Cross-Discipline Team Leader Review

Date	September 9, 2019
From	Mitra Rauschecker
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	NDA 212097
Applicant	Xeris
Date of Submission	August 10, 2018
PDUFA Goal Date	September 10, 2019 with 3 month clock extension
Proprietary Name	GVOKE Hypopen and GVOKE PFS
Established or Proper Name	Glucagon injection
Dosage Form(s)	Subcutaneous injection
Applicant Proposed Indication(s)/Population(s)	Treatment of Severe Hypoglycemia
Applicant Proposed Dosing Regimen(s)	0.5 mg for 45 lbs or less, 1 mg for 45 lbs or greater
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of Severe Hypoglycemia
Recommended Dosing Regimen(s) (if applicable)	Same as above

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Severe hypoglycemia is a serious medical condition that is most commonly the result of insulin therapy and occurs in patients with both type 1 (T1DM) and type 2 diabetes mellitus (T2DM). It is characterized by neurological impairment requiring assistance from another person for remediation that can result in loss of consciousness, seizures, or death. Severe hypoglycemia is more common in patients with T1DM, occurring in approximately 22% to 46% of patients with T1DM annually, and 7% to 25% of patients with T2DM who are treated with insulin. Treatment options include intravenous dextrose, which requires administration by a healthcare professional in a hospital or emergency medical setting, and glucagon, which can be administered by injection or intranasally, and can be given by a caregiver outside of a hospital setting. The two currently approved injectable glucacon products, GlucaGen and Glucagon for injection, require reconstitution prior to administration. Intranasal glucagon was recently approved under the trade name Baqsimi. G-Pen is an injectable glucagon that does not require reconstitution prior to administration.

The clinical development program for G-Pen consisted of eight clinical studies, which included 2 controlled studies in adults (Studies 301 and 303) and an uncontrolled study in pediatric subjects (Study 302), and two human factors studies (adults and adolescents). G-Pen did not demonstrate non-inferiority to injectable glucagon (Lilly glucagon) in Study 301 in the mITT population, but did demonstrate non-inferiority in the PP population for the pre-specified primary endpoint of treatment success/failure scores, where success was defined by increasing glucose to $\geq$ 70 mg/dL. The pre-specified primary endpoint was met in Study 303. During the clinical development for G-Pen, due to concerns that for patients with a nadir blood glucose < 40 mg/dL, the composite of blood glucose > 70 mg/dL or blood glucose increase > 20 mg/dL at 30 minutes was proposed, as it was thought to be of greater clinical relevance, and would be consistent with other glucagon products. For this reason, although it was not a prespecified primary endpoint in Study 301, and was a prespecified secondary endpoint in Study 303, the composite blood glucose definition of success was examined in a pooled analysis. The non-inferiority margin was met for this alternate composite endpoint. I recommend this composite endpoint be used for the purposes of labeling.

The overall incidence of AEs, as well as local tolerability issues in Studies 301/303, was higher in subjects treated with G-Pen compared to Lilly glucagon. However, the AEs reported with G-Pen were anticipated based on the known safety profile of injectable glucagon. There was a higher incidence of injection site reactions with G-Pen, which may be attributed to the DMSO added to the formulation of glucagon, in comparison to Lilly glucagon. Most of the injection site reactions had resolved by 90 minutes postbaseline.

In summary, the clinical development program demonstrated G-Pen has a favorable benefit-risk profile. While there was a 3-4 minute delay in comparison to Lilly glucagon in reaching blood glucose $\geq$ 70 mg/dL, G-Pen was overall efficacious, and the time lag is likely mitigated by the requirement for reconstitution with Lilly glucagon. While the Applicant provided data demonstrating that administration of G-Pen is approximately 1 minute faster than Lilly glucagon, it is reasonable to assume untrained users would likely have a greater delay in administration of injectable glucagon, due to the need for reconstitution. I recommend approval of G-Pen for the treatment of severe hypoglycemia.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Severe hypoglycemia is a serious medical condition that is often a result of insulin treatment. • It occurs in patients with both T1DM and T2DM • It occurs in approximately 22% to 46% of patients with T1DM annually, and 7% to 25% of patients with T2DM who are treated with insulin.	Severe hypoglycemia is a serious medical condition characterized by neurologic impairment, and can lead to death.
Current Treatment Options	• Intravenous dextrose infusion can be administered in a healthcare setting only • Injectable glucagon can be administered in an outpatient setting, but currently available formulations require reconstitution. • Nasal glucagon was recently approved, and is administered intranasally.	Currently approved injectable glucagon requires reconstitution prior to use.
Benefit	• G-Pen demonstrated noninferiority compared to Lilly glucagon in treatment success, as defined by achieving blood glucose of ≥70 mg/dL, or rise of blood glucose ≥20 mg/dL from nadir within 30 minutes of glucagon administration, in both adults and pediatric subjects. • G-Pen does not require reconstitution.	G-Pen was effective in increase blood glucose levels. The lack of the need for reconstitution offers a potentially easier presentation to administer glucagon product for emergency use.
Risk and Risk Management	• Safety was generally consistent with injectable glucagon products, although there was a higher incidence of non-serious AEs • Some of the injection site reactions seen with G-Pen were rated as severe, but generally resolved by 90 minutes. • The time to achieve a blood glucose of ≥70 mg/dL was delayed by 3-4 minutes for G-Pen compared to Lilly glucagon.	The safety of G-Pen can be adequately communicated in labeling. Although there was a delay to reach a blood glucose of ≥70 mg/dL for G-Pen compared to Lilly glucagon by 3-4 minutes, G-Pen does not require reconstitution. It is reasonable to assume this would offset the delay.

2. Background

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

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

G-Pen was developed as a treatment for severe hypoglycemia in both adult and pediatric patients with diabetes which is defined as requiring assistance from another person due to neuroglycopenia. The drug substance is synthetic glucagon, which is identical to human glucagon, a peptide consisting of 29 amino acids. Xeris Pharmaceuticals, hereafter referred to as the Applicant, has submitted a new drug application (NDA) under the 505(b)(2) pathway, and is relying, in part, on the FDA's previous findings of safety and efficacy for Lilly's glucagon (NDA 020928), and is seeking approval for G-Pen, a single-use injectable glucagon for rescue. G-Pen differs from Lilly glucagon in that it does not require reconstitution.

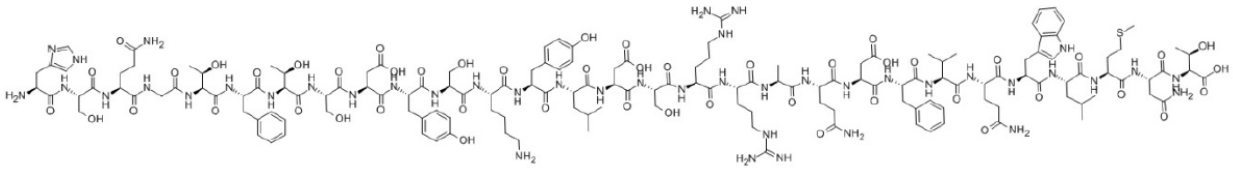
The indication for G-Pen proposed by the Applicant is *an antihypoglycemic agent indicated for the treatment of severe hypoglycemia.* The Applicant is proposing two doses for G-Pen of 0.5 mg or 1 mg, depending on age. The proposed trade name for G-Pen is GVOKE. The drug product will be administered via a prefilled device for subcutaneous administration.

In support of this NDA, the Applicant conducted a total of 8 trials, which included 2 controlled clinical studies in adults (Studies 301 and 303) and an uncontrolled study in pediatric subjects (Study 302), and two human factors studies (adults and adolescents).

3. Product Quality

Drug Substance:
The drug substance of G-Pen, synthetic glucagon, is a peptide hormone with an identical amino acid sequence as human glucagon produced by the pancreatic alpha cells. It is is a lyophilized powder composed of 29 amino acid residues, arranged in a single-chain polypeptide, with a molecular weight of 3483. The empirical formula is $C_{153}H_{225}N_{43}O_{49}S$. The chemical structure of glucagon is shown below, in Figure 1.

Figure 1: Chemical Structure of Glucagon



Source: Figure 1 from Applicant's eCTD 2.3.S

The drug substance is manufactured using solid-phase peptide synthesis (SPPS), at Bachem AG. The Applicant referenced drug substance information to Bachem's DMF.

Drug Product

Since glucagon is nearly insoluble in water at pH 3.0-9.5, the commercially available glucagon products are provided as a lyophilized powder that must be reconstituted immediately prior to use. The Applicant has added DMSO to glucagon (b) (4) (b) (4). G-Pen contains contains either 0.5 mg or 1 mg of synthetic glucagon, along with the addition of trehalose dihydrate, (b) (4) DMSO, (b) (4) sulfuric acid. The drug product is contained in a ready-to-use sterile solution which is then (b) (4) filled into (b) (4) syringes. The pre-filled syringes are then sent to a different manufacturer for final assembly into the auto-injector presentation (Configuration A), or packaged with a manual plunger rod and backstop (Configuration B). The components of G-Pen are shown below, in Table 1. All excipients are present in approved products.

Table 1: G-Pen Excipients

Excipient	Vendor	Grade	Function
Trehalose dihydrate	(b) (4)	USP	Excipient
Dimethyl Sulfoxide		USP	(b) (4)
Sulfuric Acid		NF	

Source: Table 1 from Applicant's eCTD 3.2.P.2

The applicant conducted testing to evaluate 6 month accelerated stability, 12 months of intermediate storage stability data, and 24 months of long-term storage stability data. Based on the provided stability data, Dr. Ramaswamy recommends an expiration period of 24 months when stored at 20-25°C for the pre-filled syringe/auto-injector. As the product is sensitive to light, the product label requires storage in foil pouches to prevent degradation.

The manufacturing process was found to be adequate. During development, changes to the formulation and process changes were made after the phase 2 studies were completed. The updated formulation used in phase 3 studies (b) (4), (b) (4) used sulfuric acid. The new formulation provided additional stability for glucagon, and simplified the manufacturing process.

The drug product is sterile (b) (4) (b) (4). The microbiology reviewer, Dr. Renee Marcisin, reviewed the contained closure component sterilization information, integrity of the container closure system, as well as the microbiological controls used in the drug product manufacturing process. Her review concluded that the microbiological controls are adequate to support the NDA.

For detailed discussion of the drug substance and drug product manufacturing process, see Dr. Haber's and Dr. Ramaswamy's reviews. The Office of Product Quality (OPQ) CMC review concludes that the overall recommendation is for approval. For further details, please see the OPQ review.

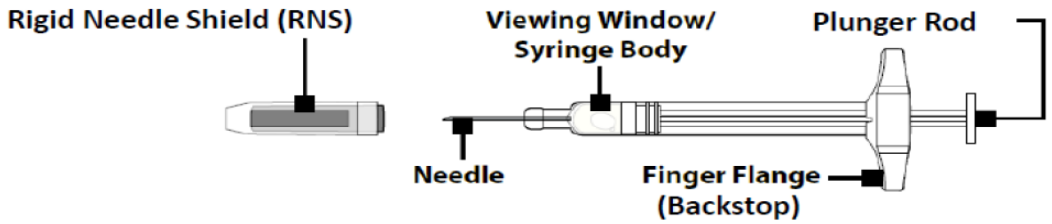
Device:

G-Pen is designed to be delivered via a pre-filled syringe (PFS)/auto-injector (AI) device (Configuration A), or a PFS, rigid needle shield, plunger rod, and backstop (Configuration B), which is intended to deliver a single dose of glucagon subcutaneously. The device is displayed below, in Figure 2.

Figure 2: Configuration A (top) and Configuration B (bottom)

(b) (4)

Source: Figure 1 from CDRH review



Source: Figure 1 from eCTD 3.2.P.7

The proposed device and its performance characteristics were reviewed by Dr. Jaqueline Gertz from the Center for Devices and Radiologic Health (CDRH). Essential performance requirements for a PFS include break loose and glide force, dose accuracy, and needle length. Essential performance requirements for an AI are failure to fire, activation force, extended needle length, injection time, and dose accuracy. These essential performance requirements for both the PFS and AI were reviewed by the CDRH reviewer. The applicant had initially evaluated only injection time and injection volume in their reliability study, and an Information Request was sent. The Applicant responded with the additional information, including updated reliability assesssments, and their response was deemed adequate by the CDRH reviewer. Additional information requests were sent regarding the Applicant's fault tree analysis, and it was determined that the initial fault tree analysis provided by the Applicant had fundamental structural issues. The CDRH review team communicated these deficiencies to the Applicant, and a restructured fault tree analysis was received on May 30, 2019 which resulted in a major amendment to the NDA and a clock extension. Additional deficiencies were noted by Dr. Gertz, which were also communicated to the Applicant. The Applicant provided additional information, and ultimately, Dr. Gertz concluded that the applicant had supported the conclusions of the fault tree analysis.

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

The applicant conducted a human factors validation studies for both the PFS and AI presentations in order to support that intended users could understand product instructions and appropriately administer the dose. The validation study results were reviewed by the Division

of Medication Error Prevention and Analysis (DMEPA), and their review determined that the human factor study results showed use errors and use difficulties. These errors, however, were not attributed to the product user interface except for three use difficulties. DMEPA recommended the Applicant implement changes to product labeling. These recommendations were communicated to the Applicant. In addition to addressing the recommendations made by DMEPA, the Applicant made additional design changes to the carton and container labeling, although the human factors validation studies were conducted using the original labels and labeling. The Applicant's changes included changes to the color scheme of the labels and labelling and revisions to the AI device labels to include an arrow that points to the needle end of the device. An IR was sent to the Applicant, and in their response, it was determined the Applicant had provided justification for the changes, however additional recommendations were made by DMEPA. The Applicant implemented the recommended changes. For further details, please see the DMEPA review by Dr. Ariane Conrad.

Facilities:
The drug product manufacturing site pre-approval inspections were conducted by Dr. Ramesh Dandu. The inspection findings indicated that the finished drug testing method and product specification did not conform to the NDA application. For this reason, Dr. Dandu initially recommended "withhold" for the manufacturing facility and overall cGMP compliance for the NDA. The manufacturing facility, Pyramid Laboratories, updated the test method and product release test specification for the proposed commercial batch record for G-Pen, which subsequently was aligned with the NDA. Pyramid Laboratories also qualified the impurities determination method and provided the method qualification report. As a result of the updated information provided by Pyramid Laboratories, the OPF reviewer, Dr. Dandu, concluded that Pyramid Laboratories is acceptable as the drug product manufacturer.

The CMC reviewers concluded that information provided in process and facilities is acceptable to support the approval of this NDA.

4. Nonclinical Pharmacology/Toxicology

The Applicant has submitted the NDA for G-Pen under the 505(b)(2) pathway, and is relying, in part on the safety information for Lilly glucagon as the listed drug. The nonclinical program for G-Pen was designed compare the toxicology, pharmacokinetic, and local tolerance profiles of G-Pen, and the listed drug, Lilly glucagon, as well as to qualify potential impurities after deliberate degradation, for the intended short-term clinical usage.

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

The applicant conducted pharmacokinetic studies in rats which demonstrated the PK profiles of G-Pen and Lilly glucagon were similar, with both products producing increases in blood glucose concentrations to comparable levels.

The applicant conducted a 14-day repeat-dose toxicity study in rats, as well as a single dose local tolerance study in rabbits. In rats, a repeat-dose study resulted in minimal to marked injection site reactions, which were reversible. These injection site reactions appeared to be more severe after the recovery period in high dose G-Pen treated rats compared with Lilly glucagon treated rats. The NOAEL in rats was the highest dose evaluated (2 mg/kg/day), with a 19-fold exposure multiple to the maximum recommended human dosage. The Applicant attributed the increase in injection site reactions to the DMSO used in the G-Pen formulation.

The Applicant also conducted a single dose toxicity study in rabbits. Injection site reactions were also noted in G-Pen treated rabbits, with minimal to mild inflammation and degeneration/necrosis observed on Day #3, which was reversible by Day #14.

The Applicant evaluated G-Pen under accelerated stability conditions, and three leachable compounds were detected which exceeded the ICH Q3A guidance; (b) (4) (b) (4). The doses observed (b) (4) were not considered to pose a toxicological risk to humans. The animal studies for rats with exposure to (b) (4) demonstrated centrilobular necrosis, but this finding is associated with exposure to glucagon, and is not thought to be due to exposure to (b) (4).

The nonclinical data provides a scientific bridge, given the similar toxicologic and pharmacokinetic profiles, to justify reliance on the listed drug. In summary, based on the data reviewed, Dr. Braithwaite recommends approval.

5. Clinical Pharmacology

The clinical development program for G-Pen included two comparative PK/PD studies in healthy volunteers, along with four studies in subjects with T1DM. These studies included one phase 2 pilot study that was uncontrolled, along with three phase 3 clinical safety and efficacy studies in which PK/PD data was obtained, and included one study in pediatric subjects with T1DM. See Table 2, below. Note that in this section, G-Pen is referred to by its proprietary name (G-VOKE) in the Clinical Pharmacology figures.

Table 2: Clinical Studies for NG with PK/PD results

Type of Study/ Study Identifier	**Objective(s) of the Study**	**Study Design**	**Dosage Regimen**	**Subjects Enrolled**	**Study Pop.**
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	HV

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	HV
Efficacy 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)
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)
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	81	T1D (Adults)
Efficacy XSGP- 202	Pilot Study; Safety, Efficacy	R, OL, 2XO	G-Pen; Single doses (0.5 and 1 mg), vial & syringe, SC	7	T1D (Adults)
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)

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)

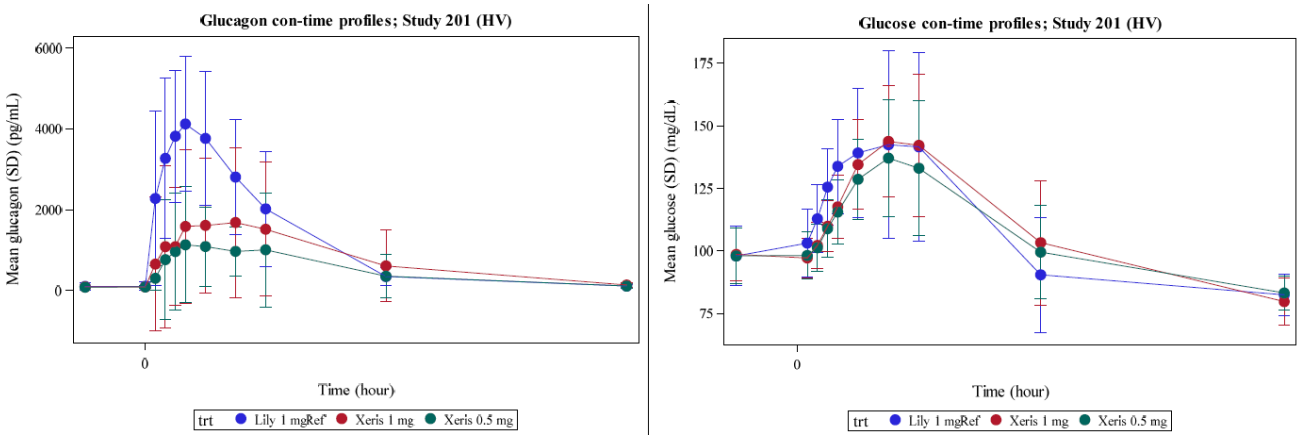
Note: R=Randomized, NR=Non-Randomized, DB=Double-Blind, SB=Single Blind, OL=Open Label, XO=Crossover, PK=Pharmacokinetics, PD=Pharmacodynamics, AI=Autoinjector (configuration A), PFS=Pre-filled-syringe (configuration B), SC=Subcutaneous, HV=Healthy volunteers, T1D=Type 1 diabetes.

Source: Adapted from Table 1 from eCTD 2.7.6

In Study 101, the Applicant conducted a comparative PK/PD study in healthy adult subjects evaluating the PFS with AI and manual plunger rod and backstop presentations of G-Pen. The PFS with AI was also used in the phase 3 studies, while the manual plunger rod and backstop presentation is another to-be-marketed device. The study demonstrated bioequivalence between the two presentations, based on PK and PD parameters, in healthy adult volunteers.

In Study 201, the mean PK (glucagon) and PD (glucose) profiles for two doses of G-Pen were compared to Lilly's subcutaneously (SC) administered glucagon after a dose of 0.5 mg or 1 mg in healthy adult subjects in a three-way crossover design. The PK and PD profiles are displayed graphically in Figure 3 and in tabular format in Table 3 below. As seen in the left panel of Figure 3 and in Table 3, although PD parameters, based on $AUC_{0\text{-}240min}$ and C_{max}, were similar between G-Pen and Lilly glucagon, PK similarity was not demonstrated, and compared to Lilly glucagon, the $AUC_{0\text{-}240min}$ and C_{max} of G-Pen were lower. For $AUC_{0\text{-}240min}$, G-Pen was 55% and 39% lower for 1.0 mg and 0.5 mg, respectively, compared to Lilly glucagon, while the C_{max} was 34% and 22% lower. Therefore, bioequivalence between G-Pen and Lilly glucagon was not demonstrated. As a result, the Applicant conducted phase 3 studies to establish similar safety and efficacy between the two products. However, the dose selection for the phase 3 trials was supported by the PD results of Study 201.

Figure 3: Mean Plasma Glucagon Concentration and Glucose Exposure- Study 201



Source: Figure 5 from Clinical Pharmacology review

Table 3: PD (Glucose) and PK (Glucagon) parameters for G-Pen versus Lilly glucagon- 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

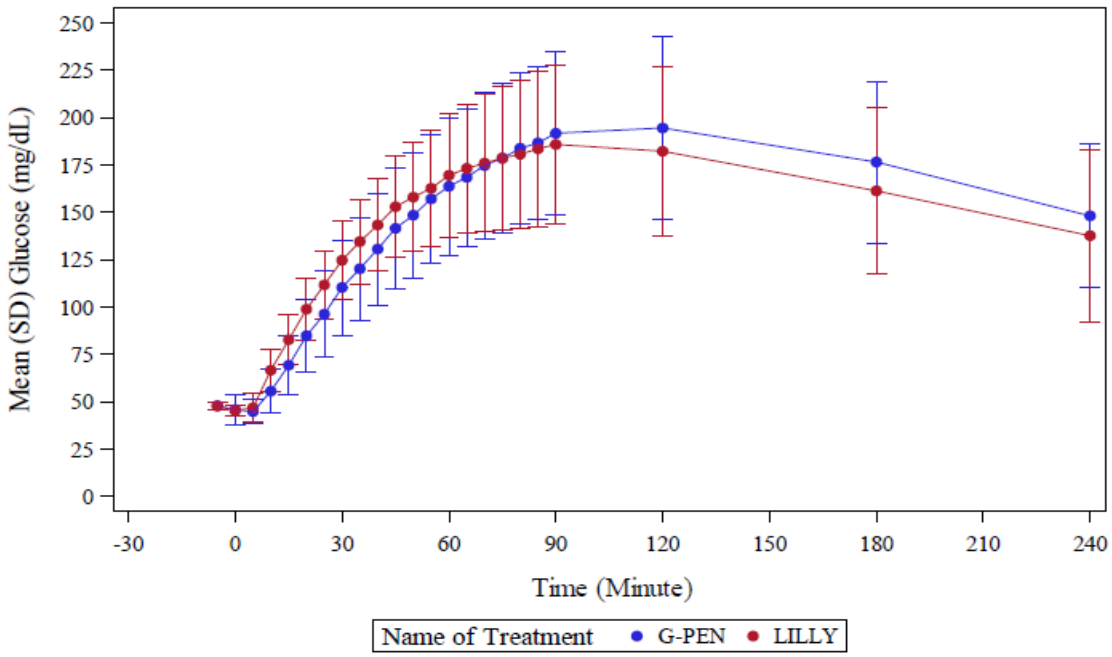
Glucagon		Treatment			p-value[a]	Ratio of Means (90% CI)
		Lilly 1.0mg	G-VOKE 1.0 mg	G-VOKE 0.5mg		
	N	27	28	28		
$AUC_{0\text{-}240min}$ (pg/mL*min)	Mean (SD)	4781.7 (2222.9)	3259.9 (3447.5)	2105.3 (2381.9)		
	Comparison	G-VOKE 1.0 mg vs Lilly 1.0 mg			0.99	0.549 (0.435, 0.693)
		G-VOKE 0.5 mg vs Lilly 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 4 from Clinical Pharmacology review

In the phase 3 clinical study (Study 301), the Applicant evaluated the PK/PD of 1 mg of G-Pen compared to Lilly glucagon in T1DM subjects.

The glucose (PD) concentration-time profiles were comparable between G-Pen and Lilly glucagon, although it was noted the rate of increase in glucose was numerically slower for G-Pen compared to Lilly glucagon. See Figure 4, below.

Figure 4: PD Parameter: Glucose Concentration-Time Profiles- Study 301



Source: Figure 7 from Clinical Pharmacology review

The mean $AUC_{0\text{-}240min}$ and C_{max} for glucagon was 3454.6 pg/mL*min and 2481.2 pg/mL, respectively, for G-Pen. Although the Applicant included PK data from all subjects who received G-Pen treatment, PK data for only 20 subjects who received Lilly glucagon was included with the submission. Therefore, PK data for the comparator are included for descriptive purposes only. See Table 4, below.

Table 4: Glucagon PK parameters- 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)

Source: Table 5 from Clinical Pharmacology review

The Applicant also evaluated PK/PD data in pediatric subjects with T1DM in Study 302. The data from Study 302 demonstrated that there was no apparent difference between age or sex and PK or PD parameters. In the 12 to under 18 years of age group, there was an increase in exposure for the 1 mg dose compared to the 0.5 mg dose, but there was no corresponding PD change, as the glucose AUC were similar between the two doses. For further details, please see Dr. Sang Chung's Clinical Pharmacology review.

Overall, the clinical pharmacology data demonstrate the glucose response curves for both G-Pen and Lilly glucagon were similar. Although the $AUC_{0\text{-}240min}$ and C_{max} for glucagon were lower for G-Pen compared to Lilly glucagon, this did not appear to impact the PD response. While the time to reach BG > 70 mg/dL was slower for G-Pen by several minutes, this difference is not clinically meaningful, as G-Pen appears to offer greater ease of use due to the lack of the need for reconstitution in comparison to Lilly glucagon.

Based on the reviewed clinical pharmacology data, which support the pharmacodynamic response of G-Pen, Dr. Chung and Dr. Khurana support approval of G-Pen for treatment of severe hypoglycemia. The Office of Study Integrity and Surveillance (OSIS) performed an inspection for Study 101, and the OSIS reviewer concluded that the data submitted are reliable for Agency review.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The Applicant conducted three Phase 3 studies in support of this application, which included two studies in adults (301 and 303), and one study in pediatric subjects (302). The efficacy discussion will focus on Studies 301 and 303, with presentation of efficacy data for Study 302 for descriptive purposes. The primary efficacy endpoint was reviewed by Dr. Anna Ketterman. The efficacy findings are summarized in this review. For a more detailed discussion, please see Dr. Ketterman's review.

Table 5: Clinical Studies Conducted with G-Pen in Support of Efficacy

Type of Study	Study Number	Study Design	Test Product, Dose Regimen, Route of Administration	Subjects Population
Phase 1	XSGP-101	R, PK/PD 2XO, OL	G-Pen; Single dose (1 mg) via AI and single dose (1 mg) via PFS, SC	Healthy (adults) N=32
Phase 2	XSGP-201	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	Healthy (adult) N=30
Phase 2	XSGP-202	R, OL, 2XO	G-Pen; Single doses (0.5 and 1 mg), vial & syringe, SC	T1D (adult) N=7
Phase 3	XSGP-301	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	T1D (adult) N=80
Phase 3	XSGP-302	N-R, OL	G-Pen; Single dose via AI (0.5 mg) and single dose via AI (1 mg) ages 12-< 18 only, SC	T1D (pediatric) N=32
Phase 3	XSGP-303	R, SB, 2XO	G-Pen and Lilly Glucagon; Single dose (1 mg) of G-Pen via AI and single dose of Lilly Glucagon (1 mg), SC	T1D (adult) N=81

AI=auto injector (configuration A), DB=double-blind, N-R=non-randomized, OL=open-label, PD=pharmacodynamic(s), PFS=pre-filled syringe (configuration B), PK=pharmacokinetic(s), R=randomized, SB=single blind, SC=subcutaneous(ly), T1D=type 1 diabetes, XO=crossover, 2XO=two-way crossover, 3XO=three-way crossover

Source: Table 1 from Applicant's Clinical Overview

Study Design- 301/303:

Study 301 was a double-blind, randomized, cross-over study with a non-inferiority design comparing the efficacy and safety of G-pen to Lilly glucagon in adult patients with T1DM. Study 303 differed from Study 301 in that it was a single-blinded study.

At each study visit, subjects were given an IV infusion of regular insulin which was stopped once blood glucose levels reached < 60 mg/dL, with a target nadir blood glucose level of < 50 mg/dL. Blood glucose levels were based on an average of 2 readings taken at each time point. After a second confirmatory blood glucose level of < 50 mg/dL was obtained at least 5 minutes after the initial reading, G-pen or Lilly glucagon was administered. Following administration of either G-pen or Lilly glucagon, blood glucose values were measured for 90 minutes in Study 301, and for 180 minutes in Study 303. There was a 7 to 28-day washout period between study visits, after which subjects crossed over to the other study treatment.

The non-inferiority of G-Pen to Lilly glucagon was based on treatment success/failure scores. Treatment success was defined as an increase in blood glucose from below 50 mg/dL to greater than 70 mg/dL, within 30 minutes after receiving study glucagon. The score was set to 0 if treatment success was achieved, and was set to 1 if treatment success was not achieved. If as a

result of missing values treatment success could not be determined, the score was set to 0.2 in the G-pen group, and 0.1 in the Lilly glucagon group.

The non-inferiority criterion for the primary endpoint was defined by the following equation:

Dht + coefficient* SE ≤ 0.1

Dht is the sample mean of treatment within-subject differences of treatment success/failure scores (G-pen minus Lilly glucagon). SE is the estimated standard error of Dht (square root of the estimated G-Pen minus control variance divided by the sample size). The Applicant used a coefficient of 2.6 in Study 301 and 2.8 in Study 303. The applicant obtained the values of the coefficient using Monte-Carlo simulations.

Study 301 was double-blinded to both subject and investigator, and only the pharmacist, who administered the glucagon, was unblinded. Due to a time delay for blinded study staff to leave the procedure room, Study 303 was single-blinded, and open label to the investigator.

Study 303 also utilized computer software to help predict 8 minute glucose values, and guide insulin dosing, due to difficulties with achieving target blood glucose values with the insulin infusion algorithm used in Study 301.

Study Design: 302

This study, conducted in pediatric subjects, was an uncontrolled phase 3 study to evaluate the blood glucose response of pediatric subjects with T1DM following administration of G-pen. The primary objective of this study was to assess the increase in blood glucose from baseline to 30 minutes in subjects in a low normal glycemic state (blood glucose < 80 mg/dL) after injection of an age-appropriate dose of G-Pen, in each of three age groups (2.0-<6.0 years, 6.0-<12.0 years and 12.0-<18.0 years). Subjects were administered 0.5 mg of G-Pen for those younger than 12 years of age, or 1 mg of G-pen in subjects 12 years of age or older, followed by a 0.5 mg dose of G-Pen given at a second visit which occurred 1 to 4 weeks later. During the study, insulin was infused until blood glucose levels reached < 80 mg/dL. Five minutes later, after a second confirmatory blood glucose reading of < 80 mg/dL, G-Pen was administered. Blood glucose levels were measured for up to 180 minutes following administration of G-Pen. Due to ethical concerns related to hypoglycemia in pediatric subjects, a low normal blood glucose target of < 80 mg/dL was used.

Statistical Methods:

The prespecified primary endpoint for both Studies 301 and 303 was the difference in treatment success scores, with treatment success defined as an increase in blood glucose from below 50 mg/dL to greater than 70 mg/dL, within 30 minutes after receiving study glucagon. The Applicant calculated the success/failure scores which were included in the calculation for non-inferiority, and performed these calculations in all randomized subjects (ITT population), and were repeated on subjects who completed both study treatments (PP population). The ITT population was used for the primary endpoint (with missing data imputed), while the mITT population was used for all other endpoints (missing data was not imputed).

In Study 303, the Applicant evaluated a prespecified secondary endpoint which defined treatment success as an increase in plasma glucose concentration > 70 mg/dL or increased ≥ 20 mg/dL within 30 minutes after receiving study glucagon.

Study 302 did not involve pre-specified comparisons and induction of hypoglycemia, the data were to be analyzed descriptively and were considered exploratory.

Study Results

The disposition of subjects in Studies 301 and 303 is displayed below in Table 6. In Study 301, all 80 subjects randomized received at least one dose of any study drug, with 78 subjects receiving G-pen and 79 subjects receiving Lilly glucagon. In Study 303, 81 subjects were randomized, with 76 subjects who received G-Pen treatment, and 78 subjects who received Lilly Glucagon treatment.

Table 6: Subject Disposition for Study 301/303

	Number (%) of Patients			
Study	301		303	
Treatment	G-Pen	Lilly Glucagon	G-pen	Lilly Glucagon
Randomized	80	80	81	81
ITT population	80	80	81	81
Received at least one dose of study drug- mITT population	78 (97.5%)	79 (98.8%)	76 (93.8%)	78 (96.3)
Subjects with Missing Data	2	1	5	3

Source: adapted from Statistical Reviewer's analysis

In Study 301 and 303, medication errors resulted in missing data for several subjects. In Study 301, 1 subject received Lilly glucagon twice, 1 subject received treatment in incorrect order, and 1 subject withdrew from the study before receiving both treatments. In Study 303, 5 subjects did not receive G-pen, while 3 subjects did not receive Lilly glucagon.

There were 31 pediatric subjects enrolled in Study 303, which included 7 subjects (22.6%) aged 2 to less than 6 years of age, 13 subjects (41.9%) aged 6 to less than 12 years of age, and 11 subjects (35.5%) aged 12 years to less than 18 years of age.

Study 301:
Following administration of G-pen and Lilly glucagon, 74 subjects (94.9%) out of 78 subjects in the G-pen group and 79 subjects (100%) out of 79 subjects in the Lilly glucagon group included in the mITT population achieved a blood glucose > 70 mg/dL within 30 minutes. Therefore, based on the test result of the difference of failure scores, G-pen did not satisfy the non-inferiority criterion to Lilly glucagon, as the Failure Scores (Dht) were > 0.1. However, the Applicant noted there were two subjects with major protocol violations in which the insulin infusion rate was increased despite blood glucose trajectories being on target. As a result, 2 subjects were excluded from the Per Protocol (PP) population, which included 76 subjects in the G-pen group and 77 subjects in the CG group. The non-inferiority criterion was satisfied in the PP population.

Table 7: Test Result of the Difference of Failure Scores (D_{ht})- Study 301

	D_{ht}	$SE_{D(ht)}$	$D_{ht} + 2.6 \times SE_{D(ht)}$	Non-inferiority Criterion
ITT population	(b) (4)			
Pre-specified PP Population				
Revised PP population	0.043	0.022	0.099	Satisfied

Source: table 10 and table 14.2.2.1, CSR for Study 301

Study 303:

Following administration of G-pen and CG, 76 subjects (100%) out of 76 subjects in the G-pen group and 78 subjects (100%) out of 78 subjects included in the mITT population in the Lilly glucagon group achieved a blood glucose > 70 mg/dL within 30 minutes. Therefore, G-pen satisfied the non-inferiority criterion to Lilly glucagon based on the test result of the difference of failure scores.

Table 8: Test Result of the Difference of Failure Scores (D_{ht})- Study 303

	D_{ht}	$SE_{D(ht)}$	$D_{ht} + 2.8 \times SE_{D(ht)}$	Non-inferiority Criterion
ITT population	0.009	0.005	0.022	Satisfied
Pre-specified PP Population	0.000	0.000	0.000	Satisfied

Source: Adapted from Applicant's Table 15, CSR for Study 303

As a result of inspectional findings by the OSI reviewer, Dr. Cynthia Kleppinger (discussed in further detail below), it was noted that 9 subjects participated in both Study 301 and Study 303. The statistical reviewer, Dr. Anna Ketterman analyzed the primary endpoint for the ITT population both with and without dual participants, and using both coefficients in the calculations. Dr. Ketterman concludes the dual participants did not affect the results of either Study 301 (which did not demonstrate non-inferiority) and Study 303 (which demonstrated non-inferiority regardless of scenario). See Table 9, below.

Table 9: Primary Endpoint- Study 301/303

Population Status	Number of subjects	D_{ht}	SE_{dht}	Primary endpoint (coefficient=2.8)	Primary endpoint (coefficient=2.6)
Study 301*					
All subjects	80	(b) (4)			
Study 303*					
All subjects	81	0.009	0.005	0.022	0.021
Without dual participants**	72	0.01	0.005	0.024	0.023

* In study 301, two subjects in G-pen arm and 1 subject in Lilly glucagon arm had success/failure scores missing; in
study 303, five subjects in G-pen arm and 3 subjects in Lilly glucagon had success/failure scores missing. Missing
values in G-Pen were replaced with 0.2 and missing values in Lilly glucagon were replaced with 0.1
**Subjects who participated in both studies
Source: Table 5 from Statistical Reviewer

The Applicant's prespecified primary endpoint was dependent on the blood glucose values at nadir, and as a result, if subjects nadir glucose was very low (i.e. < 40 mg/dL), their blood glucose values would take longer to reach the target of 70 mg/dL. In Study 301, the pre-specified primary endpoint was not met, which the Applicant argued was due to difficulty with the insulin infusion resulting in some subjects with a nadir blood glucose < 40 mg/dL, although this also occurred with subjects in the Lilly glucagon group. Of the 4 subjects in the G-pen group in Study 301 that did not achieve the pre-specified target blood glucose of > 70 mg/dL, three of the four subjects achieved an increase in blood glucose of > 20 mg/dL from their nadir blood glucose at 30 minutes. Given the possibility that in a real use scenario, patients would have a nadir blood glucose < 40 mg/dL, the composite of blood glucose > 70 mg/dL or blood glucose increase > 20 mg/dL at 30 minutes is thought to be of greater clinical relevance. Moreover, the composite blood glucose endpoint would be consistent with other glucagon products. For this reason, although it was not a prespecified primary endpoint in Study 301, and was a prespecified secondary endpoint in Study 303, the composite blood glucose definition of success was examined in a pooled analysis. The non-inferiority margin was met for this alternate composite endpoint. See Table 10, below.

Table 10: Number of Subjects with Blood Glucose > 70 mg/dL or ≥ 20 mg/dL Increase Within 30 Minutes of Dosing- Studies 301/303 (mITT population)

Blood Glucose within 30 mins post-dose	Pooled Analysis (301, 303)	
	G-Pen (N=154)	**Lilly (N=157)**
Blood Glucose > 70 mg/dL or ≥ 20mg/dL Increase	152 (98.7)	157 (100.0)
Blood Glucose > 70 mg/dL	150 (97.4)	157 (100.0)
Blood Glucose Increase ≥ 20 mg/dL	152 (98.7)	157 (100.0)

Source: Adapted from Applicant's ISE tables: 3.2.1, 3.4.1 and 3.6.1

In her review, Dr. Ketterman noted the time to blood glucose recovery (defined as either blood glucose > 70 mg/dL or increase in blood glucose >20 mg/dL was approximately 4 minutes slower for G-pen compared with Lilly glucagon in Study 301, and approximately 3 minutes slower in Study 303. See Table 11, below.

Table 11: Time to Recovery of Blood Glucose- Studies 301/303

BG Benchmark	Time to BG Benchmark (minutes) Mean (95%CI)			
	Study 301		Study 303	
	G-Pen	Lilly glucagon	G-Pen	Lilly glucagon
Increase in BG ≥ 20 mg/dL	13.1(11.6, 14.6)	8.9(8.2,9.6)	10.1(9.4,10.8)	7.3(6.9,7.7)
BG >70 mg/dL	14.9(13.4, 16.4)	10.6(9.9, 11.4)	10.7(10,11.4)	7.6(7.1, 8)
BG > 70 mg/dL or increase in BG ≥ 20 mg/dL (earliest)	12.90(11.44, 14.35)	8.79(8.12, 9.47)	9.9(9.2,10.6)	7(6.6, 7.4)

Source: Table 7 from Statistical Reviewer's analysis

In Study 303, the Applicant collected data on the timing of decision to dose glucagon, along with the timing of the actual administration of the study drug, in order to determine if the lack of the need for reconstitution of G-pen resulted in faster drug administration compared to Lilly glucagon. Glucagon was administered by trained medical professionals, however, and not by untrained users. The data are shown below, in Table 12, and demonstrate that time to administration of G-pen was one minute faster compared with Lilly glucagon.

Table 12: Time from Decision to Dose To Drug Administration (in Minutes)- Study 303

	Time in minutes							
Assigned treatment	**N**	**Median**	**Minimum**	**Maximum**	**Mean**	**Lower 95% CL**	**Upper 95% CL**	**Std Dev**
G-Pen	77	0.78	0.20	6.28	1.14	0.91	1.37	1
Lilly glucagon	79	1.80	0.37	6.88	2.15	1.86	2.44	1.30

Source: Table 8 from Statistical Reviewer's analysis

Study 302:

Following administration of either 0.5 mg or 1 mg of G-pen, statistically significant increases from baseline in mean blood glucose values were achieved in all age groups at 30 minutes ($p<0.001$ for all groups). Although the blood glucose responses achieved in the 12 to less than 18 years of age group were smaller in magnitude for both 0.5 mg and 1 mg doses of G-pen in comparison to the other age groups, the responses were still sufficient from a clinical perspective.

Table 13: Blood Glucose in Pediatric Subjects After Administration of G-Pen- Study 302

Age Group	G-Pen dose	Plasma Glucose (mg/dL), Mean (SD) [Min – Max]		
		Baseline	**30 minutes**	**Change**
2 to < 6 years (N=7)	0.5 mg	68.1 (8.3) [55-77.5]	149.6 (15.2) [130-174]	81.4 (18.3) [59-111.5]
6 to < 12 years (N=13)	0.5 mg	71.6 (7.6), [51.5-78.5]	155.8 (26.5), [107-203]	84.2 (25.3), [43-126]
12 to < 18 years (N=11)	0.5 mg	75.7 (1.9), [72-77]	128.1 (20.5), [95-155]	52.4 (19.8), [23-79]
12 to < 18 years (N=11)	1 mg	75.5 (3.6), [65-78]	129.5 (29.5), [70-163]	54.0 (27.3), [5-88]

Source: Adapted from Table 9 and 10, from CSR for Study 302

Although Study 302 was an underpowered exploratory study, and did not involve pre-specified comparisons and induction of hypoglycemia, as discussed in Dr. Sista's Clinical Pharmacology review, based on data from Study 302, the PK/PD of G-Pen is expected to be similar between pediatric and adult patients. The results from Study 302 support the efficacy of G-Pen in pediatric patients.

The applicant also included a hypoglycemia symptom questionnaire (HSQ) as a pre-specified secondary endpoint in Studies 301 and 303. It was intended to measure relief from symptoms of hypoglycemia, and was administered just after the decision to dose to 90 minutes (Study 301) and 180 minutes (Study 303) following glucagon dosing. While the instructions for the HSQ allowed the patients could respond verbally, with site staff recording their responses, if patients were unable to physically complete the questionnaire, there was concern that during episodes of hypoglycemia, patients may not be able to provide valid and reliable responses. The patient-reported outcomes were reviewed by the Clinical Outcomes Assessment (COA) reviewer, Dr. Susan Pretko. In her review, Dr. Pretko concluded the HSQ was not fit-for-purpose (b) (4)

(b) (4)

The Office of Scientific Investigations conducted inspections in support of this application, which consisted of three domestic clinical sites as well as the sponsor and contract research organization (CRO), which was added after inspectional findings at the site revealed not all source data was maintained at the sites. During inspections, regulatory violations were noted, including failure to perform confirmatory plasma glucose values as required by protocol, failure to retain investigational records, and failure to maintain accurate case histories. The

OSI reviewer noted that although the failure to obtain a second confirmatory plasma glucose value was a protocol deviation, it did not represent a safety concern. With respect to investigational records, it was noted that laptop computers with software generated an 8 minute extrapolated plasma glucose value which was relied on by the site for dosing decisions was not available for inspection as the laptop computers were no longer at the sites. The Applicant was contacted during the inspection, and using the calculation provided by (b) (4), with whom the Applicant had a contract for statistical analysis, all 8 minute extrapolated plasma glucose values were manually verified by the site. Inspections of the Applicant and (b) (4) were also conducted. It was noted that although there had been several database unlocks following completion of the studies, it did not appear that any data had been changed or manipulated, and the database unlocks were to fix incorrect or missing values that were in error. The inspectional findings support the validity of the data, and the data is considered reliable. For further details, please see the OSI review by Dr. Cynthia Kleppinger.

Overall, Dr. Ketterman concludes that based on the submitted data, G-Pen causes an increase in blood glucose levels, however she raises concerns regarding the slower time to action of G-Pen compared to Lilly glucagon. The Applicant has demonstrated a faster time of administration by approximately 1 minute for G-Pen compared to Lilly glucagon with trained medical professionals, and I believe it is reasonable to assume that the time to administration difference between the two products might be greater with untrained professionals. Overall, I believe that the greater ease of administration outweighs the issues related to the efficacy profile of G-Pen. I recommend use of the alternate composite endpoint (blood glucose > 70 mg/dL or increase of > 20 mg/dL) due to clinical relevance and consistency with other glucagon products for labeling purposes.

8. Safety

During the clinical development program for G-Pen, a total of 161 adult subjects with T1DM received G-Pen, and 157 subjects received Lilly glucagon, and an additional 31 pediatric subjects with T1DM who were aged 2-<18 years old received G-Pen. Due to the cross-over design of the adult phase 3 studies, the number of subjects is the number of subjects receiving G-Pen or Lilly glucagon, rather than unique subjects. See Table 2 for a complete table of studies conducted with G-Pen. As G-Pen is intended for the treatment of severe hypoglycemia, which is a life-threatening disease, and is intended for short-term use, the ICH guidance for industry *E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions* is not applicable, and the safety database for G-Pen is considered to be acceptable. The assessment of overall safety was conducted by Dr. Suchitra Balakrishnan. In my CDTL review, I will briefly review the overall safety findings and discuss selected safety findings that occurred with a greater frequency with G-Pen. Please refer to Dr. Balakrishnan's review for a detailed discussion of safety findings.

Description of studies reviewed:
Studies discussed in the safety review include the two adult phase 3 studies (Studies 301 and 303), and the pediatric study (Study 302).

Safety Summary
The overall incidence of AEs, as well as local tolerability issues in Studies 301/303, was higher in subjects treated with G-Pen compared to Lilly glucagon. However, the AEs reported with G-Pen were anticipated based on the known safety profile of injectable glucagon, and local tolerability issues were mostly resolved by the end of the study. Safety findings were similar in pediatric subjects as compared to the adult studies, however no comparator product was used in the pediatric study. Overall, I believe these AEs and local tolerability issues can be adequately communicated in labeling.

Deaths:
There were no deaths during the clinical development of G-Pen.

Serious Adverse Events:
There was one reported serious adverse event (SAE) in an adult female from Study 301. The patient was a T1DM who developed an episode of hypoglycemia the evening after discharge from the clinical research unit following treatment with Lilly glucagon. The patient required assistance from a friend for treatment of hypoglycemia, however no glucagon was given, and the subject was treated with saline only by the emergency medical technician. The subject continued in the study and received G-pen at her scheduled clinic visit. I agree with Dr. Balakrishnan's assessment that there is no evidence this event was caused by the study drug, as there is inadequate information about the event, especially since the patient was treated with saline only.

There was one additional SAE in an adult female in Study 202. The patient developed nausea and vomiting 2 hours after G-Pen administration, following which she had an episode of vasovagal syncope. Her blood glucose at the time of the event was 108 mg/dL. I agree with Dr. Balakrishnan's assessment that this event was possibly related to the study drug, as nausea and vomiting are known adverse effects associated with glucagon, and which may have triggered the vasovagal syncope.

Treatment-emergent Adverse Events

Studies 301/303:

Treatment emergent adverse events (TEAEs) were reported by a greater number of subjects treated with G-Pen (71 subjects, 46.1%) versus Lilly glucagon (52 subjects, 33.1%). The most common TEAEs were gastrointestinal and nervous sytem disorders such as nausea, vomiting, and headache. These are consistent with the known adverse event profile of injectable glucagon products. See
Table 14 for additional details.

Table 14: Treatment-emergent Adverse Events by System Organ Class, Preferred Term in Studies 301/303 Reported by ≥2 Patients Treated with G-Pen

System Organ Class Preferred Term	**G-Pen** Subject N=154 n (%)	**Lilly** Subject N=157 n (%)
Any TEAE	**71 (46.1%)**	**48 (30.6%)**
Gastrointestinal disorders	**58 (37.7)**	**45 (28.7)**
Nausea	46 (29.9)	36 (22.9)
Vomiting	25 (16.2)	15 (9.6)
Diarrhea	2 (1.3)	1 (0.6)
General disorders and administration site conditions	**3 (1.9)**	**3 (1.9)**
Injection site pain	2 (1.3)	1 (0.6)
Infections and Infestations	**5 (3.2)**	**0**
Upper Respiratory Tract Infection	2 (1.3)	0
Nervous system disorders	**11 (7.1)**	**7 (4.8)**
Dizziness	2 (1.3)	1 (0.6)
Headache	8 (5.2)	6 (2.8)

Source: Adapted from Table 9.1.2 from Applicant's ISS

Study 302- Pediatric Study

TEAEs were reported in 71.4% of subjects in the 2 to < 6 years of age group, 92.3% of subjects in the 6 to < 12 years of age group, 54.5% of subjects in the 12 to <18 years of age group who received G-Pen in the 0.5 mg dose, and 72.7% of subjects in the 12 to < 18 years of age group who received G-Pen in the 1 mg dose. The highest incidence of reported TEAEs were metabolism and nutrition disorders, with hypoglycemia the most frequently reported PTs, which was related to study procedures. Other TEAEs that were frequently reported were gastrointestinal disorders, with nausea and vomiting the most frequently reported PTs from this SOC, and headache and dizziness. For additional details, see Table 15.

Table 15: Treatment-emergent Adverse Events by System Organ Class, Preferred Term Occurring in ≥ 2 G-Pen-Treated Subjects in the Phase 3 Pediatric Subjects Pool - Study 302

	2.0-<6.0yr (0.5mg)		**6.0-<12.0yr (0.5mg)**		**12.0-<18.0yr (0.5mg)**		**All (0.5mg)**		**12.0-<18.0yr (1.0mg)**	
System Organ Class Preferred Term	**Subject N=7 n (%)**	**No. Of Events**	**Subject N=13 n (%)**	**No. Of Events**	**Subject N=11 n (%)**	**No. Of Events**	**Subject N=13 n (%)**	**No. Of Events**	**Subject N=11 n (%)**	**No. Of Events**
Gastrointestinal disorders	3 (42.9)	4	7 (53.8)	11	4 (36.4)	4	14 (45.2)	19	6 (54.5)	6
Abdominal pain	0	0	1 (7.7)	1	0	0	1 (3.2)	1	0	0

Nausea	3 (42.9)	3	7 (53.8)	7	4 (36.4)	4	14 (45.2)	14	4 (36.4)	4
Vomiting	1 (14.3)	1	3 (23.1)	3	0	0	4 (12.9)	4	2 (18.2)	2
General disorders and administration site conditions	0	0	1 (7.7)	1	0	0	1 (3.2)	1	1 (9.1)	1
Injection site discomfort	0	0	1 (7.7)	1	0	0	1 (3.2)	1	0	0
Injection site reaction	0	0	0	0	0	0	0	0	1 (9.1)	1
Injury, poisoning and procedural complications	0	0	0	0	1 (9.1)	1	1 (3.2)	1	0	0
Head injury	0	0	0	0	1 (9.1)	1	1 (3.2)	1	0	0
Metabolism and nutrition disorders	2 (28.6)	3	8 (61.5)	9	3 (27.3)	3	13 (41.9)	15	3 (27.3	3
Hyperglycaemia	1 (14.3)	1	1 (7.7)	1	0	0	2 (6.5)	2	0	0
Hypoglycaemia	2 (28.6)	2	7 (53.8)	8	3 (27.3)	3	12 (38.7)	13	3 (27.3)	3
Nervous system disorders	0	0	2 (15.4)	2	1 (9.1)	1	3 (9.7)	3	0	0
Dizziness	0	0	0	0	1 (9.1)	1	1 (3.2)	1	0	0
Headache	0	0	2 (15.4)	2	0	0	2 (6.5)	2	0	0
Skin and subcutaneous tissue disorders	0	0	1 (7.7)	1	0	0	1 (3.2)	1	0	0
Urticaria	0	0	1 (7.7)	1	0	0	1 (3.2)	1	0	0
Any TEAEs	5 (71.4)	7	12 (92.3)	24	6 (54.5)	9	23 (74.2)	40	8 (72.7)	10

Source: Table 12.1.2 from Applicant's ISS

Injection Site Edema/Erythema/Pain

Local tolerability issues were assessed in the adult phase 3 studies, as well as in the pediatric study. The modified Draize scale was used to assess edema and erythema by the Investigators, and the incidence of edema and erythema were analyzed descriptively.

Studies 301/303

Overall, there was a higher percentage of subjects that reported injection site edema, erythma, and pain in the G-Pen group compared to the Lilly glucagon group, at all time points. Most events had resolved by the end of visit timepoint, but there was still a higher percentage of subjects reporting edema, erythema, and pain in the G-Pen groups. See Table 16 and Table 17 for more details below.

Table 16: Edema- Studies 301/303

Time	Edema	G-Pen N=154 n (%)	Lilly N=157 n (%)
10 minutes	**None**	**97 (63.0)**	**128 (81.5)**
	Very slight	31 (20.1)	20 (12.7)
	Well defined	21 (13.6)	8 (5.1)
	Moderate	4 (2.6)	0
	Severe	1 (0.6)	0
30 minutes	**None**	**78 (50.6)**	**134 (85.4)**
	Very slight	46 (29.9)	15 (9.6)
	Well defined	20 (13.0)	7 (4.5)
	Moderate	8 (5.2)	0
	Severe	2 (1.3)	0
End of Visit[1]	**None**	**78 (50.6)**	**58 (36.9)**
	Very slight	11 (7.1)	2 (1.3)
	Well defined	1 (0.6)	1 (0.6)
	Moderate	0 (0.0)	0
	Severe	2 (1.3)	0

Source: Table 18 from Applicant's Summary of Clinical Safety

Table 17: Erythema- Studies 301/303

Time	Erythema	G-Pen N=154 n (%)	Lilly N=157 n (%)
10 minutes	**None**	**82 (53.2)**	**86 (54.8)**
	Very slight	56 (36.4)	54 (34.4)
	Well defined	15 (9.7)	16 (10.2)
	Moderate	1 (0.6)	1 (0.6)
	Severe	0	0
30 minutes	**None**	**90 (58.4)**	**96 (61.1)**
	Very slight	49 (31.8)	46 (29.3)
	Well defined	15 (9.7)	14 (8.9)
	Moderate	0	0
	Severe	0	0
End of Visit[1]	**None**	**87 (56.6)**	**54 (34.4)**
	Very slight	2 (1.3)	5 (3.2)
	Well defined	4 (2.6)	2 (1.3)
	Moderate	0	0
	Severe	0	0

Source: Table 22 from Applicant's Summary of Clinical Safety

302- Pediatric Study

As with the adult studies, the majority of subjects reported events of edema and erythema during treatment with G-Pen, however most events had resolved by the end of treatment. See Table 18 and Table 19 for further details.

Table 18: Edema in Study 302

Age Group	G-Pen Dose	Incidence of Edema [a]					
		10 minutes		30 minutes		180 minutes	
		n	%	n	%	n	%
2 to < 6 years (N=7)	0.5 mg	3	42.9	3	42.9	1	16.7
6 to < 12 years (N=13)	0.5 mg	9	69.2	8	61.5	4	30.8
12 to < 18 years (N=11)	1 mg	5	45.5	5	45.5	1	9.1
12 to < 18 years (N=11)	0.5 mg	6	54.5	5	45.5	1	9.1

Source: Table 20 from Applicant's CSR for Study 302

Table 19: Erythema in Study 302

Age Group	G-Pen Dose	Incidence of Erythema [a]					
		10 minutes		30 minutes		180 minutes	
		n	%	n	%	n	%
2 to < 6 years (N=7)	0.5 mg	4	57.1	2	28.6	0	0.0
6 to < 12 years (N=13)	0.5 mg	8	61.5	7	53.8	0	0.0
12 to < 18 years (N=11)	1 mg	5	45.5	6	54.5	1	9.1
12 to < 18 years (N=11)	0.5 mg	5	45.5	4	36.4	0	0.0

Source: Table 19 from Applicant's CSR for Study 302

9. Advisory Committee Meeting

Not applicable.

10. Pediatrics

The applicant conducted a pediatric assessment for children aged 2 to less than 18 years of age (Study 302). In the agreed iPSP, the applicant had requested a partial waiver for study in children < 2 years of age because studies are impossible or highly impractical. The Applicant

also requested a pediatric exclusivity determination, but was ineligible because a Written Request was never issued, and a PPSR was never submitted by the applicant. The pediatric assessment in children ages 2 to less than 18 was discussed with PeRC on April 24, 2019. The applicant's pediatric assessment for children ages 2 to less than 18 years of age was found to be acceptable.

11. Other Relevant Regulatory Issues

Not applicable.

12. Labeling

Prescribing Information

The applicant has proposed the following indication for G-Pen: for the treatment of severe hypoglycemia in adult and pediatric patients with diabetes. I agree that the submitted data supports the use of G-Pen for the proposed indication for pediatric patients, as the Applicant is referencing Lilly glucagon, which also has a pediatric indication, and they also conducted a pediatric assessment. See Pediatrics section for more information.

The applicant has proposed a contradindication for patients with a known hypersensitivity to glucagon, as well as in patients with pheochromocytoma and insulinoma. Warnings and Precautions include catecholamine release in patients with pheochromocytoma, hypoglycemia in patients with insulinoma, hypersensitivity and allergic reactions, and lack of efficacy in patients with decreased glycogen stores. The applicant has not proposed to include Necrolytic Migratory Erythema (NME) in the Warnings and Precautions, as this is associated with continuous intravenous infusion, however, since the drug could be removed from the PFS and used in an infusion, the risk of NME is still a concern, and I recommend adding it to the label. The applicant has also not included hypoglycemia in patients with glucagonoma. Since this is a known risk for glucagon products, I recommend adding it to the label.

The clinical trial data proposed by the applicant to describe AE data should be limited to data from G-Pen, without comparator data. It may be misleading to present data comparing AEs to Lilly glucagon. In addition, the applicant proposed (b) (4). (b) (4) (b) (4). In addition, due to concerns with the initial primary endpoint for the phase 3 studies, the description of clinical studies should present the composite of blood glucose > 70 mg/dL or rise > 20 mg/dL at 30 minutes.

Other Labeling:
The applicant has proposed the proprietary name GVOKE PFS and GVOKE HypoPen. These names were reviewed by Dr. Ariane Conrad of DMEPA, who has found the names to be acceptable.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

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

Postmarketing Requirements (PMRs) and Commitments (PMCs)

The Applicant has already conducted a pediatric assessment for pediatric patients ages 2 to less than 18 years of age. There are no additional PMRs or PMCs recommended for this product.

14. Recommended Comments to the Applicant

None

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MITRA RAUSCHECKER
09/09/2019 01:05:42 PM

LISA B YANOFF
09/09/2019 02:09:59 PM