Office of Clinical Pharmacology Review

NDA Number	212097
Link to EDR	\\CDSESUB1\evsprod\NDA212097
Submission Date	August 9, 2018
Submission Type	505(b)(2), Standard Review
Brand Name	G-VOKE
Generic Name	Glucagon injection
Dosage Form and Strength	0.5 mg per 0.1 mL or 1 mg per 0.2 mL pre-filled syringe for HypoPen (auto-injector) or a manual plunger rod and backstop
Route of Administration	Subcutaneous injection
Proposed Indication	Treatment of severe hypoglycemia
Applicant	Xeris Pharmaceuticals
Associated IND	115091
OCP Reviewer	Sang M Chung, Ph.D.
OCP Final Signatory	Manoj Khurana, Ph.D. (Team Leader)

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1. EXECUTIVE SUMMARY

The sponsor submitted this New Drug Application (NDA, G-VOKE) for the treatment of severe hypoglycemia.

The efficacy and safety of G-VOKE for the proposed indication was supported by results of the pivotal study (XSGP-301), additional exploratory clinical study results, and clinical pharmacology information.

The active ingredient, glucagon, has been approved for the same indication and this NDA is a 505(b)(2) referring Glucagon (glucagon injection, NDA 020928).

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP2) has reviewed the Clinical Pharmacology information of NDA 212097, and concludes that the clinical pharmacology information of G-VOKE is acceptable and recommend approval for the proposed indication as follows:

Review Issue	Comments and Recommendations
Pivotal or supportive evidence of effectiveness	Data supporting effectiveness is based on the results of a pivotal Phase 3 study (XSGP-301) in Type 1 Diabetes Mellitus (T1DM) and results from supportive Phase 3 studies with clinical pharmacology information.
General dosing instructions	Administer 1 mg GVOKE subcutaneously as soon as possible when severe hypoglycemia is recognized. If there has been no response after 15 minutes, an additional dose (i.e., 1 mg for adult or 0.5 mg who weigh less than 45 kg for pediatrics) of GVOKE from a new device may be administered while waiting for emergency assistance.
Dosing in patient subgroups (intrinsic and extrinsic factors)	The recommended dose for pediatric patients aged 2 to under 12 years of age is 0.5 mg.
Bridge between the to-be-marketed and clinical trial formulations	The to-be-marketed formulation was used in the pivotal study for a pre-filled syringe (PFS) with an auto-injector (AI) (Configuration A). The pivotal clinical pharmacology bridge study was conducted for additional to-be-marketed configuration (PFS with a manual plunger rod and backstop, Configuration B).

1.2 Post-Marketing Requirements and Commitments

None

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Regulatory Background

Glucagon is endogenous hormone with 29 amino acids (Figure 1) acting as an anti-hypoglycemic agent and a gastrointestinal motility inhibitor.

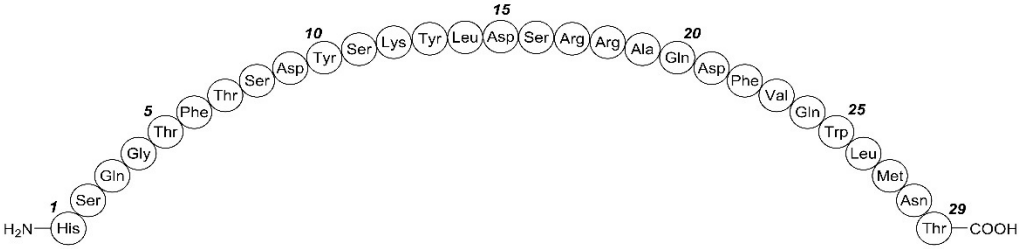


Figure 1 Primary sequence of glucagon (Source: Proposed labeling)

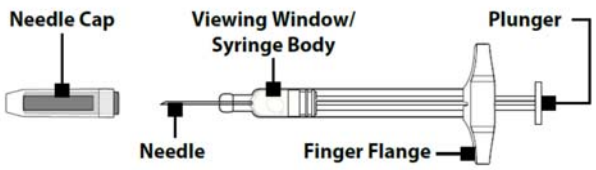
Glucagon injection (e.g., NDA 20918 by Novo Nordisk, NDA 20928 by Lilly) has been approved for the treatment of severe hypoglycemia which may occur in patients with diabetes mellitus treated with insulin. Glucagon is also indicated for a diagnostic aid during radiologic examinations to temporarily inhibit movement of the gastrointestinal tract.

The sponsor conducted pivotal Phase 3 studies with G-VOKE for the proposed indication and refers FDA's previous findings of safety and effectiveness for Glucagon (glucose injection, NDA 20928). The review division generally agreed to the sponsor's approaches.

G-VOKE consists of:

- Configuration A: PFS with an auto-injector

- Configuration B: PFS with a manual plunger rod and backstop



- Formulation (Table 1): two fill volumes of G-Pen PFS common to both configurations
  - 0.5 mg for pediatric patients and 1 mg for patients 12 years and older

Table 1 Quantitative Composition of G-Pen Formulation 1 mg and 0.5 mg (Source: Table 1, eCTD 2.3.P)

Component	Concentration (% w/w)	PFS 1 mg		PFS 0.5 mg		Function
		To deliver at least (mg/unit)	To fill [1] (mg/unit)	To deliver at least (mg/unit)	To fill [1] (mg/unit)	
Glucagon	(b) (4)	1.00	(b) (4)	0.50	(b) (4)	Drug Substance
Trehalose Dihydrate		11.1		5.6		(b) (4)
DMSO		(b) (4)		(b) (4)		Diluent
(b) (4) Sulfuric Acid		1.2 (b) (4)		0.6 (b) (4)		(b) (4)
Totals		(b) (4)		(b) (4)		N/A

[1] Overfill to guarantee label claim

2.2 Clinical Development

Clinical pharmacology information, efficacy and safety of glucagon following G-VOKE administration were evaluated through a total of 8 clinical studies (Table 2).

The primary efficacy endpoint was the failure rate of plasma glucose to have a measured value > 70 mg/dL within 30 minutes of administration of treatment following a state of insulin-induced hypoglycemia in T1DM. An alternate combined glucose-response endpoint was evaluated where failure was defined as the event when either plasma glucose remained ≤ 70 mg/dL or increased <20 mg/dL throughout the 0 to 30-minute period starting from administration of study drug.

Table 2 Overview of clinical studies for G-VOKE development (Source: Table 1, eCTD 2.7.6)

Study Type	Study Identifier	Objective(s) of the Study	Study Design	Dosage Regimen	Number of Subjects Enrolled	Subjects	Duration of Treatment
BE	XSGP- 101	Bioequivalence PK/PD	R, PK/PD 2XO, OL	G-Pen; Single dose (1 mg) via AI and single dose (1 mg) via PFS, SC	32	Healthy Adults	<1 min
PK	XSGP- 201	Comparative PK/PD	R, DB, PK/PD, 3XO,	G-Pen, Lilly Glucagon; Single doses (0 5 and 1 mg) of G-Pen via PFS and single dose (1 mg) Lilly Glucagon, SC	30	Healthy Adults	<1 min
Efficacy PK	XSGP- 301	Plasma Glucose recovery from <50mg/dL, Efficacy/Safety	R, DB, PD, 2XO	G-Pen and Lilly Glucagon; Single dose (1 mg) of G- Pen via AI and single dose of Lilly Glucagon (1 mg), SC	80	T1D (Adults)	<1 min
Efficacy	XSGP- 302	Plasma Glucose recovery from <80 mg/dL	NR, OL	G-Pen; Single dose via AI (0.5 mg) and single dose via AI (1 mg) ages 12-<18 only, SC	31	T1D (Pediatrics)	<1 min

Efficacy	XSGP- 303	Plasma Glucose recovery from <50mg/dL, Efficacy/Safety	R, SB, 2XO	G-Pen and Lilly Glucagon; Single dose (1 mg) of G- Pen via AI and single dose of Lilly Glucagon (1.0 mg), SC	81	T1D (Adults)	<1 min
Efficacy	XSGP- 202	Pilot Study; Safety, Efficacy *Return of glucose (>70 mg/dL) within 30 min from <50 mg/dL*	R, OL, 2XO	G-Pen; Single doses (0.5 and 1 mg), vial & syringe, SC	7	T1D (Adults)	<1 min
Human Factors	XSGP- HF-3	Summative Human Factors Usability for Configuration A (Autoinjector)	Human Factors validation	Configuration A (AI) (0.5 mg and 1mg)	75	First responders, experienced caregivers, Naïve caregivers (Adult and pediatric)	N/A
Human Factors	XSGP- HF-5	Summative Human Factors Usability for Configuration B (PFS)	Human Factors validation	Configuration B (PFS) (1mg)	75	First responders, experienced caregivers, Naïve caregivers (Adult and pediatric)	N/A

Note: R=Randomized, NR=Non-Randomized, DB=Double-Blind, SB=Single Blind, OL=Open Label, XO=Crossover, PK=Pharmacokinetics, PD=Pharmacodynamics, AI=Autoinjector (configuration A), PFS=Pre-filled-syringe (configuration B), SC=Subcutaneous, T1D=Type 1 diabetes.

2.2 Clinical Pharmacokinetics

2.2.1 PK/PD of G-VOKE in healthy subjects from the pivotal bridging study for the to-be-marketed presentation

Glucagon PK and PD was evaluated for the to-be-marketed configurations (Study XSGP-101). Study XSGP-101 was a two-way crossover comparative PK/PD study between a PFS with an AI (Configuration A) and manual plunger rod and backstop (Configuration B) presentation of G-Pen, where 1 mg subcutaneous dose was administered in fasted healthy subjects with low to normal blood glucose. Configuration A was used in the pivotal Phase 3 study, and Configuration B is new to-be-marketed presentation/device using the same formulation as Configuration A.

Venous blood samples were collected at 0, 10, 20, 30, 45, 60, 90, 120, 180 and 240 minutes post dose for glucagon, and at 0, and every 5 minutes through 45 minutes, and at 60, 90, 120, 180 and 240 minutes post dose for glucose measurements.

Concentration-time profiles of PK and PD are shown in Figure 2. Subcutaneous injection of 1 mg dose of G-VOKE from the two presentations resulted in comparable glucagon PK and glucose (PD) profiles. subjects resulted in a mean glucagon C_{max} of 2481.3 pg/ml, t_{max} of 50.0 minutes and $AUC_{0-240min}$ of 3454.6 pg*min/ml.

Statistical analysis of primary PK and PD parameters for glucagon demonstrated bioequivalence of glucagon PK and PD between Configurations A and B using the pre-specified criteria of (b) (4) % for geometric mean ratios and confidence intervals (Table 3).

Therefore, results from this study, while being informative of the G-VOKE PK/PD in healthy, also establish the scientific bridging needed to support the approval of the to be marketed presentation of G-VOKE.

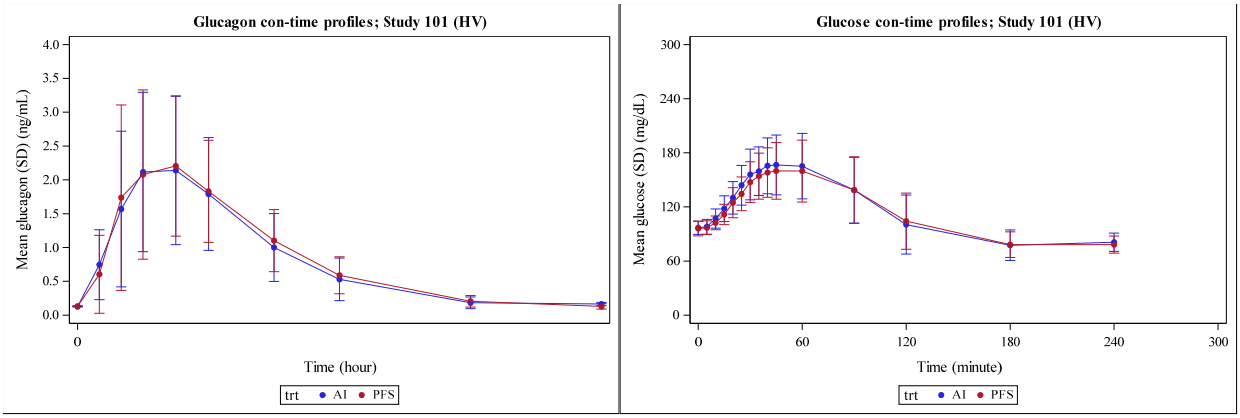


Figure 2 Mean (SD) glucagon (left) or glucose (right) concentration-time profiles following 1 mg sc administration with Configuration A and B in HV (Study 101)

Table 3 Summary of statistical analysis for bioequivalence (Source, Table 10, 13, 28 and 31, CSR)

PD	Treatment	N	Geometric Mean Estimate (SE)	Mean Ratio (%)	90% CI
$AUC_{0\text{-}240min}$ (mg/dL*min)	AI (Configuration A)	32	26441.3 (63907.24)		
	PFS (Configuration B)	32	26178.8 (63272.96)		
	Configuration B / A			**99.01**	**96.22, 101.88**
C_{max} (mg/dL)	AI (Configuration A)	32	173.7 (5.3)		
	PFS (Configuration B)	32	169.3 (5.1)		
	Configuration B / A			**97.50**	**94.54, 100.54**
Tmax (min)*	AI	32	49.9		
	PFS	32	50.7		

PK	Treatment	N	Geometric Mean Estimate (SE)	Mean Ratio (%)	90% CI
$AUC_{0\text{-}240min}$ (ng/mL*min)	AI (Configuration A)	32	166.4 (1048.16)		
	PFS (Configuration B)	32	177.4 (1117.88)		
	Configuration B / A			**106.65**	**95.05, 119.67**
C_{max} (ng/mL)	AI (Configuration A)	32	2.1 (15.66)		
	PFS (Configuration B)	32	2.1 (16.11)		
	Configuration B / A			**102.87**	**85.25, 124.12**
Half-life (min)*	AI	32	41.4		
	PFS	32	35.9		

* arithmetic mean

Reviewer's Comments:

- Inspection was requested for Study XSGP-101 to the Office of Study Integrity and Surveillance, and the OSIS review concluded that the clinical data and clinical chemistry data from the audited study were reliable to support a regulatory decision (see the review in DARRTS dated 3/6/2019)
- The conclusions of BE remained unchanged following a baseline adjustment in PK and PD parameters (Data are not shown).
- From a mechanistic perspective, there was apparent counter-clockwise hysteresis (Figure 3) in the time-matched mean glucagon concentration-mean glucose responses, which also were comparable for the two treatments.

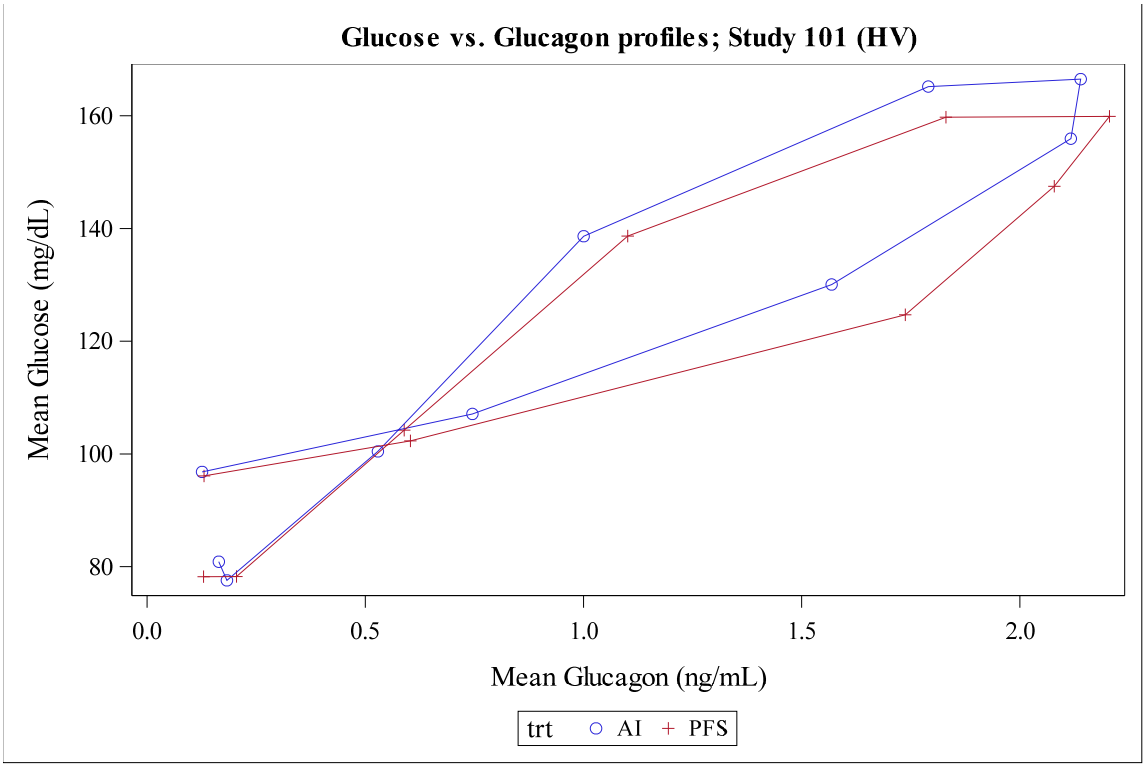


Figure 3 Relationship between mean glucagon and glucose in HV (Study 101)

2.2.2 Comparative PK/PD following G-VOKE referencing those of GLUCAGON (NDA 20928 by Lilly)

Glucagon PK/PD was evaluated in a randomized, Phase 2, double-blind, 3-ways crossover study to evaluate safety, tolerability and comparative PK and PD of 0.5 or 1 mg G-VOKE to those of 1 mg GLUCAGON, a reference product, in healthy volunteers (Study 201, see Figure 4 for study design).

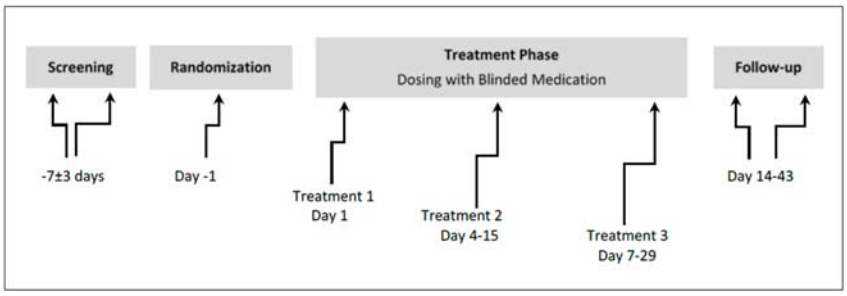


Figure 4 Schematic summary of study design (Study 201)

Concentration-time profiles of glucagon and glucose are shown in Figure 5. Glucose AUC and Cmax) were similar among treatments (Table 4). However, glucagon AUC and Cmax were lower following G-VOKE (G-VOKE) compared to those of the reference (Lilly) (Table 5);

- 55 and 39% for AUC following 1.0 and 0.5 mg G-VOKE, respectively
- 34 and 22% for Cmax following 1.0 and 0.5 mg G-VOKE, respectively

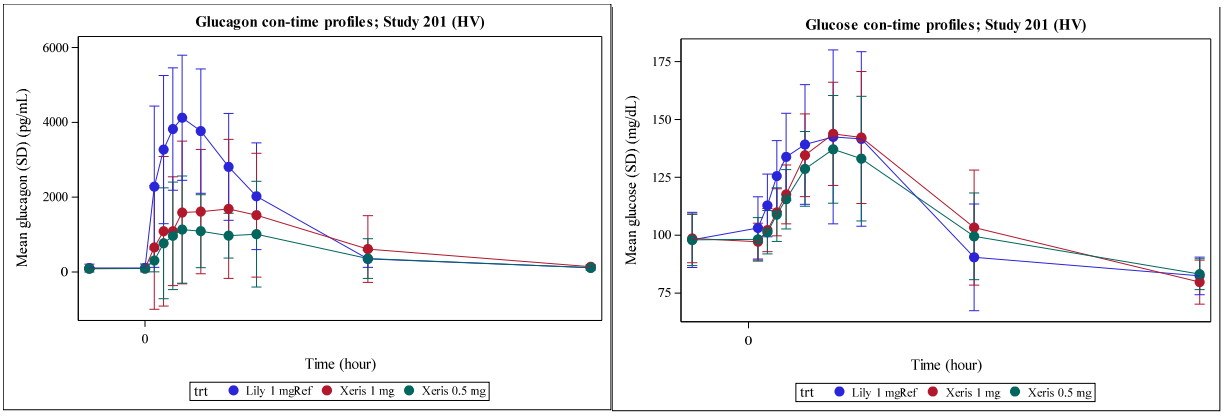


Figure 5 Glucagon (left) and glucose – time profiles following G-VOKE 0.5 or 1 mg compared to those of Lilly 1.0 mg.

Table 4 Summary of statistical analysis for bioequivalence (Study 201)

Glucose		Treatment			p-value[a]	Ratio of Means (90% CI)
		Lilly 1.0 mg	G-VOKE 1.0 mg	G-VOKE 0.5mg		
	N	27	28	28		
$AUC_{0\text{-}240min}$ (mg/dL*min)	Mean (SD)	473.5 (72.9)	481.1 (64.9)	467.0 (47.9)		
	Comparison	G-VOKE 1.0 mg vs Lilly 1.0			<0.001	1.030 (0.993, 1.033)
		G-VOKE 0.5 mg vs Lilly 1.0			<0.001	0.992 (0.977, 1.017)
		G-VOKE 0.5 mg vs G-VOKE			<0.001	0.963 (0.964, 1.004)
C_{max} (mg/dL)	Mean (SD)	154.85 (28.02)	148.04 (24.94)	140.32 (23.59)		
	Comparison	G-VOKE 1.0 mg vs Lilly 1.0			<0.001	0.965 (0.908, 1.027)
		G-VOKE 0.5 mg vs Lilly 1.0			<0.001	0.909 (0.854, 0.967)
		G-VOKE 0.5 mg vs G-VOKE			<0.001	0.942 (0.883, 1.003)

a: based on a two one-sided test for BE in natural log units
(Source; Table 18, 20, CSR)

Glucagon		Treatment			p-value[a]	Ratio of Means (90% CI)
		Lilly 1.0mg	G-VOKE 1.0 mg	G-VOKE 0.5mg		
	N	27	28	28		
$AUC_{0-240min}$ (pg/mL*min)	Mean (SD)	4781.7 (2222.9)	3259.9 (3447.5)	2105.3 (2381.9)		
	Comparison	G-VOKE 1.0 mg vs Lilly 1.0 mg			0.99	0.549 (0.435, 0.693)
		G-VOKE 0.5 mg vs Lilly 1.0 mg			1.00	0.392 (0.310, 0.497)
		G-VOKE 0.5 mg vs G-VOKE 1.0 mg			0.97	0.715 (0.562, 0.908)
C_{max} (pg/mL)	Mean (SD)	4429.9 (1776.4)	2055.4 (2052.0)	1318.8 (1435.8)		
	Comparison	G-VOKE 1.0 mg vs Lilly 1.0 mg			1.00	0.338 (0.247, 0.463)
		G-VOKE 0.5 mg vs Lilly 1.0 mg			1.00	0.224 (0.163, 0.306)
		G-VOKE 0.5 mg vs G-VOKE 1.0 mg			0.96	0.661 (0.484, 0.903)

(Source; Table 31, 33, CSR)

Reviewer's Comment:

- BE of G-VOKE was not shown referencing GLUCAGON. Therefore, clinical evaluation was pivotal to support this application.
- Mean (SD) glucagon half-lives were 51.0 (3.89), 63.7 (4.86) and 71.3 min following Lilly's, G-VOKE 1.0 mg and 0.5 mg, respectively. It is apparent that a flip-flop PK was shown as the half-life following IV was in the range of 8-18 min (Glucagon Label NDA 20928, Eli Lilly and Graf *et al*. J Pharm Sci, 88:991-995, 1999). The mean apparent half-life after IM was 45 min according to GlucaGen labeling.
- It appears that glucagon concentrations following 1.0 mg Lilly reached apparent Emax but not following G-VOKE 1.0 or 0.5 mg (Figure 6). The difference may explain the PD similarity with the significant PK difference among treatments. Nonetheless, knowing the steep nature of exposure-response relationship for glucagon, the PD results supported sponsor's dose selection for the Phase 3 trials.

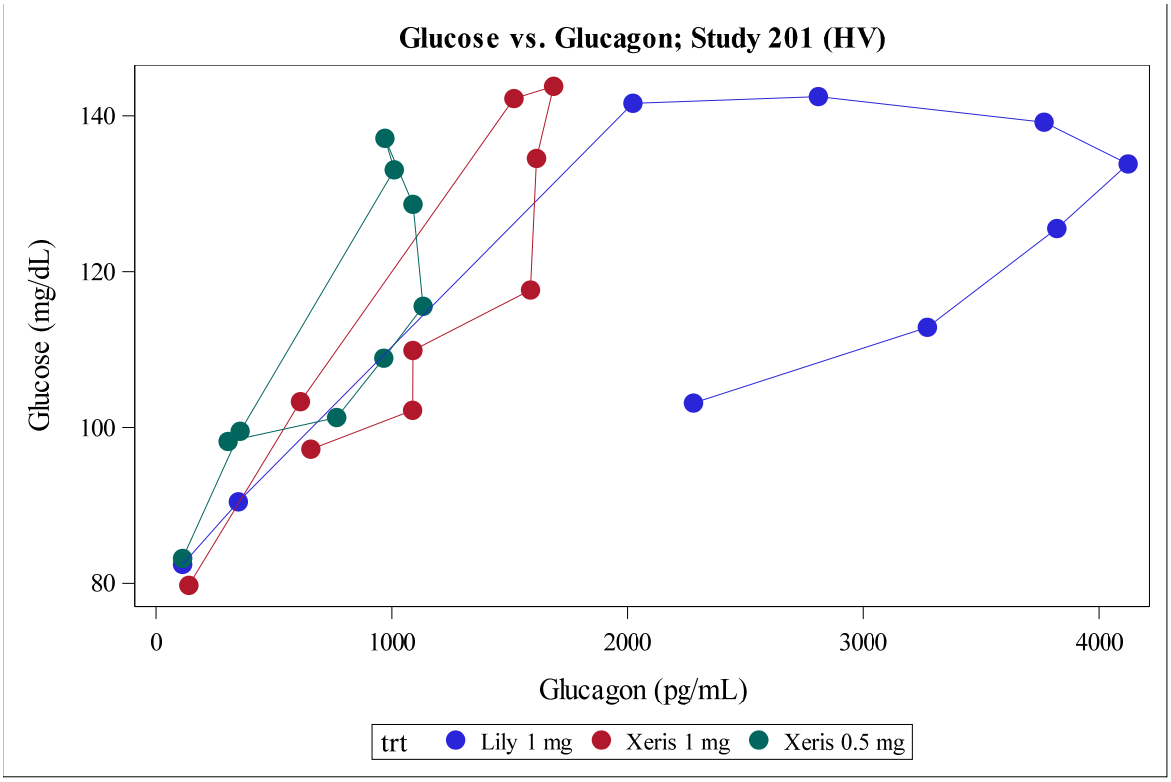


Figure 6 Relationship between mean glucagon and glucose among treatments (Study 201)

2.2.3 PK/PD in subjects with T1DM

Glucagon PK and PD was evaluated as part of the pivotal Phase 3 study (Study 301). The primary objective of this study was to demonstrate the efficacy (plasma glucose) of G-VOKE 1 mg to be non-inferior to Lilly's GLUCAGON 1 mg in subjects with T1DM who are in a state of insulin-induced hypoglycemia as assessed by the failure rate of plasma glucose to have a measured value > 70.0 mg/dL within 30 minutes of administration of treatment.

This was a non-inferiority, randomized, controlled, double-blinded, 2-treatment, 2-way crossover comparative efficacy and safety study in subjects with T1DM.

A combination of 1 or more IV bolus doses of insulin along with an IV infusion of insulin was used to decrease a subject's plasma glucose to a target value<50 mg/dL. The IV insulin infusion was stopped once the plasma glucose was<50 mg/dL. All plasma glucose levels were based on the average of 2 readings taken at each time point. After a confirmatory plasma glucose of <50 mg/dL was obtained at least 5 minutes after the initial reading < 50 mg/dL, the subject was treated SC in the upper arm, leg or abdomen with either 1 mg Lilly's GLUCAGON or 1 mg G-VOKE.

Pharmacodynamics: Following G-VOKE or Glucagon injection, mean (SD) maximum glucose concentrations of 202.7 (41.80) mg/dL and 193.5 (42.25) mg/dL were achived at median Tmax of 111.3 minutes and 100.4 minutes, respectively with the two treatments. The data thus showed that the glucose concentration-time profiles were comparable between G-VOKE and Lilly's products, although, on average the rate of inclrease in glucose was appeared to be slower for G-VOKE (Figure 7).

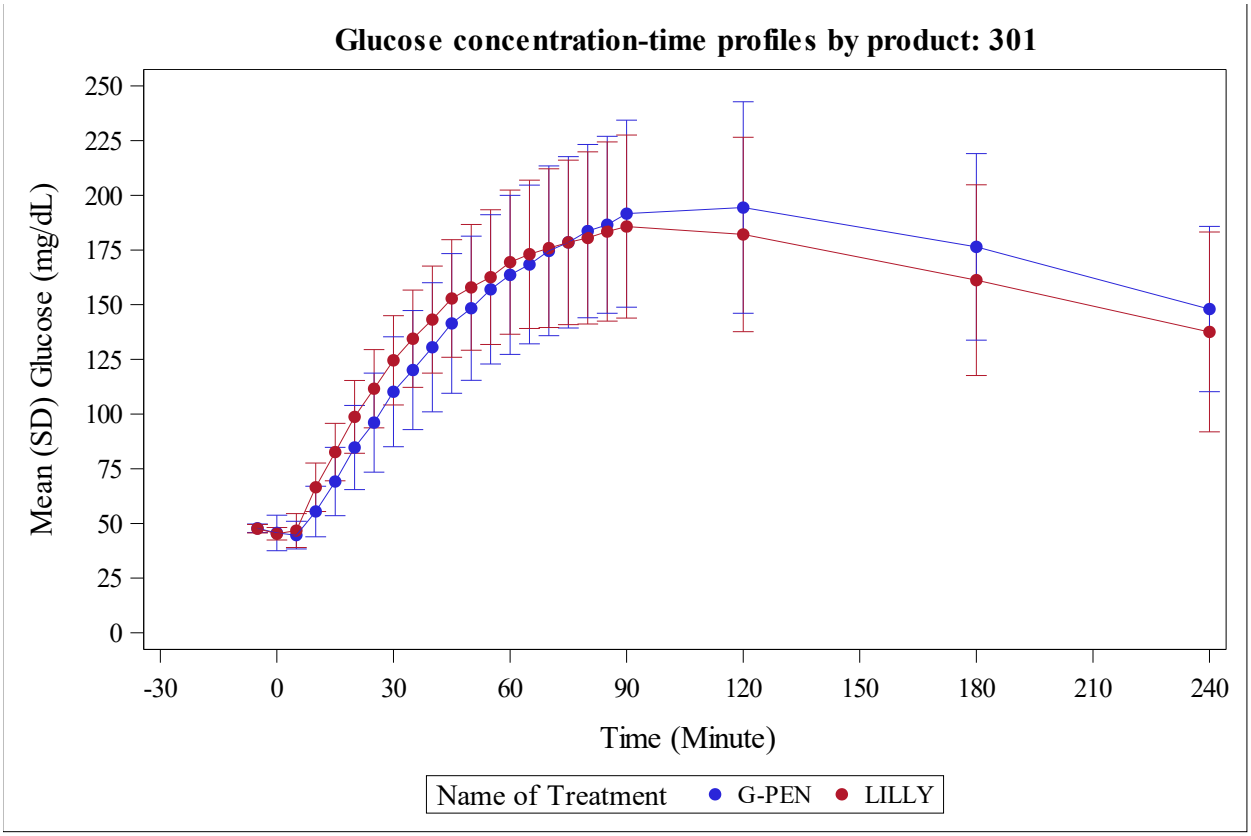


Figure 7 Mean (SD) glucose concentration-time profiles following G-VOKE or Lilly's product (Study 301)

Pharmacokinetics:

- Mean (SD) AUC and Cmax of glucagon following G-VOKE was 3454.6 (1268.40) pg/mL*min and 2481.2 (1140.12) pg/mL, respectively. Median tmax (range) was 30 (10, 120) minutes (Table 5).
- There was no apparent difference in glucagon PK from G-VOKE among ethnicity/race sub-groups (i.e., African American, Hispanic White, Non-Hispanic White, and Other)
- PK data, even though not the primary objective of this study, was evaluated considering it often helps in understanding the nature of pharmacodynamic responses. Sponsor included PK data for all subjects with G-VOKE treatment. However, PK data for only for 20 subjects were included in the submission for the reference treatment. Therefore, comparative PK assessments cannot be fully derived from this data, though being complete, the data is fully informative for describing the PK/PD behavior of G-VOKE. The summary statistics for the PK data for two treatments is presented for descriptive purposes only without any intent to draw any comparative conclusions.
- The applicant presented PK analysis following the baseline adjustment, and results of baseline adjusted PK were comparable to those of unadjusted PK
- There was no apparent PK difference between visits following G-VOKE (Figure 8).

Table 5 Summary of glucagon PK parameters by products (Study 301)

Parameter	Product	N	Mean	SD
$AUC_{0\text{-}240min}$ (pg/mL*min)	G-VOKE	78	3454.6	1268.40
	GLUCAGON*	20	3705.4	1743.72
C_{max} (pg/mL)	G-VOKE	78	2481.2	1140.12
	GLUCAGON*	20	3759.6	1982.28
t_{max}** (min)	G-VOKE	78	30	10, 120
	GLUCAGON*	20	20	10, 45

** medial with range (minimum, maximum)

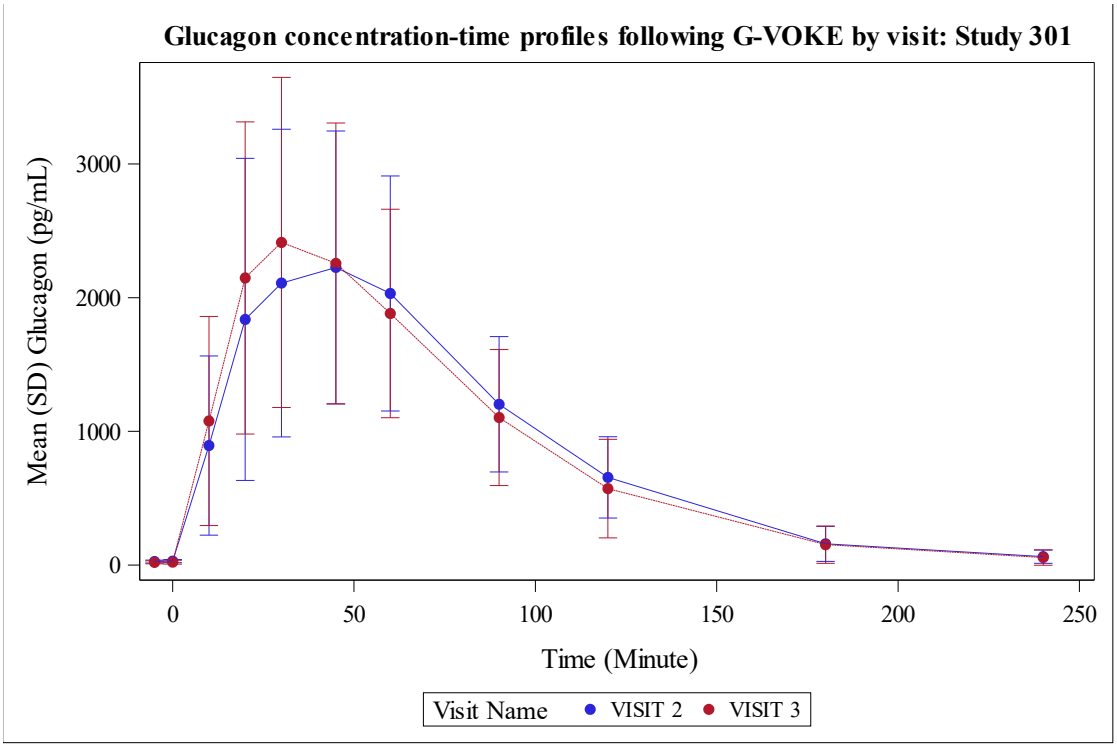


Figure 8 Mean (SD) glucagon concentration-time profiles by visits following G-VOKE (Study 301)

2.2.4 PK/PD in pediatric subjects with T1DM

Glucagon PK and PD was assessed in an exploratory Phase 3 study to evaluate the glucose response of G-VOKE in pediatric patients with T1DM (Study XSGP-302).

After a confirmatory plasma glucose of < 80 mg/dL was obtained at least 5 minutes after stopping the insulin infusion, subjects were administered G-VOKE subcutaneously in the upper arm, leg or abdomen as follows;

- 0.5 mg to subjects aging 2 to < 12 years
- Both G-VOKE 0.5 and 1 mg to subjects aging 12 to <18 years following 1 to 4 weeks wash-out between treatments

The applicant concluded that there was no age associated glucagon PK difference (Table 6).

Table 6 Summary of pediatric glucagon PK and PD parameters by treatments (Study 302)

PD parameters

Age Group	G-Pen Dose		C_{max} (mg/dL)	t_{max} (min)	$AUC_{0\text{-}90min}$ (min*mg/dL)	Adjusted* $AUC_{0\text{-}90min}$ (min*mg/dL)	T_{ex}** (minutes)
2 to < 6 years	0.5 mg	N	7	7	6	6	7
		Mean (SD)	202.29 (35.938)	66.6 (10. 52)	14440.83 (2114.856)	8147.71 (2162.379)	16.4 (3.78)
6 to < 12 years	0.5 mg	N	13	13	12	12	13
		Mean (SD)	216.31 (51.162)	68.5 (15.33)	14392.27 (2698.354)	8001.59 (2510.799)	16.2 (4.63)
12 to < 18 years	1.0 mg	N	11	11	11	11	11
		Mean (SD)	19.00 (56.974)	81.2 (14.91)	13105.45 (3025.700)	6377.54 (2700.448)	23.6 (9.51)
	0.5 mg	N	10	10	10	10	11
			212.10 (40.619)	78.2 (11.55)	13809.58 (2096.187)	7042.85 (2011.071)	23.6 (5.95)

* baseline-adjusted

** Time to increase by ≥ 25 mg/dL from Baseline

PK parameters

Age Group	N	Dose		$AUC_{0\text{-}180min}$ (ng/mL*min)	C_{max} (ng/mL)	T_{max} (min)
2 to < 6 years	5	0.5	Mean	138.9	2.3	41.4
			SD	77.59	1.08	12.82
6 to < 12 years	13	0.5	Mean	104.7	1.6	33.8
			SD	55.24	0.84	14.96
12 to < 18years	11	0.5	Mean	73.4	1.1	40.4
			SD	28.05	0.49	15.38
	10	1	Mean	134.3	1.9	51.0
			SD	56.03	1.18	22.96

Reviewer's Comment:

- There was no apparent association between age or sex and PK or PD parameters (Figure 9)
- There was proportional exposure change to dose in 12-18 years age sub-group (Figure 9, upper). However, there was no corresponding PD change (Figure 9, upper).
- PK/PD data indicate that glucagon concentrations reach apparent Emax (Figure in Appendix).

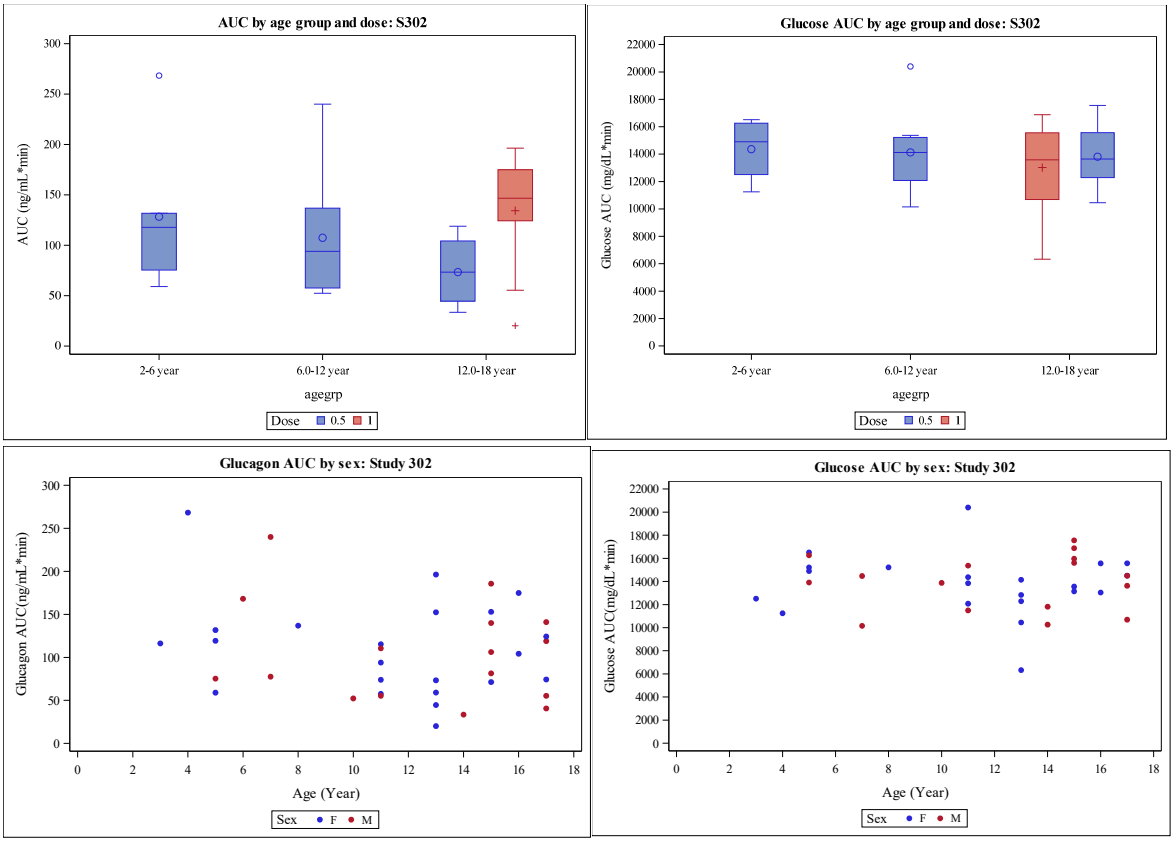


Figure 9 Box plot for glucagon PK (upper, left) or PD (upper, right) parameters by age sub-groups and products, and scatter plots between glucagon AUC (lower, left) or glucose AUC (lower, right) vs. age and sex (Study 302)

2.3 Bioanalytical studies

Throughout the clinical program, two analytical methods were used to quantify glucagon in plasma samples:

1) liquid chromatography tandem mass spectrometry (LC-MS/MS)

2) radioimmunoassay (RIA)

Table 7 Summary of bioanalytical methods used in clinical studies

CRO	Assay Format	Range	Matrix	Sample Volume	Comment
(b) (4)	RIA	25-200 pg/mL	Human	100 µL	(b) (4) conducted bioanalysis of study samples for XSGP-201
	LC-MS/MS	0.1– 10 ng/mL	Human	450 µL	Validated (Validation Report No. GUO-V1-732). XSGP-101, XSGP-302
	LC-MS/MS	10 – 500 pg/mL	Human	450 µL	Validated (Validation Report No. GUO-V4-519). XSGP-301

a; (b) (4)

The method used for Phase 1 study XSGP-101 was validated as summarized in the following table and the bioanalytical study is acceptable.

Table 8 Bioanalytical assay validation summary table

Analytical Validation Report	XRI-W7-065(R1)	
Short description of method	Solid-phase with 96 well plate Reversed-phase HPLC with MS/MS detection	
Biological matrix	Human plasma	
Analyte	Glucagon	
Internal standard (IS)	(b) (4)	
Calibration concentrations	0.100 ng/mL to 10.000 ng/mL.	
QC concentrations	In Proxy Matrix: 0.100 ng/mL, 0.300 ng/mL, 2.000 ng/mL, 5.000 ng/mL and 7.500 ng/mL. In Human Plasma: 0.139 ng/mL, 0.345 ng/mL, 2.045 ng/mL, 5.032 ng/mL and 7.545 ng/mL	
Specificity	No significant interference observed in the 6 blank matrix lots screened.	
Specificity in presence of concomitantly administered compounds	No significant interference observed.	
Carryover	Refer to section 5.2.4.	
Lower limit of quantification	In Proxy Matrix: 0.100 ng/mL Between-run accuracy 96.1% Between-run precision 18.0% Within-run accuracy 107.2% Within-run precision 6.8% In Human Plasma: 0.139 ng/mL Between-run accuracy 106.9% Between-run precision 9.8% Within-run accuracy 114.5% Within-run precision 6.5%	
Between-run accuracy in Proxy Matrix	95.6% to 96.4%	
Between-run precision in Proxy Matrix	4.8% to 18.0%	
Within-run accuracy in Proxy Matrix	94.5% to 107.2%	
Within-run precision in Proxy Matrix	4.5% to 6.8%	
Between-run accuracy in Human Plasma	89.9% to 108.2%	
Between-run precision in Human Plasma	2.0% to 10.6%	
Within-run accuracy in Human Plasma	86.8% to 114.5%	
Within-run precision in Human Plasma	2.9% to 7.7%	
Largest batch size	192 injections	
Matrix Effect (Calculation of Matrix Factor (MF)) IS normalized MF C.V.% of IS normalized MF	Low QC Mean Analyte MF: 0.8403 Mean IS MF: 0.9046 Mean IS-Normalized: 0.9298 % C.V.: 6.8	High QC Mean Analyte MF: 0.9369 Mean IS MF: 0.9192 Mean IS-Normalized: 1.0196 % C.V.: 2.1
Dilution integrity	20.045 ng/mL diluted 5-fold. Accuracy (% nominal): 109.8% Precision: 7.3%	

Recovery of analyte (P.E.Y.)	Proxy Matrix: 46.0 % to 48.9 % Human Plasma: 40.8% to 50.3%
Recovery of IS (P.E.Y.)	Proxy Matrix: 51.5 % Human Plasma: 48.6%
Short-term stability of the stock solution and working solutions (Observed change %)	Confirmed up to 24.5 hours for Glucagon in Dissolution Solution at 100.00 µg/mL at 22°C nominal. % deviation: 11.2%. Confirmed up to 24.5 hours for Glucagon in Dissolution Solution at 5.00 ng/mL at 22°C nominal. % deviation 8.6%. Confirmed up to 19.4 hours for (b) (4) in Dissolution Solution at 100.00 µg/mL at 22°C nominal. % deviation: 2.8%.
Long-term stability of the stock solution and working solutions (Observed change %)	Confirmed up to 63 days for Glucagon in Dissolution Solution at 100.00 µg/mL at 4°C nominal. % deviation: -10.6%. Confirmed up to 63 days for Glucagon in Dissolution Solution at 0.50 ng/mL at 4°C nominal. % deviation: 1.0%. Confirmed up to 102 days for (b) (4) in Dissolution Solution at 100.00 µg/mL at 4°C nominal. % deviation: -13.0%.
Short-term stability in biological matrix at room temperature or at sample processing temperature. (Observed change %)	Confirmed up to 25.5 hours at 4°C nominal in proxy matrix. Accuracy (% nominal): 89.9% for Low Stability QC and 89.7% for High Stability QC. Confirmed up to 22.5 hours at 4°C nominal in human plasma. Accuracy (% nominal): 90.7% for Low Stability QC and 87.1% for High Stability QC. Confirmed up to 1.0 hours at 4°C nominal without preservative in human plasma. Accuracy (% nominal): 95.3% for Low Stability QC and 99.5% for High Stability QC.
Stability in whole blood	Confirmed up to 2.0 hours in an Ice/Water Bath. % deviation: -8.1% for Low QCs and 3.5% for High QCs.

Freeze and thaw stability (Observed change %)	3 cycles in proxy matrix. Accuracy (% nominal): 90.0% for Low Stability QC and 87.5% for High Stability QC. 3 cycles in human plasma. Accuracy (% nominal): 88.4% for Low Stability QC and 96.5% for High Stability QC.
Autosampler storage stability (Observed change %)	Confirmed up to 161.0 hours at 4°C nominal in proxy matrix. Accuracy (% nominal): 94.4% for Low Stability QC and 95.3% for High Stability QC. Confirmed up to 161.0 hours at 4°C nominal in human plasma. Accuracy (% nominal): 90.0% for Low Stability QC and 102.7% for High Stability QC.
Long-term stability in biological matrix (Observed change %)	Confirmed up to 412 days at -80°C nominal in proxy matrix. Accuracy (% nominal): 100.1% for Low Stability QC and 94.8% for High Stability QC. Confirmed up to 412 days at -80°C nominal in human plasma. Accuracy (% nominal): 105.0% for Low Stability QC and 98.3% for High Stability QC.
Partial validation	NA
Cross validation(s)	NA

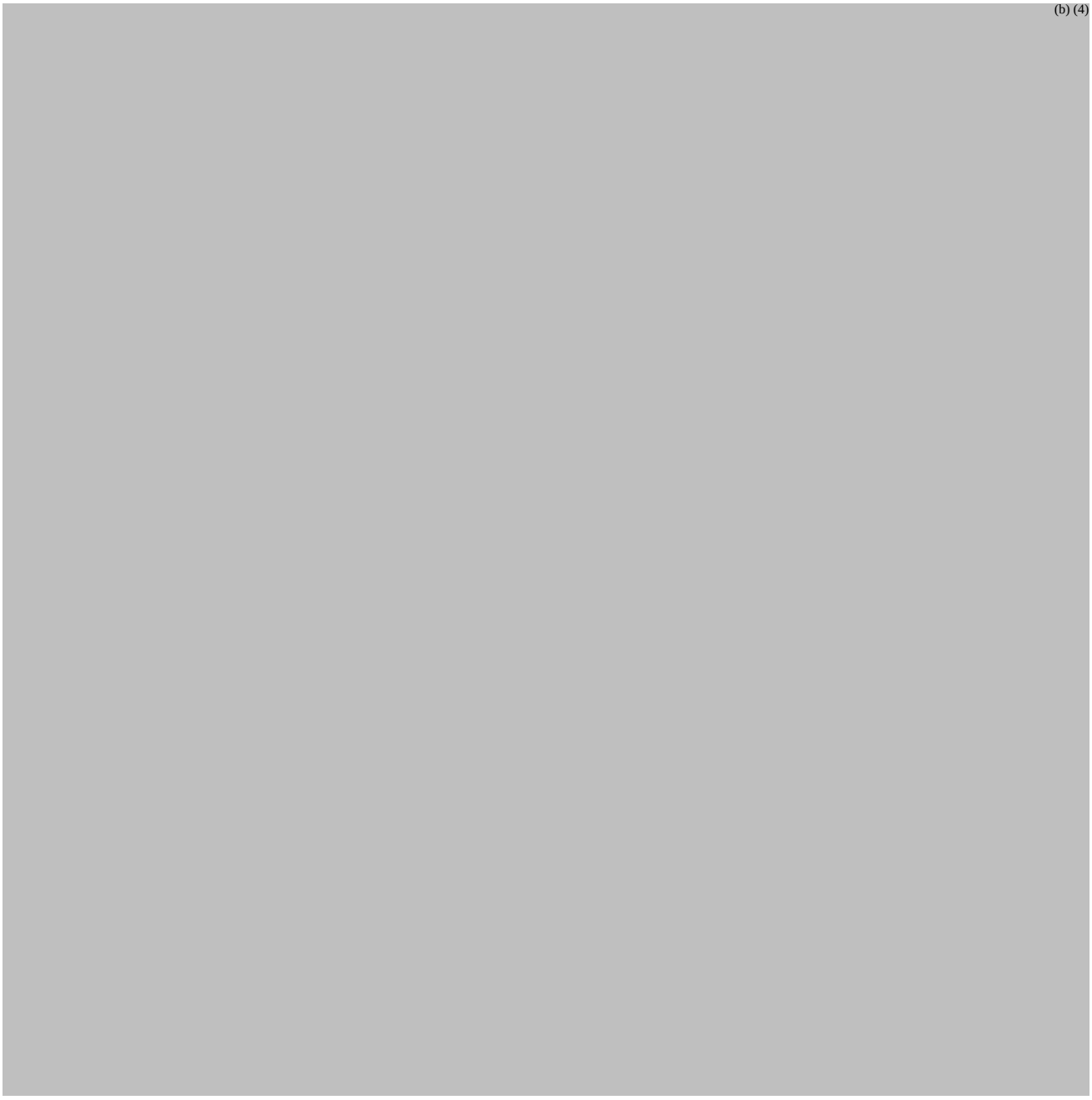
3. Sponsor's proposed labeling related to clinical pharmacology related information

Reviewer's Comment: In general, the proposed labeling is acceptable.

(underlined rex text indicates new proposed labeling and ~~strikethrough text~~ indicates deletion)

12.2 Pharmacodynamics

(b) (4)



(b) (4)

12.3 Pharmacokinetics

(b) (4)

Absorption

Subcutaneous injection of 1 mg PRODUCT NAME in adult type 1 diabetes mellitus subjects resulted in a mean glucagon C_{max} of 2481.3 pg/ml, t_{max} of 50.0 minutes and $AUC_{0\text{-}240min}$ of 3454.6 pg*min/ml.

Figure 3: Mean (± SEM) Plasma Glucagon Concentration vs. Time for PRODUCT NAME Injection in Adults with Type 1 Diabetes Mellitus

(b) (4)

(b) (4)

Figure 4: Mean (± SEM) Plasma Glucagon Concentration vs. Time from PRODUCT NAME Injection in (b) (4) (b) (4) **with Type 1 Diabetes Mellitus**

Elimination

The half-life of PRODUCT NAME was determined to be 32 (b) (4) minutes.

Metabolism

Glucagon is extensively degraded in liver, kidney, and plasma.

Excretion

Urinary excretion of intact glucagon has not been measured.

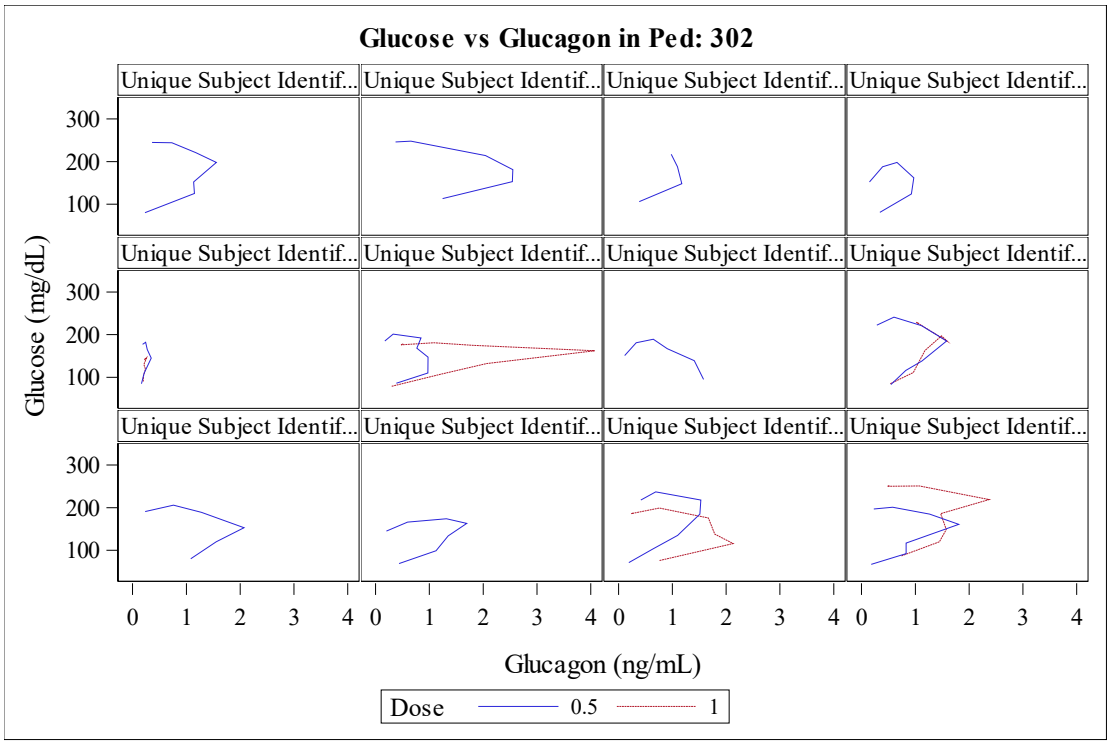
Specific Populations

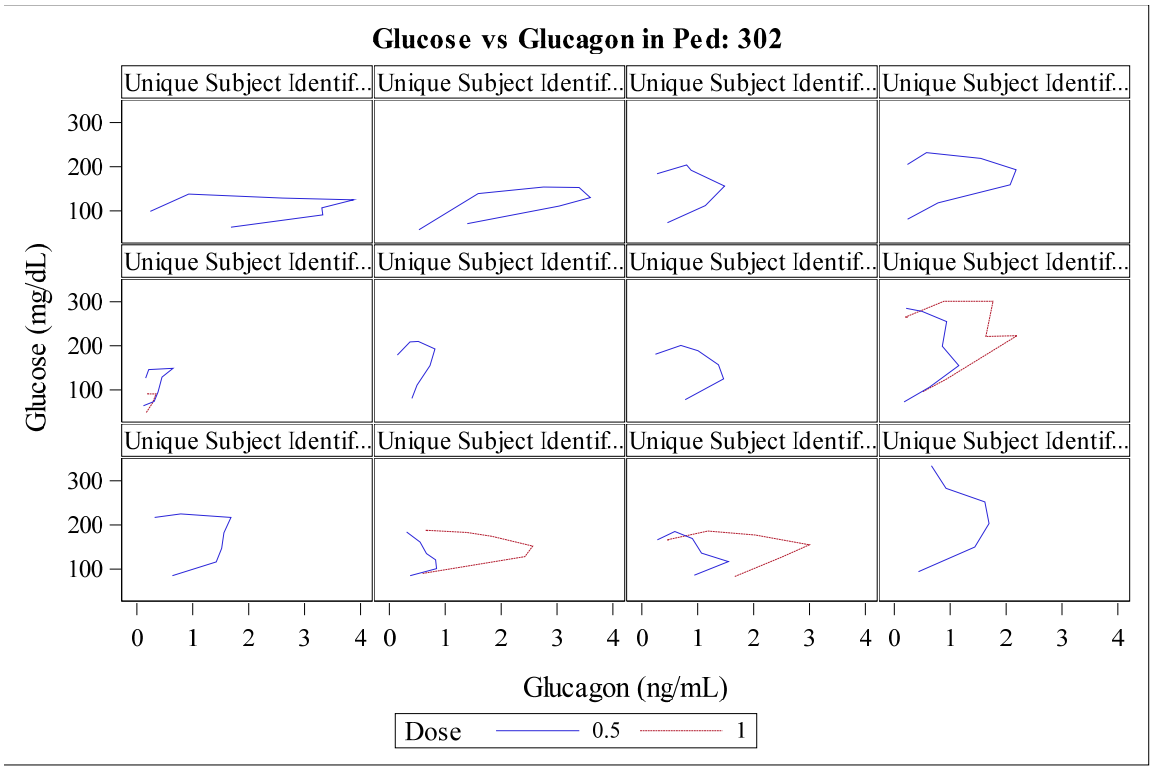
Pediatrics

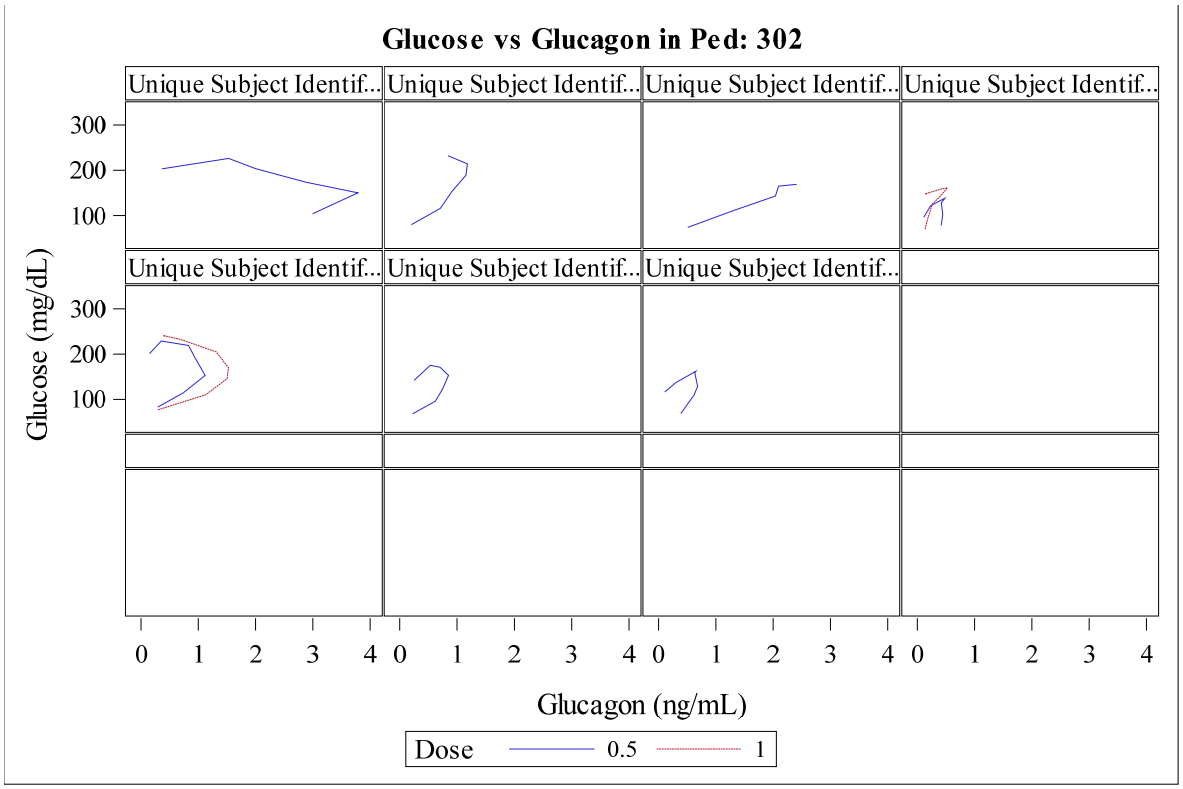
Subcutaneous injection of 0.5 mg PRODUCT NAME in (b) (4) ages 2 to < 6 years resulted in a mean glucagon C_{max} of (b) (4), t_{max} of 41 (b) (4) minutes, and $AUC_{0\text{-}180min}$ of (b) (4). Subcutaneous injection of 0.5 mg PRODUCT NAME in (b) (4) ages 6 to < 12 years resulted in a mean C_{max} of (b) (4), median t_{max} of (b) (4) minutes and $AUC_{0\text{-}180min}$ of (b) (4). Subcutaneous injection of 1 mg PRODUCT NAME in (b) (4) subjects ages 12 to < 18 years resulted in a mean C_{max} of (b) (4) t_{max} of 51 minutes $AUC_{0\text{-}180min}$ of (b) (4). Mean plasma glucagon levels were similar across the age groups following (b) (4) of PRODUCT NAME.

4. Appendix

4.1 Relationship between glucagon and glucose (individual): Study 302







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/s/

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