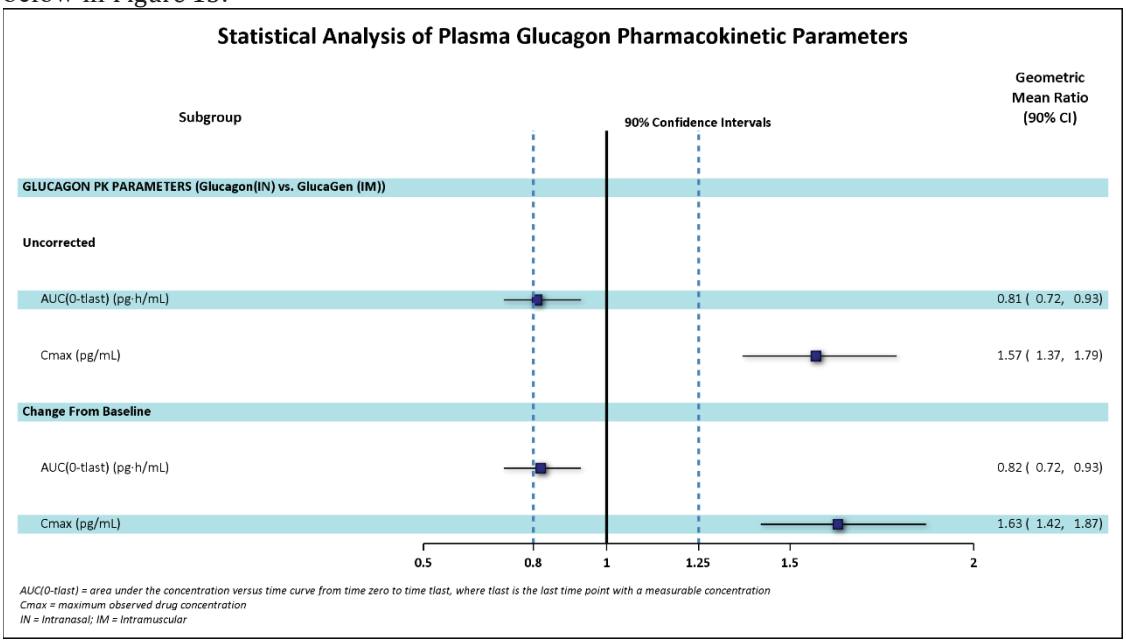
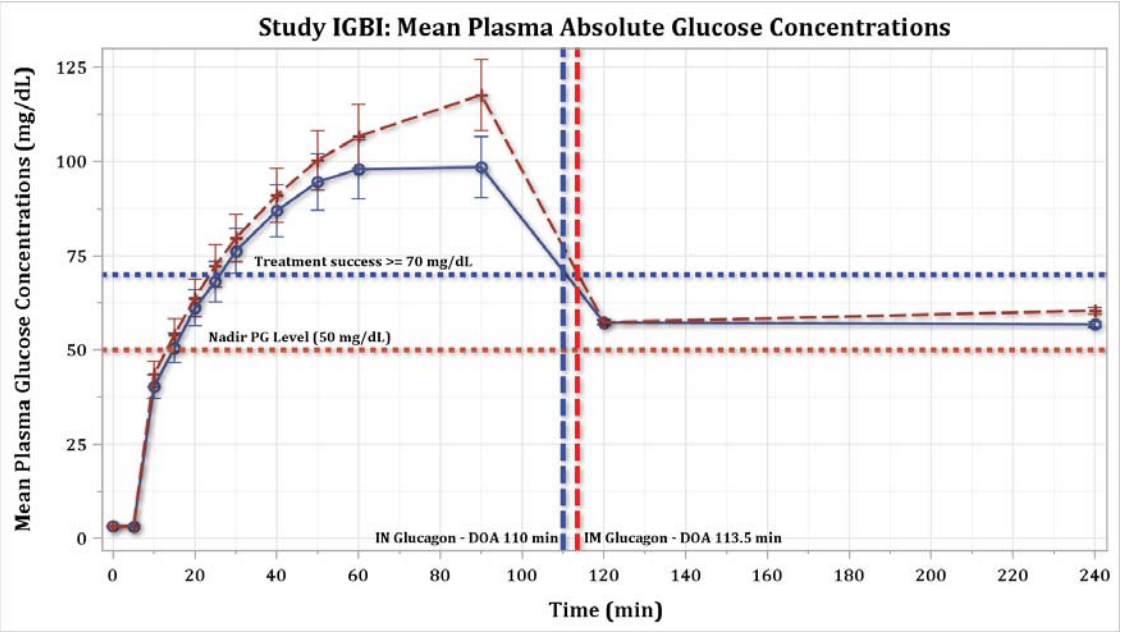


Figure 15 Statistical Analysis of Plasma Glucagon Pharmacokinetic Parameters
(Source: Reviewer generated plot)

Glucose:

Mean concentration-time profiles for glucose from the two treatments are shown in Figure 16 below:



PG = Plasma Glucose

Figure 16 Study IGBI: Mean Plasma Absolute Glucose Concentrations
(Source: Reviewer generated plot)

Similar plasma glucose responses were observed with both 3 mg nasal glucagon and 1 mg GlucaGen® for the first 40 minutes postdose. While a continuous increase of PG up to 1.5 hour was observed for 1 mg GlucaGen®, a plateau was reached for 3 mg nasal glucagon by 60 minutes. The mean time to treatment success in adult patients with type 1 diabetes was 16.2 and 12.3 minutes in the 3 mg IN and 1 mg IMG treatment groups, respectively. The mean maximum glucose increase was 140 mg/dL.

A cumulative distribution plot shows that more than 90% of the patients achieve treatment success within 15 minutes of dosing (Figure 17).

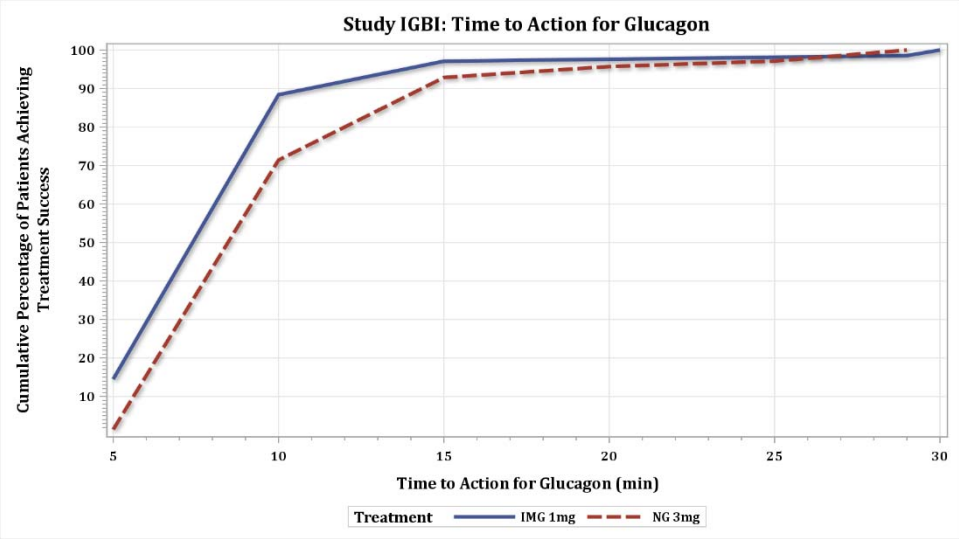


Figure 17 Cumulative Distribution Plot of Percentage of patients achieving treatment success following NG 3 mg or IMG 1 mg

(Source: Reviewer generated plot)

The BG_{max} change from baseline was statistically different between treatment groups: geometric LS mean values were 160.3 mg/dL and 131.2 mg/dL for 1 mg GlucaGen® and 3 mg nasal glucagon, respectively (Figure 18). The $AUC_{0\text{-}1\,5}$ change from baseline was also statistically different between treatments: geometric LS mean values were 154.90 mg·hour/dL and 132.83 mg·hour/dL for 1 mg GlucaGen® and 3 mg nasal glucagon, respectively (Figure 19). Median time to maximum blood glucose concentration was slightly earlier for the NG treatment compared to IMG treatment (Figure 20).

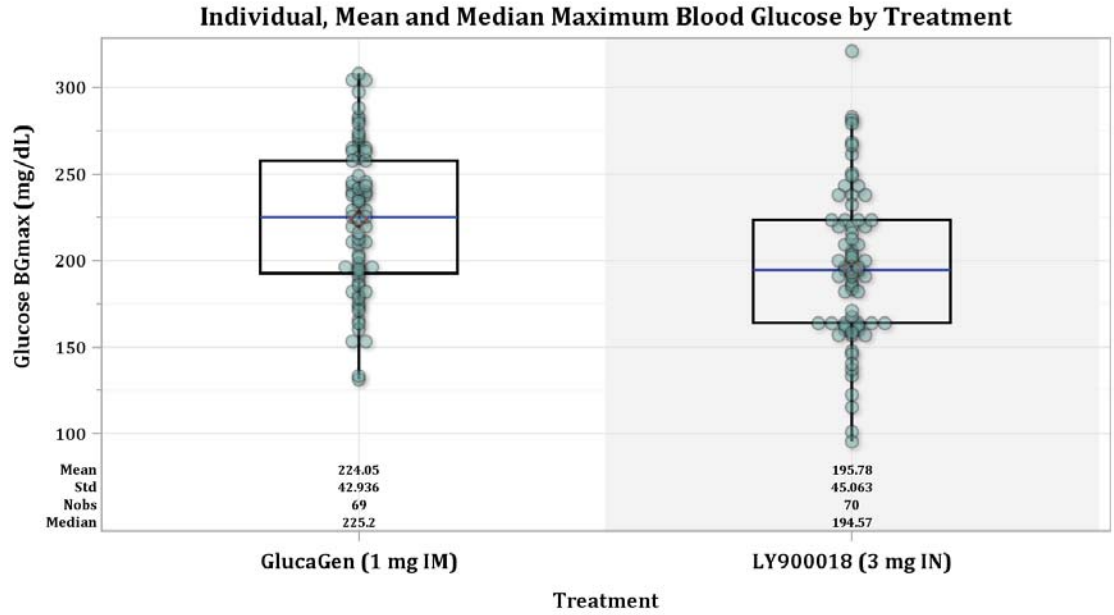


Figure 18 Individual, Mean and Median Maximum Blood Glucose by Treatment

(Source: Reviewer generated plot)

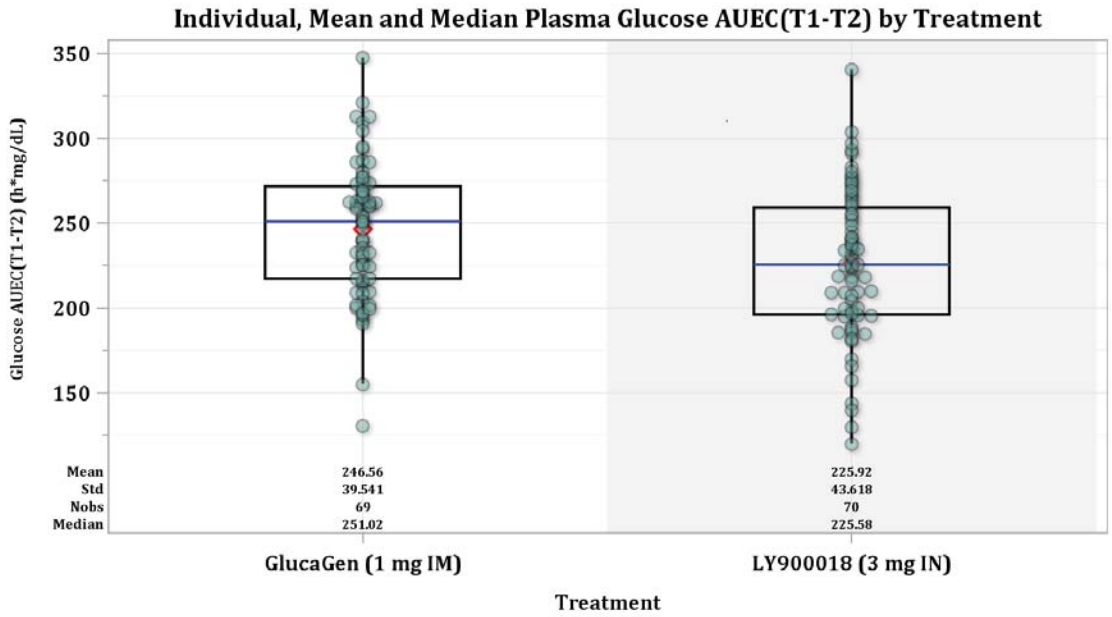


Figure 19 Individual, Mean and Median Plasma Glucose $AUEC_{(T1-T2)}$ by Treatment
(Source: Reviewer generated plot)

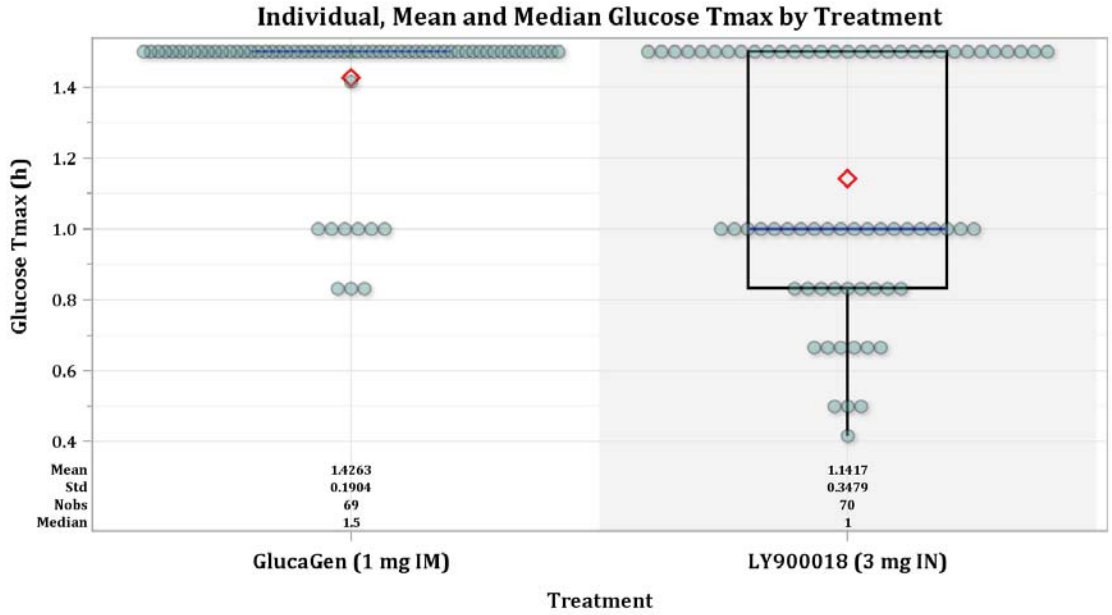


Figure 20 Individual, Mean and Median Time to Maximum Blood Glucose by Treatment
(Source: Reviewer generated plot)

A Forest plot of relative bioavailability of glucose from 3 mg NG compared to 1 mg IMG is shown in Figure 21 below:

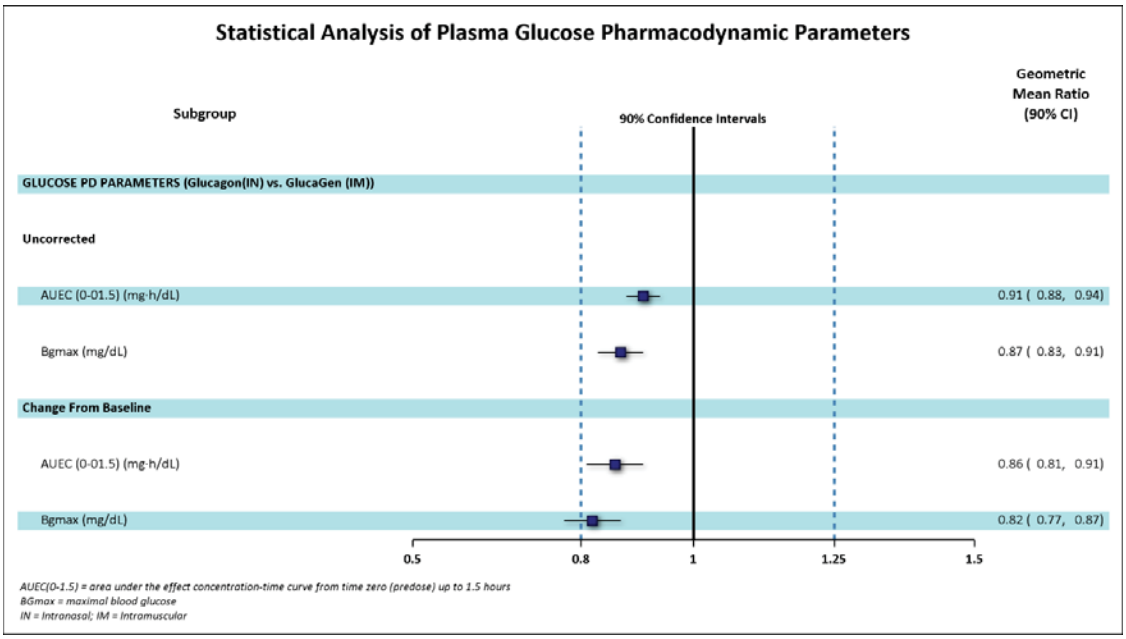


Figure 21 Statistical Analysis of Plasma Glucose Pharmacodynamic Parameters)
(Source: Reviewer generated plot)

Safety:

The majority of treatment emergent adverse events (TEAEs) were mild and none were classified as severe for either treatment. Overall, the number of patients reporting a TEAE and the number of TEAEs reported were generally similar between treatments. The most frequently reported TEAEs for both the 1 mg GlucaGen® and the 3 mg nasal glucagon treatment groups were nausea and vomiting, consistent with nausea and vomiting being the most common adverse reactions of currently marketed injectable glucagon products.

In the 3 mg NG group, 22 events of nausea were reported by 22 patients reported compared to 29 events of nausea reported by 29 patients receiving 1 mg IMG. Similarly 10 events of vomiting were reported by10 patients reported receiving 3 mg NG compared to 12 events of vomiting reported by 12 patients in the 1 mg IMG group (Figure 22).

The time of onset and the duration of nausea and vomiting TEAEs were generally comparable between treatment groups. The majority of nausea events resolved within 3 hours of onset for both treatments, and all events of vomiting in both treatment groups resolved within 4 hours of onset for both treatments.

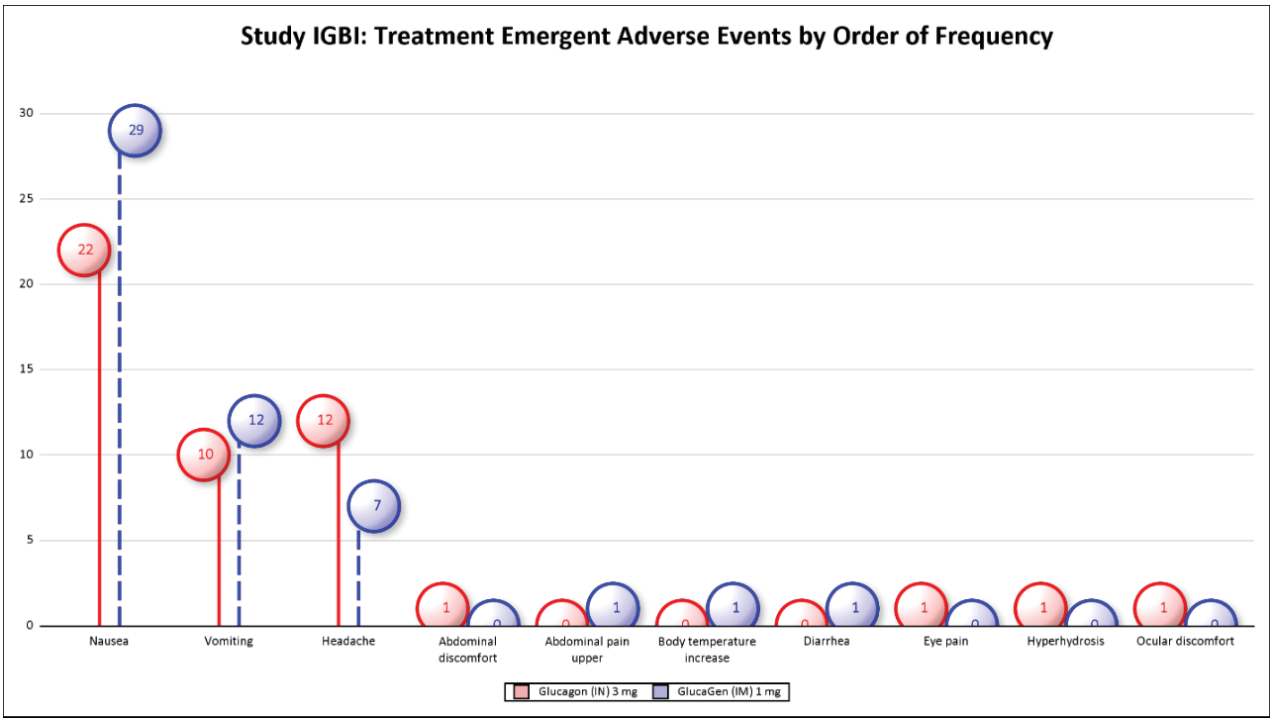


Figure 22 Study IGBI: Treatment Emergent Adverse Events by Order of Frequency
(Source: Reviewer generated plot)

3.3.5 Are there clinically relevant drug-drug interactions and what is the appropriate management strategy?

No drug-drug interaction studies were conducted with NG.

The current US label for GlucaGen list the following drug interactions relevant to treatment of severe hypoglycemia:

- Warfarin: glucagon may increase the anticoagulant effect of warfarin
- Beta-blockers: Patients taking beta-blockers might be expected to have a greater increase in both pulse and BP, which will be temporary because of glucagon's short half-life.
- Indomethacin: When used with indomethacin, glucagon may lose its ability to raise blood glucose or paradoxically may even produce hypoglycemia.

3.3.6 Do common cold and the concomitant administration of nasal decongestant affect the PK and PD of NG in otherwise healthy subjects?

The impact of nasal decongestant and common cold on NG 3 mg PK and PD was assessed in 36 otherwise healthy adults in Study IGBE.

In Cohort 1 of Study IGBE, 18 subjects (9 males, 9 females, mean age 32 ± 9 years) with nasal congestion due to common cold received a single NG 3 mg dose. After a 7- to 28-day washout period, and after being cold-symptom-free for at least 2 days, these subjects received a second NG 3 mg dose. In Cohort 2, 18 subjects (8 males, 10 females, mean age age 29 ± 8 years) with cold symptoms were given a dose of oxymetazoline, a nasal decongestant, in both nostrils 2 hours before a single NG 3 mg dose. This cohort did not receive a second dose of NG.

Glucagon:

Mean concentration-time profiles for glucagon from the two treatments are shown in Figure 23 below:

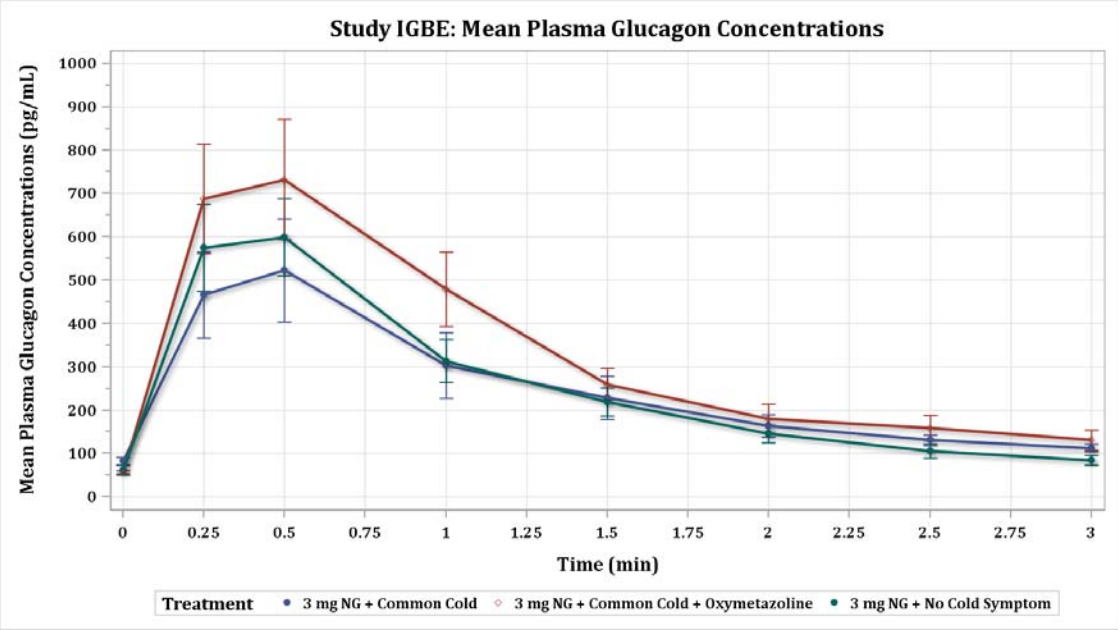


Figure 23 Study IGBE: Mean Plasma Glucagon Concentrations
(Source: Reviewer generated plot)

Administration 3 mg NG during Common Cold symptoms resulted in higher glucagon concentrations compared to administration of 3 mg NG during Common Cold pre-treated with oxymetazoline or 3 mg NG during Cold free symptoms. Higher AUC_{0-t} and C_{max} were observed for 3 mg NG during Common Cold symptoms, with similar T_{max} across treatments.

Glucose:

Mean concentration-time profiles for glucose from the two treatments are shown in Figure 24 below:

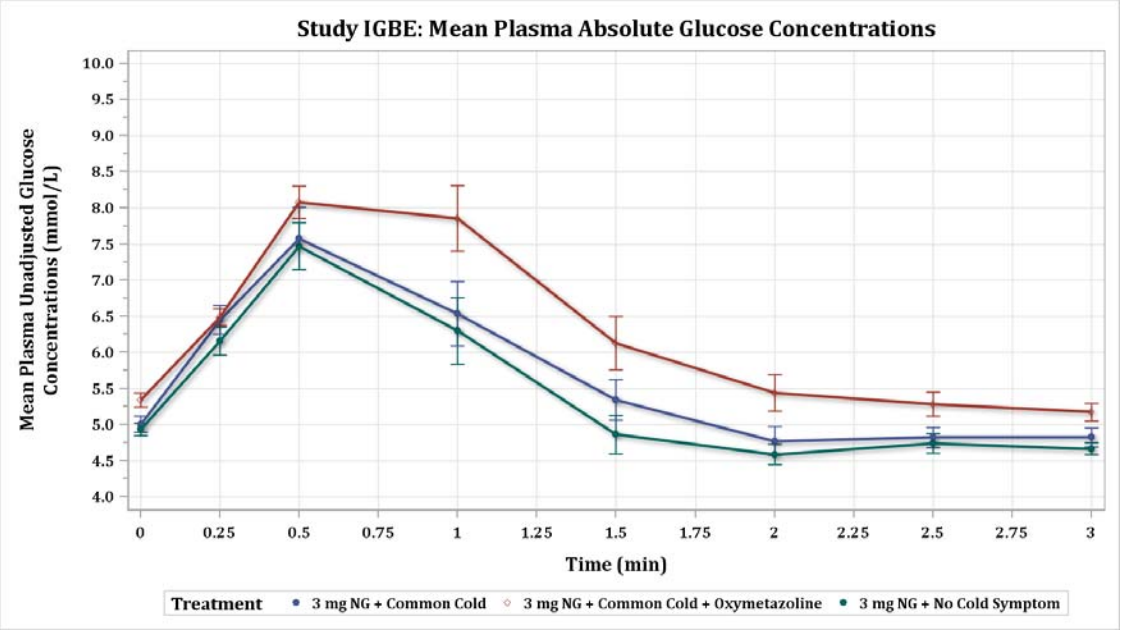


Figure 24 Study IGBE: Mean Plasma Absolute Glucose Concentrations
(Source: Reviewer generated plot)

The PD profile of 3 mg NG when administered during the symptoms of Common Cold was comparable to the other two treatments, both in terms of AUC_{0-t} and C_{max}.

3.3.7 Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support the to-be-marketed formulation?

The formulation of the pivotal trial IGBI is identical to the proposed commercial formulation (Table 3).

Table 3 Unit Formula for Nasal Glucagon Drug Powder

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

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

(b) (4)

(Source: Module 3.2.P.1, Description and Composition of the Drug Product, Table 3.2.P.1-1, Page 1)

4. APPENDICES

4.1 Bioanalytical Method Report

Pharmacokinetic samples to measure glucagon concentrationsused 3 different methods over the course of clinical development. The initial bioanalytical method was a validated enzyme-linked immunosorbent assay (ELISA). The second method was a radioimmunoassay (RIA). The final method was a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) assay. These assays measured both endogenous and exogenous glucagon.

Only details of the LC-MS/MS assay used in the pivotal study IGBI will be discussed in this section.

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 10.0 pg/mL to 500.0 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. The lower limit of quantitation was 10.0 pg/mL. The inter-assay accuracy (% RE) during validation ranged from -1.7% to 2.4%. The inter-assay precision (%CV) during validation ranged from 3.7% to 6.2% (Table 4). Quality control samples across the standard curve range were included in each sample analysis batch. Plasma samples with concentrations of glucagon above the upper limit of quantitation of 500.0 pg/mL were determined by up to a 5-fold dilution. Incurred sample reanalysis was also conducted for Study IGBI, the results demonstrating a passing rate of 95.2%, which is within acceptable method performance based on the established acceptance criteria for incurred sample reanalysis.

Table 4 Method Validation Parameters for Plasma Glucagon

Method/Validation	Analyte	Matrix	Validation Range (pg/mL)	Inter-Assay Precision (%CV)	Inter-Assay Accuracy (%RE)	Stability Data
LC-MS/MS GUO-V4-519	Glucagon	Plasma + inhibitors + phosphoric acid	10 to 500	3.7% to 6.2%	-1.7% to 2.4%	3 freeze/thaw cycles at -80°C. 11.7 hours at 4°C. 504 days at -80°C.

(Source: Module 2.7.1.4, Appendix to the Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table APP.2.7.1.4, Page 8)

During the NG clinical development program, plasma glucose was measured using qualified glucose assays, performed at central laboratories.

4.2 Sponsor's Modeling and Simulation Analysis

Due to the concern of the robustness of the supportive evidence of effectiveness for IN-glucagon due to potency issues of the final formulation, and the final delivered dose being less than the claimed dose of 3 mg., the sponsor was asked to conduct an exposure-response analysis for NG 2 and 3 mg compared to IMG 1 mg, through a modeling and simulation approach, and assess the effectiveness of NG 2 mg commercial product to support the shelf-life of NG 3 mg..

Six clinical studies with PK and and 5 clinical studies with PD data were included in the exposure-response analysis (Table 5). These studies included doses ranging from 0.5 mg to 6 mg. The proposed commercial dose of 3 mg was studied with commercially representative drug product in Study IGBI. The NG 2 mg dose was administered in 3 studies using clinical trial drug product; NG 2 mg was not administered in any study as commercially representative drug product.

Table 5 Index of Clinical Studies of Nasal Glucagon used in Population PK and Exposure-Response Analyses

Brief Description of Study	Trial Alias	Insulin induction
Dose Selection Studies		
Single dose (0.5, 1, 2 mg NG; 1 mg SCG) in healthy adult subjects	IGBD	No
Single dose (1, 2, 3 mg NG; 1 mg SCG) in adult T1D	IGBA	Yes
Single (3 mg NG) and double dose (6 mg NG) in adult T1D and T2D	IGBG	No
Single dose (2, 3 mg NG; 0.5/1 mg IMG) in pediatric T1D	IGBB	Yes
Dose Confirmation Studies		
Single dose (3 mg NG; 1 mg IMG) in adult T1D and T2D	IGBC	Yes
Single dose (3 mg NG; 1 mg IMG) clinical bridging and confirmatory study in adult T1D	IGBI	Yes

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

Note: Insulin induction refers to studies where blood glucose was lowered with insulin prior to glucagon administration. All 6 study were included in the PK modeling. Study IGBD was excluded from PD modeling due to limited exposures to 0.5 mg and 1 mg NG which precluded defining the exposure-response relationship.

(Source: Population PK and PD Analyses of Nasal Glucagon Studies IGBA, IGBB, IGBC, IGBD, IGBG, and IGBI, Table 7.1, Page 12)

Note: Text in Section 4.2 of this review with a light background should be inferred as copied from the sponsor's document.

Model Development: PK

Base Model Development

A one-compartment model was used to describe the glucagon concentration data. Estimates of the PK parameters and error terms were obtained by fitting the concentration-time data by means of the nonlinear mixed-effects modeling program NONMEM Version 7.4.2 (ICON Development Solutions, Hanover, MD). The first order conditional (FOCE) with epsilon-eta interaction estimation method was used for all analyses (NONMEM User's Guide, Part VII). The interpatient variability was assumed to be log-normally distributed, and variability terms were investigated for all parameters. Covariance between parameters was assessed using an omega block. In addition, 2 residual error models – proportional and combined additive and proportional – were also evaluated. Since many subjects/patients received multiple doses of glucagon (one dose of IMG/SCG and one dose of NG, or multiple doses of NG at different occasions), the inter-occasion variability (IOV) was also evaluated.

Selection of the most appropriate PK base model structure was based upon agreement between predicted and observed glucagon concentrations, lack of pattern (that is, randomness) in the weighted residuals versus the predicted values, changes in the inter-patient variability, and significant decreases in the minimum objective function (MOF).

A visual predictive check (VPC) was also performed on the base model to investigate the agreement between the observed and predicted concentrations.

Precision of parameter estimates was evaluated through bootstrapping of the final base model to confirm that all PK parameters were well estimated. A VPC was also performed on the final model to investigate the agreement between the observed and predicted concentrations.

Covariate Model Development

Upon establishment of an appropriate structural and statistical model, the effect of patient factors and Study ID was assessed for their clinical relevance on the disposition of glucagon. IMG PK appears to be correlated with body weight (Summary of Clinical Pharmacology Studies, Figure 2.7.2.24); therefore, standard allometry scaling factors were applied to CL and V. The injectable glucagon (IMG or SCG) showed a similar PK profile. Hence, IMG and SCG were grouped together as injectable glucagon (IMG/SCG). Bioavailability (F) and Rate of absorption (Ka) were estimated separately for injectable glucagon versus NG. Study ID, including commercially representative drug product and clinical trial drug product, was assessed. Baseline glucagon was also assessed in the model.

A listing of factors and the specific PK parameters on which they were tested are specified in Table 6.

Table 6 Factors Assessed in the Population Pharmacokinetic Analysis

Covariate	Type	Parameters Tested
Age	Continuous	F, Ka, CL/F, V/F, BLCGC
Gender	Categorical	F, Ka, CL/F, V/F, BLGCG
Study ID	Categorical	F, Ka

Abbreviations: BLGCG = baseline glucagon; CL/F = apparent clearance; F = bioavailability; Ka = absorption rate constant; V/F = apparent volume of distribution.

(Source: Population PK and PD Analyses of Nasal Glucagon Studies IGBA, IGBB, IGBC, IGBD, IGBG, and IGBI, Table 7.2, Page 17)

Potentially significant covariates were then tested individually for their effect on each of the relevant model parameters (for example, CL only, V only) using NONMEM 7.4.2. If a covariate was selected on more than 1 parameter, the covariate was tested in combination on the parameters (for example, CL and V, in combination).

Continuous covariates were tested using linear, power, or exponential models as shown in Equation 1 through Equation 3. Categorical covariates were tested using a categorical model, as shown in Equation 4 below.

Linear Model	$P = \Theta_1 \cdot (1+ \Theta_2 \cdot (COV-MED))$	Equation 1
Power Model	$P = \Theta_1 \cdot (COV/MED)^{\Theta_2}$	Equation 2
Exponential Model	$P = \Theta_1 \cdot EXP(\Theta_2 \cdot (COV-MED))$	Equation 3
Categorical Model	$P = \Theta_1 \cdot (1+ \Theta_2 \cdot IND)$	Equation 4

where P is the individual's estimate of the parameter (for example, CL, V), Θ_1 represents the typical value of the parameter, Θ_2 represents the effect of the covariate, COV is the value of the covariate, and MED is the population median of the covariate. IND is an indicator variable with a value of either 0 or 1 assigned for values of a dichotomous categorical covariate (for example, female or male) and 1 to *n* for various values of a categorical covariate ranging from 1 to *n*, where *n* is the number of categories (for example, *n* geographies).

A full model was developed by combining the covariates individually identified as significant in the covariate selection step. Highly correlated or physiologically related factors were evaluated separately and the covariate with the greatest drop in the MOF was retained.

Once a full model was established, the significance of the potential covariates was evaluated using backward elimination. Beginning with the full model, each covariate was individually removed and its effect on the MOF evaluated. The least significant covariate not resulting in an increase □10.828 points ($p<0.001$) was dropped. This process was repeated, applying the same reduction technique and criterion, until all remaining covariates were deemed statistically significant and relevant to the model. The next step was to evaluate the increase in the interpatient variability on the omission of each covariate, to determine whether the covariate met the 5% criterion for inclusion in the final model.

Final Model Development

The final model was developed taking into account the following criteria:

- Convergence of the estimation and covariance routines
- Reasonable parameter and error estimates based upon the known PK of glucagon
- Good precision of the parameter and error estimates
- Statistically significant difference in MOF (criterion: ≥10.828 point drop in MOF ($p<0.001$) for 1 degree of freedom)
- Decrease in the inter-individual variability (IIV) in the relevant parameters of >5%
- Agreement between predicted and observed glucagon concentrations, as assessed by visual inspection
- Random distribution of the weighted residuals versus the predicted values, as assessed by visual inspection
- Clinical relevance of the change in the parameter estimate caused by the addition of the covariate in the model.

Bootstrap

A bootstrap analysis was performed to assess the precision of the final parameter estimates of the final model. The bootstrap was carried out by sampling from the analysis dataset with replacement, to produce resampled datasets with the same number of patients. A total of 500 bootstrap datasets were created in this way, and the model fit to each one. The 95% confidence intervals (CIs) for each parameter were calculated using the 2.5th and 97.5th percentile values from the distribution of bootstrap parameter values.

Visual Predictive Check

A VPC was performed on the model to ensure that the model maintained fidelity with the data used to develop it. The VPC approach entails simulating PK data with the developed model, taking into account variability in all parameters as given by the IIV, IOV, and residual error terms. The distributions of simulated concentrations, conditional on the posterior distribution of model parameters, were compared to the observed distributions to ensure concordance. Simulated and observed distributions were compared by calculating the median, 5th, and 95th percentiles for each. Prediction-correction of VPCs were applied, where appropriate (Bergstrand et al. 2011), to allow comparison of model performance across dosing regimens.

Model Development: PD

The same model development and validation processes used for PK were adopted for the PD model. An indirect response model was used to describe the glucose response. PD modeling: The relationship between glucagon plasma concentration (Cg) and changes in glucose (Glu) was described by an indirect response model (Equation 5).

$$\frac{dGlu}{dt} = K_{in} \times \left(1 + \frac{E_{max} \times Cg}{EC_{50} + Cg}\right) - k_{out} \times Glu \qquad \text{Equation 5}$$

where K_{in} and K_{out} are the production rate and elimination rate of glucose, respectively. It is assumed that glucagon plasma concentration (Cg) increases the production rate of glucose. Emax (stimulation maximum) is the maximum effect that glucagon can achieve upon K_{in}, and EC50 is the glucagon plasma concentration that results in 50% of Emax increase on K_{in}. Note: At predose, the production and elimination of glucose is at steady state, therefore $K_{in} = K_{out} *$ baseline glucose.

Due to the use of different strategies to lower glucose, the above system was not at steady state at the time of baseline glucose measurements. This meant that the usual initialization of the system to the ratio of Kin to Kout for an indirect response model could not be used. Therefore, the system was initialized to the observed baseline glucose measurements, whilst the typical steady state parameters (Kin and Kout) were estimated.

Covariate Model Development

Upon establishment of an appropriate structural and statistical model, the effect of patient factors was assessed for their clinical relevance on the glucose response of NG. A listing of patient factors and the specific PD parameters on which they were tested are specified in Table 7. Baseline glucose was also assessed in the model.

Table 7 Patient Factors Assessed in the Population Pharmacodynamic Analysis

Covariate	Type	Parameters Tested
Age	Continuous	KOUT, EMAX, EC50
Body Weight	Continuous	KOUT, EMAX, EC50
Gender	Categorical	KOUT, EMAX,EC50
Study pooling[a]	Categorical	KOUT, EMAX, EC50
Baseline Glucose	Continuous	KIN, EMAX, EC50
Insulin induction	Categorical	KOUT

[a] Studies with similar patient groups were pooled together in the covariate testing. Studies IGBA, IGBC, and IGBI formed one study stratification category; Studies IGBB and IGBG were separate categories.

Abbreviations: 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.

Note: Insulin induction refers to studies where blood glucose was lowered with insulin prior to glucagon administration. These are Studies IGBA, IGBB, IGBC, and IGBI.

(Source: Population PK and PD Analyses of Nasal Glucagon Studies IGBA, IGBB, IGBC, IGBD, IGBG, and IGBI, Table 7.3, Page 19)

Insulin was administered to some patients as a means to lower their BG prior to administration of glucagon. To empirically account for carryover of the insulin effect in the absence of insulin PK measurements, an exponential reduction of this effect on glucose Kout was implemented. This empiric description is shown below.

$$Kout_t = Kout_{ss} \times (1 + Ins_{eff} \times exp^{-k \times t})$$

Where $Kout_t$ is the elimination rate constant of glucose at time, t; Koutss is (steady-state) elimination rate constant in the absence of insulin induction; k is the rate of decay of the insulin effect; and t is time after the glucagon dose.

Results:

PK:

Model parameters are given in Table 8.

Table 8 Pharmacokinetic Parameters in Base Population Model

Parameter Description	Population Estimate (%SEE, 95% CI[a])	Inter-Patient Variability (%SEE[b])
Bioavailability		
F1 for IMG/SCG	1 (FIXED)	NE
Rate of Absorption		
Ka (hr^{-1}) of IMG/SCG	1.39 (4.35%, 1.28 - 1.49)	NE
Absorption Lag for NG		
ALAG1	0.0673 (0.98%, 0.0662 - 0.0688)	NE
Clearance		
CL/F (L/hr)	363 (4.27%, 341 - 391)	29.9% (23.4)
Volume of Distribution		
V/F (L)	37.3 (5.95%, 33.6 - 41)	49.6% (20.3)
Baseline Glucagon		
BLGCG (pg/mL)	64.3 (5.69%, 58.2 - 72.1)	107.2% (15.7)
Covariates		
Effect of Nasal administration on F1[c]	-0.843 (1.46%, -0.864 - -0.819)	
Effect of Nasal administration on Ka[d]	0.698 (12.7%, 0.541 - 0.876)	
Effect of study IGBG and IGBI on F1[c]	0.809 (19.3%, 0.538 - 1.11)	
Effect of IGBG and IGBI on Ka[d]	0.304 (21.1%, 0.188 - 0.446)	
Inter-occasion Variability on F1	57.3% (12.1, 49.7 - 64.4)	
Inter-occasion Variability on Ka	48.6% (9.43, 43.1 - 53.2)	
Residual Error (proportional)	29.6 (2.52%)	

Abbreviations: CL/F = apparent clearance; F1 = bioavailability of NG relative to IMG/SCG; IMG = intramuscular glucagon; Ka = absorption rate constant; NE = not estimated; SEE = standard error of the estimate; V/F = apparent volume of distribution.

[a] 95% CI values obtained from bootstrap

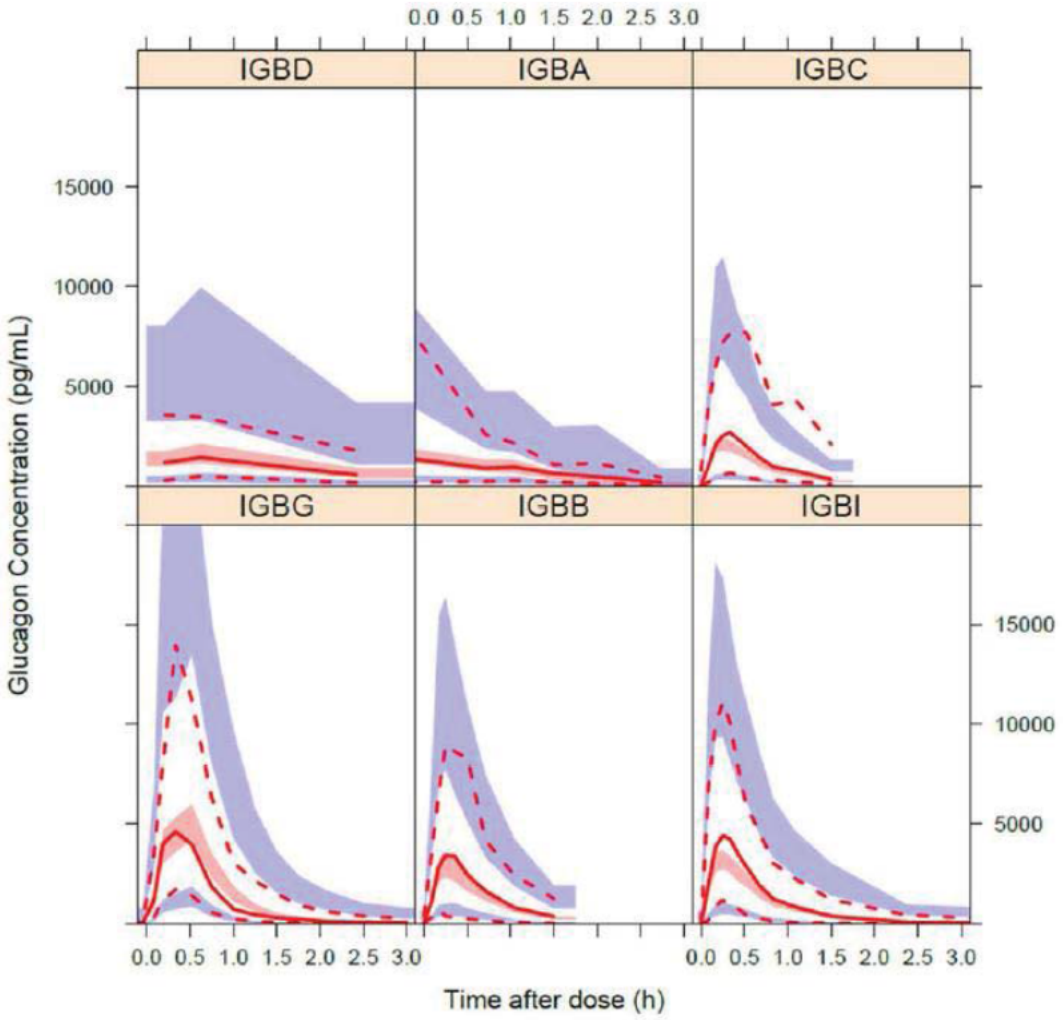
[b] Reported as %CV, calculated by the equation $100 \times \sqrt{e^{OMEGA(N)} - 1}$ where OMEGA(N) is the NONMEM output for the inter-subject variability of the N^{th} parameter

[c] $F1 = 1 \times (1 + I1 \times -0.843) \times (1 + I2 * 0.809)$, where I1 is set to 1 when route of administration is nasal and I2 is set to 1 when STDY = 4 (IGBG) or STDY = 7 (IGBI)

[d] $Ka = 1.39 \times (1 + I1 \times 0.698) * (1 + I2 * 0.304)$, where I1 is set to 1 when route of administration is nasal and I2 is set to 1 when STDY = 4 (IGBG) or STDY = 7 (IGBI)

(Source: Population PK and PD Analyses of Nasal Glucagon Studies IGBA, IGBB, IGBC, IGBD, IGBG, and IGBI, Table 8.2, Page 24)

Bootstrap results of the final model show that the parameters were estimated with reasonable precision, and the VPC shows the model fits the data well (Figure 25).



Note: The solid red line is the median and the dashed red lines are the 2.5th and 97.5th percentiles of the observed glucagon concentrations; the red shared region is the median and the blue shaded region is the 95% confidence interval of the 2.5th and 97.5th percentiles of the model-predicted glucagon concentrations.

Figure 25 Visual predictive check for the final PK model

(Source: Population PK and PD Analyses of Nasal Glucagon Studies IGBA, IGBB, IGBC, IGBD, IGBG, and IGBI, Figure 8.2, Page 26)

PD:

Model parameters are given in Table 9.

Baseline glucose has an effect on Emax and Kin. Lower baseline glucose was associated with higher Emax and lower Kin. This means there is a maximum BG concentration that a patient can achieve after glucagon administration. A higher baseline glucose brings a patient closer to that maximum; hence, the additive effect of glucagon administration on glucose elevation is reduced. A higher baseline glucose can be expected to be associated with a higher Kin since Kin is the endogenous glucose production rate. Study related covariates relative to IGBA, IGBC, and IGBI are:

- Studies IGBB and IGBG have 83% higher E_{max} and 32% lower K_{in}
- Study IGBG has 80% higher EC_{50}

Insulin induction reduced the glucose levels in patients by increasing Kout. The carryover effect of exogenously administered insulin on Kout starts at a relatively high value and then decreases

rapidly after the discontinuation of insulin administration.

Table 9 Pharmacodynamic Parameters in Final Model

Parameter Description	Population Estimate (%SEE, 95% CI[a])	Inter-Patient Variability % (%SEE[b])
KIN (h^{-1}) [c]	104 (1.77%; 73.9, 120)	-
KOUT ($mg/dL.h^{-1}$)	1.11 (4.32%; 0.964, 1.36)	41.5 (11.6%; 33.9, 49.4)
EMAX	1.98 (4.38%; 1.53, 3.27)	-
EC50 (pg/mL)	551 (12.9%; 254, 919)	226 (12.0%; 163, 430)
Insulin effect on Kout	4.48 (9.67%, 3.10, 5.39)	47.6 (19.3%; 35.7, 49.4)
Half-life of insulin effect (h)	0.0548 (7.81%; 0.0467, 0.0691)	-
Covariate Impact		
Baseline glucose on KIN	0.00383 (11.8%; 0.00188, 0.00687)	
Baseline glucose on EMAX	-0.00277 (22.1%; -0.00573, -0.00041)	
Increase in EMAX for IGBB and IGBG	0.83 (16.5%; 0.0983, 1.66)	
Decrease in KIN for IGBB and IGBG	-0.315 (7.14%; -0.455, -0.0362)	
Increase in EC50 for IGBG	0.804 (62.3%; 0.0957, 2.72)	
Residual Error (proportional)	12.6 (2.09%; 11.6, 13.3)	

Abbreviations: 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 $100 \times \sqrt{e^{OMEGA(N)} - 1}$ where OMEGA(N) is the NONMEM output for the inter-subject variability of the Nth parameter

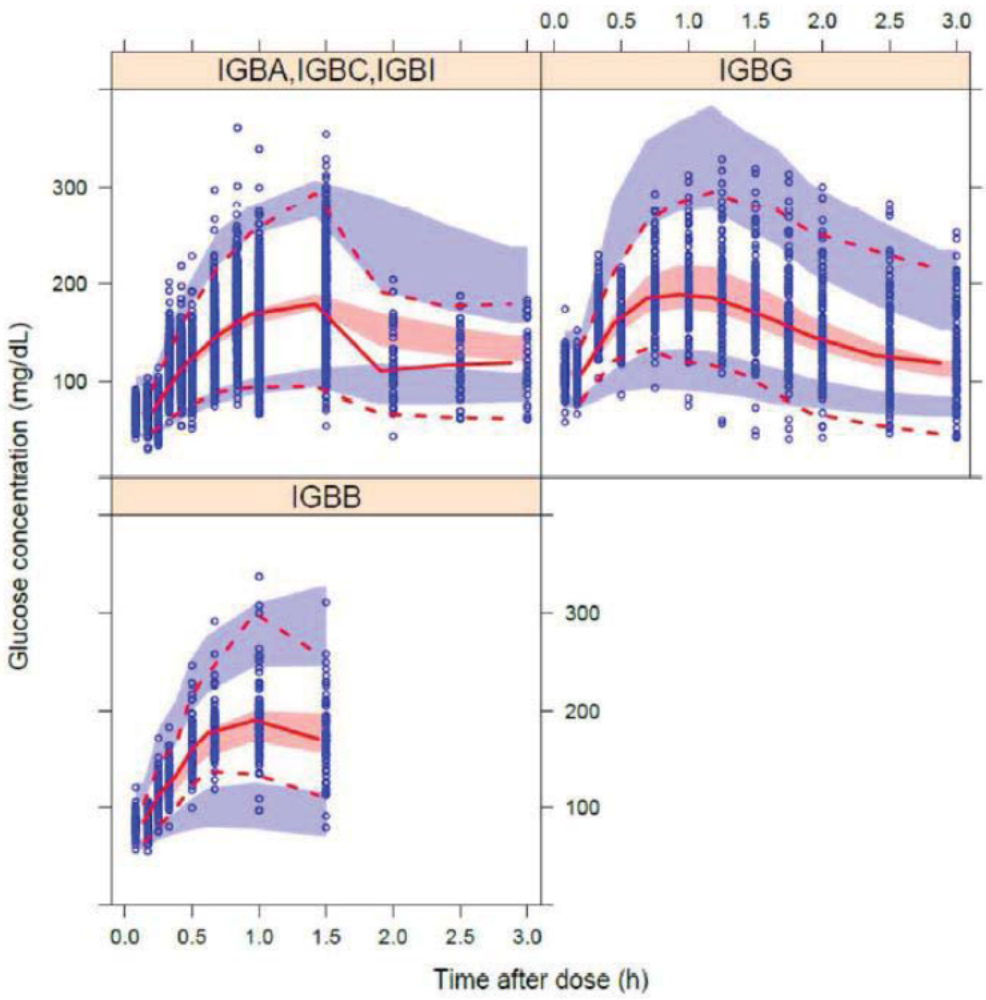
c KIN=TVKIN* $(1 - 0.315 * COV) * EXP(0.00383 * (baselineglucose - 54.00))$, where COV is set to 1 for study IGBB and IGBG

d EC50 = $EC50 * (1 + I1 \times 0.804)$, where I1 is set to 1 for study IGBB otherwise it is 0.

e EMAX = $EMAX \times (1 + 0.83) * ((1 + I1 \times -0.00277) * (baselineglucose - 54.00))$, where I1 is set to 1 for study IGBB and IGBG

(Source: Population PK and PD Analyses of Nasal Glucagon Studies IGBA, IGBB, IGBC, IGBD, IGBG, and IGBI, Table 8.4, Page 30)

Bootstrap results show that the parameters were estimated with reasonable precision, and the VPC shows the model fits the data well (Figure 26).



Note: The dashed red lines are the 2.5th , median, and 97.5th percentiles of the observed glucose concentrations; the blue shaded region is the 95% confidence interval of the 2.5th, median, and 97.5th percentiles of the model-predicted glucose concentrations.
Note: Glucose was collected up to 1.5 hour in Study IGBB, IGBC, and IGBI, and up to 3 hours in Studies IGBA and IGBG.

Figure 26 Visual predictive check for the final glucose exposure-response model
(Source: Population PK and PD Analyses of Nasal Glucagon Studies IGBA, IGBB, IGBC, IGBD, IGBG, and IGBI, Figure 8.4, Page 31)

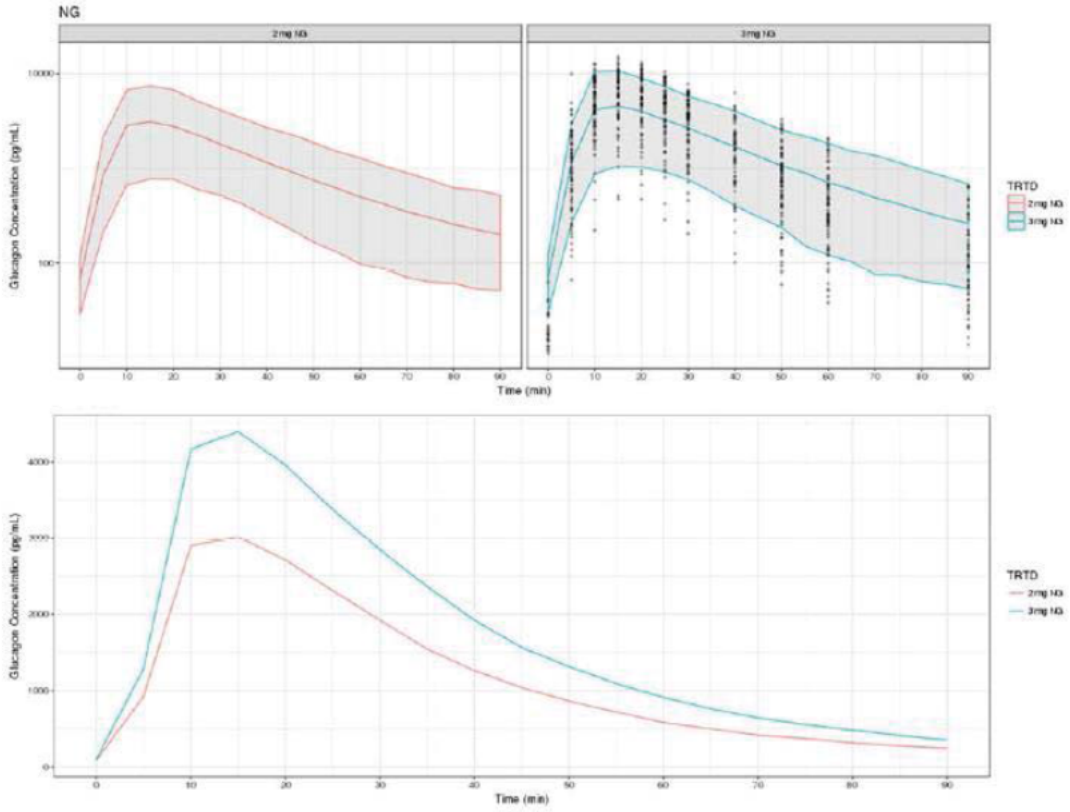
Simulation of Exposure and Response Following 2 mg of Commercial NG

The glucagon assay (b) (4) (not less than (b) (4) %), in conjunction with the (b) (4), ensures that in a "worst-case scenario", a dose of at least 2.0 mg glucagon/device is delivered (*Regulatory Response, NDA 210134, Sequence No. 0015*). The VPCs of PK and exposure-response model in this report have confirmed that the model robustly captures exposure and response of NG with both clinical trial drug product and commercial drug product. The final PK and exposure-response models presented in this report were used to simulate glucagon exposure and glucose response for patients administered a 2 mg dose of NG commercial drug product. In these simulations, the PK and PD parameters were fixed to the estimated values for Study IGBI, the clinical study using commercially representative drug product. Baseline characteristics of Study IGBI were applied in the simulation. Glucagon exposure and glucose response after NG 2 mg were simulated from 1,000 patients, including all sources of variability in the model. The projected glucagon exposure of NG 3 mg overlays

well with observations from Study IGBI, further validating the model's performance. Therefore, the model has the ability to predict exposure and response of NG 2 mg with commercial drug product.

The simulated data for glucagon exposure and glucose response with the median baseline glucose (40 mg/dL) were used to generate the plots shown in Figure 27 and Figure 28. These simulation results were used to assess probabilities of "treatment success" of NG 2mg (commercial drug product). Treatment success was defined as either an increase from baseline BG of at least 20 mg/dL at 30 minutes post-dose, or an increase in BG to at least 70 mg/dL at 30 minutes post-dose.

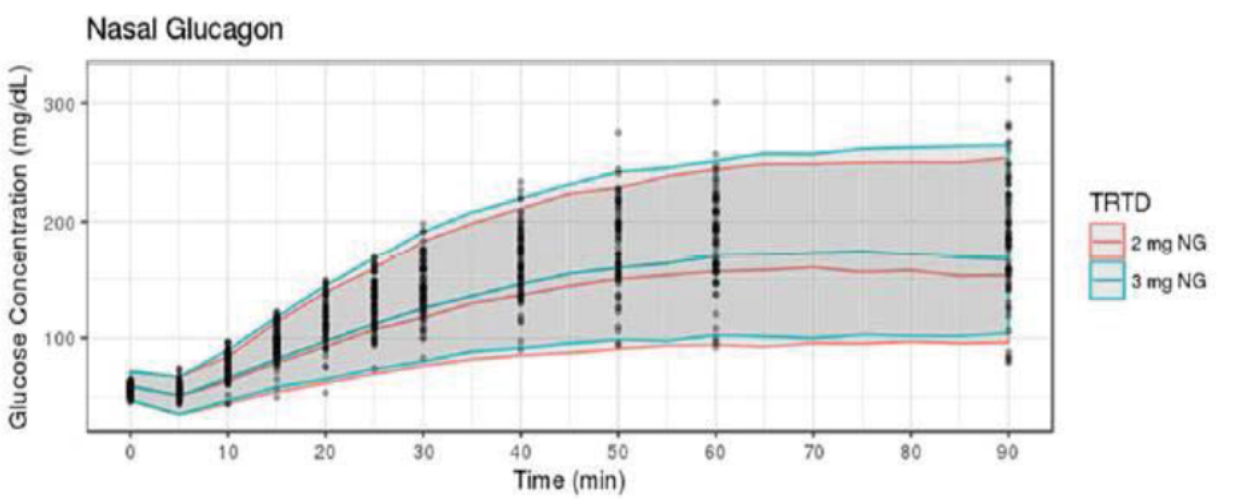
These results show that, for patients with baseline BG of 40 mg/dL, at 30 minutes postdose, a single dose of NG 2 mg would lead to 97% of patients achieving treatment success, with 97% having at least a 20 mg/dL BG increase and 92% having BG increase to at least 70 mg/dL. The median BG increase is 67 mg/dL after NG 2 mg treatment.



Note: Solid line represents median of model predictions; shaded area represents the 95% prediction interval.

Figure 27 **Predicted glucagon exposure over time of NG 2 mg (top left), NG 3 mg (top right) overlay with observation of IGBI with commercially representative drug product; median glucagon exposure over time of NG 2 mg and NG 3 mg with commercial drug product (bottom)**

(Source: Population PK and PD Analyses of Nasal Glucagon Studies IGBA, IGBB, IGBC, IGBD, IGBG, and IGBI, Figure 9.1, Page 33)



Note: Solid line represents median of model predictions; shaded area represents the 95% prediction interval; black dots are observation of NG 3 mg of IGBI, red represents NG 2 mg and blue represents NG 3 mg.

Figure 28 Predicted glucose response over time of NG 2 mg (red) and NG 3 mg (blue) overlay with observation of NG 3 mg in IGBI with commercially representative drug product

(Source: Population PK and PD Analyses of Nasal Glucagon Studies IGBA, IGBB, IGBC, IGBD, IGBG, and IGBI, Figure 9.2, Page 34)

Reviewer's Comments:
The relative bioavailability of NG compared with IMG/SCG was 28% in Study IGBI. Studies IGBG and IGBI showed a faster rate of absorption and slightly higher bioavailability relative to other studies. The particle size distributions of Studies IGBI and IGBG are similar suggesting that particle size distribution may have an effect on rate of absorption and bioavailability of NG, as explained by higher glucagon C_{max} in Study IGBI compared to the other studies. Results of simulation showed that lower baseline glucose resulted in a higher E_{max}. A higher baseline glucose was associated with a higher K_{in}. The model using IGBI PK and PD parameters showed that treatment success would be achieved in 97% of patients with a baseline glucose of 40 mg/dL. These findings are in line with previously submitted dose-response analysis that indicated 96% of patients would achieve treatment success. The modeling and simulation showed that in a "worst-case scenario", a dose of at least 2.0 mg glucagon/device is delivered from the labeled 3 mg device, the glucose response would match that from a 1 mg intramuscular injection (also see figure X). With a relative bioavailability of 28% for NG, a 2 mg NG dose would be equivalent to 0.56 mg of IMG. It is known from previously reported findings that glucose response following glucagon administration saturates beyond 0.25 mg dose. Consequently, the modeling and simulation findings based on results of Study IGBI are as expected.

4.3 Sponsor's Dose-Response Analysis for Glucagon

A dose-response analysis for glucagon was conducted using individual patient data from studies IGBA, IGBC, IGBI, IGBD and IGBG. The response variable was the change from baseline glucose at 30 minutes and was linked to the glucagon dose using an E_{max} model. The final model parameter estimates are shown in Table 10.

Table 10 Pharmacodynamic Parameters in Final Population Model

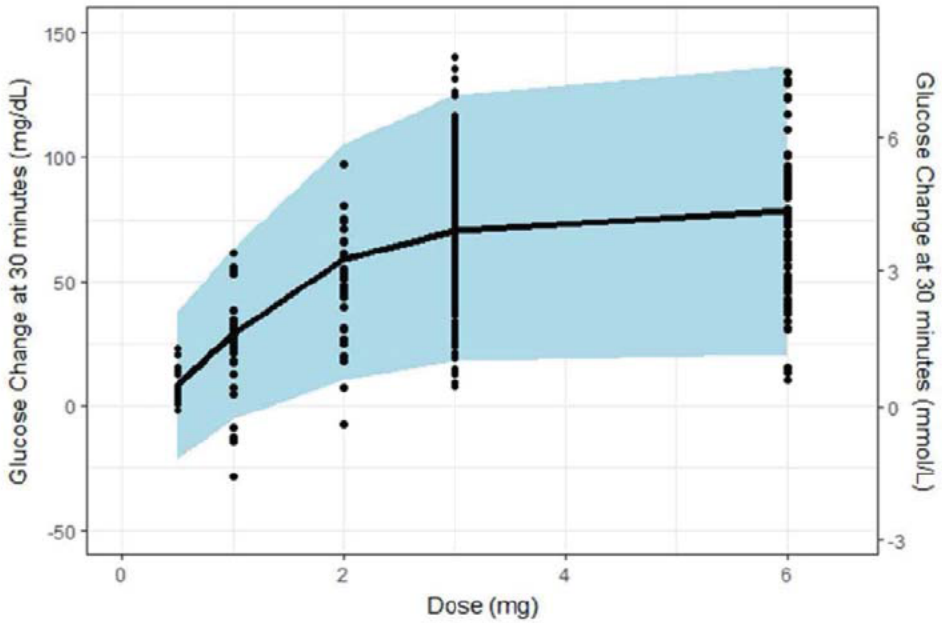
Parameter Description	Population Estimate (90% CI)	Inter-Individual Variability (90% CI)
Maximum Effect		
Parameter for E_{max} (mg/dL)	81.0 (75.8 – 85.9)	32.6% (28.3 – 36.1%)
Parameter for baseline glucose covariate (1/(mg/dL))	-0.00308 (-0.00405 – -0.00216)	
ED_{50}		
Parameter for ED_{50} (mg)	1.29 (1.07 – 1.52)	---
Hill		
Parameter for Hill	2.25 (1.96 – 2.83)	---
Residual Error (additive) (mg/dL)	15.0 (13.0 – 16.6)	

Abbreviations: E_{max} = maximum effect; ED_{50} = dose which produces 50% of maximum effect; Hill = shape parameter; 90% CI = 90% confidence interval as evaluated by bootstrap.

$E_{max} = 81.0 * (1 - 0.00308 * (\text{baseline glucose} - 57.6))$

(Source: Dose-Response Analyses of Nasal Glucagon Studies IGBA, IGBC, IGBD, IGBG, and IGBI, Table 7.4, Page 20)

Dose-response (change in glucose at 30 minutes post-dose) is shown in Figure 29. The probability of achieving an increase from baseline glucose of at least 20 mg/dL, and a glucose increase to at least 70 mg/dl by baseline glucose levels and ng doses within 30 minutes post dose are shown in Table 11 and Table 12, respectively.



Note: Solid line represents median of model predications; blue shaded area represents the 95% prediction interval. Symbol represented observed data.

Figure 29 Dose response (change from baseline of glucose at 30 minutes) of NG in adult population

(Source: Dose-Response Analyses of Nasal Glucagon Studies IGBA, IGBC, IGBD, IGBG, and IGBI, Figure 8.1, Page 23)

Table 11 Probability (%) of Achieving an Increase from Baseline Glucose of at Least 20 mg/dL for Various Baseline Glucose Levels and Various Doses, Based on Simulations of 10,000 Patients per Baseline/Dose Group from the Fitted Dose-Response Model

Baseline Glucose (mg/dL)	NG Dose (mg)			
	1	2	3	6
30	75.3	96.3	97.9	98.6
40	72.5	95.6	97.4	98.1
50	71.2	94.8	96.9	98.0
60	69.6	94.4	96.4	97.4

(Source: Dose-Response Analyses of Nasal Glucagon Studies IGBA, IGBC, IGBD, IGBG, and IGBI, Table 8.1, Page 24)

Table 12 Probability (%) of Achieving a Glucose Increase to at Least 70 mg/dL by Baseline Glucose Levels and NG Doses Within 30 Minutes Post Dose Based on Simulations of 10,000 Patients per Baseline/Dose Group from the Fitted Dose-Response Model

Baseline Glucose (mg/dL)	NG Dose (mg)			
	1	2	3	6
30	32.3	83.5	90.2	93.2
40	51.1	90.7	94.3	96.1
50	71.2	94.8	96.9	98.0
60	85.8	97.5	98.3	98.9

Reviewer's Comments:
Sponsor's dose response analysis is reasonable and captures the overall trend of dose-response indicating that 30 minutes after administration of a dose of NG 3 mg in hypoglycemic patients with a range of baseline glucose, there is a high probability of achieving both a 20 mg/dL increase in glucose and an increase to at least 70 mg/dL.

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